purpose of this study was to assess the long-term (4 weeks) safety and efficacy of a various fixed MNTX SC doses (1 mg to 20 mg). Thirty-three patients were randomly assigned to receive double-blind, fixed SC doses of MNTX (1, 5, 12.5, or 20 mg QOD) during Week 1 of the study. Each MNTX dose was administered SC on Days 1, 3, and 5.

After completing the first week of this study, patients were then eligible for treatment with open-label MNTX starting at an initial dose of 5 mg administered on study Day 7. Subsequent dosing was as needed, with escalation to a maximum dose of 20 mg as needed every other day for up to three weeks.

Medical Reviewer's Comments

- *These dosages differ from the Applicant's proposed to be marketed dosages but were used to study dose ranging and safety.*
- *The original protocol randomized patients on a 1:1:1 basis to one of three dosages of MNTX (1 mg, 5 mg, or 12.5 mg). After the first 22 patients were enrolled, based on data monitoring done on a blinded basis for the first 16 patients, the Applicant decided to extend the range of dosing to 20 mg SC to assess tolerability at that dosage level (Amendment 3). As a result, no new patients were assigned to the 5 mg MNTX dose level and subsequent patients were randomized on a 1:1:3 basis.*

The primary efficacy endpoint of this study was the 4-hour laxation response on Day 1 of the double-blind phase. Secondary efficacy endpoints included patient-recorded evaluation of bowel movements with regards to consistency and difficulty and assessment of constipation severity and distress, pain. In addition, opioid withdrawal effects, opioid non-bowel adverse effects, and patient satisfaction during Week 1 (double-blind treatment) and Weeks 2-4 (open-label treatment). The Cochran-Mantel-Haenszel (CMH) test was used to analyze these secondary endpoints.

Protocol Amendments

There were 3 amendments to the original study protocol which was dated 30 October 2001:

Amendment 1 (2/12/2002): The purpose of this amendment was to clarify the study objectives for the open-label treatment phase of the study. In addition, the study design was revised to state that 10 patients were to be randomized to each of 3 dose levels in a randomized sequence. Finally, the statistical objectives and methodology were redefined.

Amendment 2 (5/10/2002): In the original protocol constipation was defined as no bowel movement for 3 or more days prior to the first dose of study drug with a rating of 3 or 4 on a 5 point scale assessing constipation related distress. This definition was changed to no bowel movement for more than 2 days prior to study drug dosing with a rating of 3 or greater on the 5 point constipation related distress scale. This amendment also changed the inclusion criterion of stable laxative use from at least 5 days to 4 or more days.

Amendment 3 (9/5/2002): This amendment revised the dose levels of MNTX following a preliminary review on a blinded basis of 4-hr laxation response data of 16 patients who received 3 doses each of MNTX. Patients were initially randomized 1:1:1 to receive 1 of 3 fixed doses of MNTX: 1 mg, 5 mg, or 12.5 mg administered SC QOD. It was decided to extend the range of dosing to 20 mg to assess tolerability and activity at that dose level. The study design was then amended to allow for evaluation of patients receiving a dose of 20 mg MNTX during the double-blind phase. No new patients were assigned to the 5 mg MNTX dose level per Amendment 3. This change took effect after a total of 22 patients had been randomized. Eleven patients were randomized subsequent to the amendment. Per Amendment 3, the randomization scheme was modified to include a ratio of 1:1:3 for the 1, 12.5, and 20 mg doses, respectively. This allowed more patients to be treated at the highest dose level during the double-blind phase.

Inclusion Criteria

1. Advanced medical illness (e.g., advanced metastatic cancer and AIDS) for which they were receiving palliative care.
2. Receipt of opioid medication for at least 2 weeks for palliation of pain, with no expectation of a significant change in regimen during the duration of the study.
3. Constipation (no bowel movement in >2 days [per Amendment 2] prior to study drug dosing) and a rating of 3 or greater (per Amendment 2) on a 5-point scale assessing constipation-related distress. Prior to Amendment 2, the wording for the definition of constipation was no bowel movement in ≥3 days prior to randomization and a rating of 3 or 4 on the 5-point scale.
4. Maintained on a stable laxative regimen of any type for more than 4 days (per Amendment 2). Amendment 2 permitted rescue laxatives, but they were not to be used within 24 hours of Day 1 of study treatment. Prior to Amendment 2, the wording for this inclusion criterion was maintenance on a stable laxative regimen of any type for at least 5 days.
5. Life expectancy of >4 weeks.
6. Liver function test (LFT) results <3.0 x upper limit of normal (ULN), and creatinine <2 x ULN. Laboratory evaluations required during the week prior to Day 1.
7. Platelet count >50,000/mm^3. Laboratory evaluations required during the week prior to Day 1.
8. Afebrile, with stable vital signs.
9. Understand and sign an informed consent form.
10. 18 years of age or older.
11. Both men and women were eligible; women of childbearing potential were to have a negative pregnancy test.

Exclusion Criteria

1. Concurrent use of medications other than opioids that might interfere with gastrointestinal motility (e.g., antimuscarinic drugs, chemotherapy etc.)
2. Known hypersensitivity to methylnaltrexone, naltrexone, or naloxone.
3. Receipt of any investigational new drug (experimental) in the previous 30 days.

4. A disease process suggestive of gastrointestinal obstruction.
5. Any potential non-opioid cause of bowel dysfunction.
6. A diagnosis of active peritoneal cancer (e.g., ovarian, or other malignancy involving the bowel) that may have interfered with bowel function (per Amendment 2).
7. History of/or current peritoneal catheter for intraperitoneal chemotherapy or dialysis.
8. Clinically significant active diverticulitis or diverticulosis.
9. A surgically acute abdomen.
10. Fecal ostomy.

Study Procedures

In this study, patients were randomized to 1 of 3 fixed MNTX SC dose levels (1 mg, 5 mg, or 12.5 mg, and later as per protocol Amendment 3, 1 mg, 12.5 mg, or 20 mg) QOD starting on Day 1. On study drug treatment days (Days 1, 3, and 5), vital signs were taken before the dose, and at 20, 30, 60, and 180 minutes after the dose. Any injection site reactions were recorded as AEs. Laboratory assessments (hematology and serum chemistry) were performed on Day 7 (end of treatment period). Bowel movements were assessed daily throughout the 7-day double-blind treatment phase. Other clinical assessments were performed on the dosing day and on Day 7 which was the end of the treatment period. These included constipation severity/distress, pain score, opioid withdrawal scale, opioid side effects and patient satisfaction.

After completing the double-blind phase, patients were given the option of continuing open-label MNTX SC therapy for up to 3 additional weeks. After providing informed consent for this phase of the study, all participants received an initial 5 mg MNTX SC dose on Day 1. Subsequent doses were given on an as needed basis every other day. Vital signs were taken before the first dose, and 20, 30, 60, and 180 minutes after the first dose and at the end of the open-label treatment phase. Any injection site reactions were recorded as AEs. Laboratory assessments (hematology and serum chemistry) and a physical examination performed on Day 21 (or the end of treatment period). Bowel movements were assessed daily throughout the 21-day open-label treatment phase. Other clinical assessments identical to those taken during the double-blind phase were performed on the dosing day and Day 21 or at the end of the treatment period if sooner.

Demographics

The mean age of the 33 randomized patients overall was 61.1 years (range: 20 to 87 years), with a mean body weight of 63.8 kg (range: 38.6 to 112.7 kg). Just over one-half (18/33; 55%) of the patients across all dose groups were female, with the majority (26/33; 79%) of patients being Caucasian. The 1 mg, 5 mg, and 12.5 mg dose groups were similar with regard to demographic and baseline characteristics, although the number of patients in each dose group was small. Patients randomized to the 20 mg dose group were older and weighed less compared with the other 3 dose groups. The majority of these patients had cancer (85%) although 9% had Sickle cell disease and 6% had AIDS.

Table 29 Demographics and Baseline Characteristics: MNTX 251

Characteristic	MNTX Dose Level				All Patients (N=33)
	1 mg (N=10)	5 mg (N=7)	12.5 mg (N=10)	20 mg (N=6)	
Gender, N (%)					
Male	6 (60)	3 (43)	4 (40)	2 (33)	15 (45)
Female	4 (40)	4 (57)	6 (60)	4 (67)	18 (55)
Race, N (%)					
Caucasian	7 (70)	6 (86)	7 (70)	6 (100)	26 (79)
Black	2 (20)	0 (0)	3 (30)	0 (0)	5 (15)
Hispanic	0 (0)	1 (14)	0 (0)	0 (0)	1 (3)
Asian	1 (10)	0 (0)	0 (0)	0 (0)	1 (3)
Age, years					
Mean	59.1	59.0	60.2	68.5	61.1
SD	22.7	19.1	19.3	14.2	19.0
Range	20 – 87	33 – 85	24 – 84	50 – 87	20 – 87
Weight, kg					
Mean	63.0	68.2	64.6	57.0	63.8
SD	12.8	21.9	16.6	15.7	16.1
Range	38.6 – 77.9	56.4 – 112.7	31.8 – 89.1	40.0 – 70.4	31.8 – 112.7
Opioid (morphine equivalent) dose at baseline, mg					
Mean (SD)	266.5 (209.7)	320.1 (322.7)	238.4 (315.4)	379.5 (454.7)	289.9 (308.0)
Median	196.0	360.0	110.0	152.5	180.0
Range	9 – 780	30 – 960	10 – 1067	30 – 1207	9 – 1207

Source: Adapted from CSR, MNTX 251, Table 13, Page 41

Subject Disposition

A total of 39 patients were assessed for inclusion into this study. Six of the 39 patients failed screening procedures; therefore, 33 were randomized to treatment with one of four SC doses of MNTX (1 mg, 5 mg, or 12.5 mg originally [n=22], and then 1 mg, 12.5 mg, or 20 mg following Amendment 3 [n=11]). For the double-blind phase, 10 patients each were randomly assigned to the 1 mg and 12.5 mg dose levels, seven patients were assigned to the 5 mg dose level, and six patients were assigned to the 20 mg dose level. All of the 6 patients randomized to the 20 mg dose group were from study site 2. Twenty-two of the 33 patients enrolled completed the double-blind treatment phase. Four of these 22 patients chose not to proceed further after completing the double-blind phase and 18 entered the open-label. Of these 18 patients, 14 completed the 3-week open-label phase.

Subject Discontinuations

A total of 15 out of 33 randomized patients were withdrawn from the study before completion. Eleven patients were withdrawn during the double-blind phase. The primary reason for early withdrawal was patient request (one patient in the 1 mg dose group, one patient in the 5 mg dose group, three patients in the 12.5 mg dose group, and two patients in the 20 mg dose group).

In the double-blind and open-label phase of the study, the 7 patients who withdrew per "Patient Request" did so for the following reasons:

- Increased shortness of breath due to lung cancer after first dose of 1 mg.
- Suicide attempt after second 5 mg dose.
- Diarrhea following the first 12.5 mg dose
- Abdominal pain and nausea following the 12.5 mg dose
- Reason not provided (12.5 mg dose)
- Confusion/agitation (20 mg dose)
- Reason not provided (20 mg dose)

Other reasons included death (one patient), intolerable AE (one patient), and other medical reasons/disease progression (two patients). During the open-label phase, four patients were withdrawn from the study. Each of the four was withdrawn as a result of one of the following reasons: intolerable AE, patient request, death, other medical reasons/disease progression.

Table 30 Patient Discontinuations: MNTX 251 DB

	MNTX Dose Level (N=33)			
Double-Blind Treatment Phase	1 mg (n=10)	5 mg (n=7)	12.5 mg (n=10)	20 mg (n=6)
Completed	7	5	7	3
Withdrawn	3	2	3	3
Patient Request	1	1	2	2
Intolerable Adverse Event	0	0	1	0
Disease Progression	1	0	0	1
Study Death	0	1	0	0

Source: Adapted from CSR, MNTX 251, Table 10, Page 38

Table 31 Patient Discontinuations: MNTX 251 OL

	MNTX Dose Level (N=18)			
Open-Label Treatment Phase	1 mg (n=6)	5 mg (n=4)	12.5 mg (n=5)	20 mg (n=3)
Completed	4	3	4	3
Withdrawn	2	1	1	0
Patient Request	0	1	0	0
Intolerable Adverse Event	1	0	0	0
Disease Progression	0	0	1	0
Study Death	1	0	0	0

Source: Adapted from CSR, MNTX 251, Table 11, Page 38

At the end of the 30-day follow-up period, survival was confirmed for 22 (66.7%) patients and 11 patients (33.3%) had died. Of deaths occurring during the 30-day follow-up period, 5 occurred following termination or completion of the double-blind phase and 4 occurred following termination of completion of the open-label phase.

Primary Efficacy Endpoint

Initially, the primary efficacy analysis was to be the comparison of the 4-hour laxation response on Day 1 for patients in the highest (initially 12.5 mg, then revised to 20 mg) dose group versus the lowest (1 mg) dose group. Because of the small number of subjects in each arm of the study, the focus of the primary efficacy analysis in the revised plan was to determine the 4-hour laxation response for all doses (1 mg, 5 mg, 12.5 mg, and 20 mg).

The ITT analysis set included all randomized patients who received MNTX. For the double-blind phase, the ITT analysis set was comprised of the 33 patients who received at least 1 dose of study medication (10 patients each in the 1 mg and 12.5 mg dose groups, 7 in the 5 mg dose group, and 6 in the 20 mg dose group). For the open-label phase, the ITT analysis set included the 18 patients who received at least one dose of open-label MNTX. The safety analysis set for both the double-blind and the open-label treatment phases was the same as the ITT analysis set. Table 32 summarizes the proportion of patients who reported laxation within 4 hours, and then within 24 hours of dosing on Days 1, 3, and 5 during the double-blind phase.

Table 32 4-Hour Laxation Responses at All Doses: MNTX 251 DB

Dosing Day	MNTX Dose Level					
	1 mg	5 mg	12.5 mg	20 mg	≥5 mg combined	Chi-Square P-Value for all treatment groups
4-hour response						
1	1/10 (10%)	3/7 (43%)	6/10 (60%)	2/6 (33%)	11/23 (48%)	0.1346
3	2/9 (22%)	4/6 (67%)	5/7 (71%)	2/4 (50%)	11/17 (65%)	0.1927
5	0/7 (0%)	4/5 (80%)	4/7 (57%)	3/4 (75%)	11/16 (69%)	0.0193
24-hour response						
1	5/10 (50%)	5/7 (71%)	7/10 (70%)	2/6 (33%)	14/23 (61%)	0.4136
3	3/9 (33%)	4/6 (67%)	5/7 (71%)	3/4 (75%)	12/17 (71%)	0.3316
5	1/7 (14%)	4/5 (80%)	4/7 (57%)	3/4 (75%)	11/16 (69%)	0.0903

Source: Adapted from CSR, MNTX 251, Table 18, Page 44

Medical Reviewer's Comment

- *The Applicant proposes for marketing doses of 8 mg for patients who weigh between 38 and 62 kg and 12 mg for patients who weigh between 62 and 114 kg. The efficacy at the 5 mg and 12.5 mg dosages is summarized in Table 33 below.*

Table 33 4-Hour Laxation Responses at MNTX 5 mg and 12.5 mg: MNTX 251

Dosing Day	5 mg	12.5 mg	5 mg and 12.5 mg combined doses
4-hour response			
1	3/7 (43%)	6/10 (60%)	9/17 (53%)
3	4/6 (67%)	5/7 (71%)	9/13 (69%)
5	4/5 (80%)	4/7 (57%)	8/12 (66%)
24-hour response			
1	5/7 (71%)	7/10 (70%)	12/17 (71%)
3	4/6 (67%)	5/7 (71%)	9/13 (69%)
5	4/5 (80%)	4/7 (57%)	8/12 (66%)

Source: Adapted from CSR, MNTX 251, Adapted from Table 18, Page 44

Table 34 Laxation Responses, Weight-Based Dosing: MNTX 251 DB

Dosing Day	MNTX Dose Level					
	< 0.05 mg/kg (N=10)		0.05-< 0.24 mg/kg (N=13)		≥ 0.25 mg/kg (N=6)	
	No. (%) of pts.	No. of pt. doses	No. (%) of pts.	No. of pt. doses	No. (%) of pts.	No. of pt. doses
4-hour response						
1	1 (10%)	10	6 (46%)	13	3 (50%)	6
3	2 (20%)	10	8 (80%)	10	2 (67%)	3
5	0 (0%)	7	6 (60%)	10	4 (100%)	4
Total	3 (11%)	27	20 (61%)	33	9 (69%)	13
24-hour response						
1	6 (60%)	10	8 (62%)	13	3 (50%)	6
3	3 (30%)	10	8 (80%)	10	3 (100%)	3
5	1 (14%)	7	6 (60%)	10	4 (100%)	4
Total	10 (37%)	27	22 (67%)	33	10 (77%)	13

Source: Adapted from CSR, MNTX 251, Table 23, Page 49

Medical Reviewer's Comment

- *Analysis of the results from the mg/kg dosing of MNTX is similar to the fixed mg doses since the < 0.05 mg/kg dose group roughly corresponds to the 1 mg fixed dose level. The responses of the two higher dose groups were similar in both the fixed dose and the mg/kg dose.*

Changes in the following secondary endpoints were also analyzed on Days 1, 3, 5, and 7 of the double-blind phase of the study:

- Bowel Movement Evaluation: Compared to baseline, patient self-assessment for bowel function satisfaction indicated improvement. Of all the MNTX dose groups, patients receiving 12.5 mg indicated more improvement in bowel function satisfaction than patients in the 1 mg, 5 mg, or 20 mg dose groups.
- Constipation Evaluation: Some improvement in constipation severity and distress were noted.
- Pain Evaluation: There were no differences in pain assessments among the MNTX dose groups at baseline, on dosing Days 1, 3, or 5, or at the end of the double-blind treatment period (Day 7) or any apparent dose trends for worsening pain.
- Opioid Withdrawal Scale: MNTX administered SC in doses ranging from 1 mg to 20 mg had minimal or no effect on the occurrence or intensity of symptoms relating to opioid withdrawal during the double-blind phase of the study.
- Opioid Adverse Effects (non-bowel): The occurrence and intensity of non-bowel opioid adverse effects following the Day 1, Day 3, and Day 5 doses of MNTX were similar to baseline scores.

- Patient Satisfaction: On Day 1, three of the 15 patients who provided a response indicated they were satisfied with their medication; by Day 5, nine of the 22 patients who responded rated satisfaction with medication as better.
- Use of Rescue Laxative Medication: On Day 1, patients in the 1 mg dose group required rescue laxatives twice as frequently as those in the higher dose groups. Roughly equivalent numbers of patients in the 5 mg, 12.5 mg, and 20 mg MNTX dose groups required rescue medication.

6.1.4 Efficacy Findings

Results from the three primary studies reviewed demonstrate that the 0.15 mg/kg and 0.30 mg/kg SC dosages were both effective in the treatment of opioid induced constipation as measured by the four hour laxation rate versus placebo. Other measures of laxation including laxation within 24 hours after the first dose and laxation after two of the first four double-blind doses also showed a consistent advantage for MNTX over placebo. The durability of the successful response was demonstrated in MNTX 302 over the two week double-blind period, in the four week open-label treatment period in MNTX 301 and in the two open-label extension studies. Table 35 is a summary of the pooled results of the placebo-controlled double-blind data derived from the double-blind phases of studies MNTX 301 and 302.

Table 35 Pooled DBPC Data Using Weight-Based Dosing: MNTX 301 and 302

Protocol	Treatment	Patients with a Positive Laxation Response/Patients Dosed	% (95% CI)	P-Value
MNTX 301 Double-Blind	Placebo	7/52	13.5 (4.2-22.7)	
	MNTX 0.15 mg/kg	29/47	61.7 (47.8-75.6)	p<0.0001
	MNTX 0.30 mg/kg	32/55	58.2 (45.1-71.2)	p<0.0001
MNTX 302	Placebo	11/71	15.5 (7.1-23.9)	p<0.0001
	MNTX 0.15 mg/kg	30/62	48.4 (35.9-60.8)	p<0.0001
Summary	Placebo	18/123	14.6	
	MNTX 0.15 mg/kg	59/109	54.1	
	MNTX 0.30 mg/kg	32/55	58.2	

Source: Medical Reviewer's compilation of data

Medical Reviewer's Comments

- *In the placebo-controlled, double-blind phases of the above studies, 109 patients were treated with MNTX at a dosage level of 0.15 mg/kg which generally corresponds to the proposed fixed dosing that the Applicant is proposing for marketing. 54% of these patients reported a positive laxation response within four hours as opposed to 14.6% positive laxation response in the group taking the placebo.*
- *MNTX in the proposed 8 mg and 12 mg doses has been shown by the Applicant to be very effective in this group of patients.*

6.1.5 Clinical Microbiology

The study drug is not an antimicrobial so this section is not applicable.

6.1.6 Efficacy Conclusions

The results of the studies submitted in support of this NDA must be interpreted with caution because of the relatively small sample sizes and the relatively short durations of the primary trials. However the differences between placebo and MNTX 0.15 mg/kg were highly significant despite the small numbers in each group. MNTX 0.15 mg/kg has been proven to be highly effective when given SC in treating OIC in patients receiving terminal care.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The primary safety data is derived from the phase 2 study (MNTX 251) and the two phase 3 studies (MNTX 301/301EXT, MNTX 302/302EXT) with the open-label extensions. The longest study submitted to this NDA was MNTX 301/301EXT in which SC MNTX was given for up to four months. There is additional safety data from the four phase 1 studies (MNTX 103, MNTX 1105, MNTX 1106, and MNTX 1107) as well as earlier studies performed at the University of Chicago. The total safety data base from the studies conducted by the Applicant is approximately 286 patients and 144 volunteers who received SC MNTX. Of the 286 patients who took MNTX, 225 had a primary diagnosis of cancer, 174 had renal dysfunction, 120 had CNS disease, 54 had heart failure, and 60 had COPD.

The following safety assessments were performed: Adverse Events (AEs), laboratory assessments, physical examinations, and vital signs.

An AE was defined as any new, undesirable experience or undesirable change (i.e., exacerbation) in an existing condition that occurred following enrollment, either before, during, or after treatment, irrespective of its relationship to study drug. AEs also included clinical worsening due to the underlying disease.

A treatment-emergent adverse event was defined as an adverse event that began after the first dose of study drug was administered, or that had been present prior to the administration of the

first dose of study drug but increased in severity during the study. Adverse events were counted as treatment-emergent for the DBPC Pool if they occurred 1) at any time between administration of the first dose of study drug and the start of open-label MNTX treatment for patients who received open-label treatment, or 2) at any time between administration of the first dose of study drug and 30 days after the last dose of study drug for patients who received only double-blind treatment. Adverse events were counted as treatment-emergent for the MNTX Exposure Pool if they occurred at any time between administration of the first dose of MNTX and 30 days after the last dose of MNTX was given.

A serious adverse event (SAE) was defined as any AE, occurring at any dose and regardless of causality, that:

- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.

Medical Reviewer's Comment

- *The major items for a clinical safety review include deaths, discontinuations due to adverse events and serious adverse events. As one might expect from a patient population with terminal illness, clinical worsening of the underlying disease processes occurred frequently thus making evaluation of drug safety more challenging.*

Vital signs were monitored pre- and post-dosing during double-blind dosing and for the first open-label dose. The type of temperature assessment was to remain constant for a given patient throughout the study. Pre- and postdose vital signs were recorded 5 minutes prior to dosing and 30 min (± 5 min), 60 min (± 5 min), and 4 hours (± 15 min) postdose.

Physical Examinations which included recordings of height and weight were performed.

Laboratory Assessments included serum chemistry consisting of ALT, AST, albumin, alkaline phosphatase, total bilirubin, bicarbonate, total protein, glucose, sodium, potassium, chloride, calcium, creatinine, and blood urea nitrogen.

Hematology included a complete blood count (CBC) with differential consisting of WBC, RBC, hematocrit, hemoglobin, and differential (neutrophils, basophils, monocytes, eosinophils, lymphocytes, platelets, and pregnancy tests for women (urine or serum) of childbearing potential.

Analysis Pools

Four analysis pools were constructed to analyze the safety data across the phase 2 and phase 3 studies.

1. The Double-Blind, Placebo-Controlled Pool (DBPC Pool): Safety data from the double-blind period of the two placebo-controlled studies, MNTX 301 (one double-blind dose)

and MNTX 302 (maximum of seven double-blind doses over two weeks) are included in this pool. (N=288 of whom 123 received placebo and 165 received MNTX.)

2. Double-Blind Pool: This pool consists of the DBPC Pool above and adds the data from the 33 patients in the double-blind phase of MNTX 251 (Maximum of three double-blind doses over one week). (N=321 of whom 123 received placebo and 198 received MNTX.)
3. MNTX Exposure Pool (MNTX Pool): This pool includes all patients who received at least one dose of MNTX (N=286) in studies MNTX 301/301EXT, MNTX 302, MNTX 302EXT and MNTX 251.
4. Healthy Volunteers Pool: This pool contains safety data from the healthy volunteers who enrolled in four studies (MNTX 103, MNTX 1105, MNTX 1106, and MNTX 1107) and received SC MNTX. MNTX was given SC in MNTX 1105, MNTX 1106 and MNTX 1107 and was given both IV and SC in MNTX 103. This pool consists of data obtained from a total of 186 subjects, 142 who received MNTX and 44 who received placebo. The data from subjects who received IV MNTX in study MNTX 103 are not included in this pool. MNTX 103 and MNTX 1106 enrolled only healthy volunteers, whereas MNTX 1105 and MNTX 1107 enrolled both healthy volunteers and subjects with renal and hepatic impairment, respectively.

Medical Reviewer's Comments

- *This safety review will emphasize the DBPC Pool (N=288) and the MNTX Pool (N=286).*
- *The DBPC Pool provides the best match of the exposure of MNTX to placebo and allows a better evaluation of the treatment-emergent AEs that are drug related. Study results from the double-blind phase of MNTX 251 are not included in this pool because there was no placebo group included in this study.*

7.1.1 Deaths

A total of 159 deaths were reported among patients who participated in the clinical studies. A total of 41 deaths occurred during double-blind treatment (23 on MNTX and 18 on placebo), one death occurred in a placebo-treated patient who entered an open-label phase but did not receive MNTX, and an additional 117 deaths occurred during open-label MNTX treatment (two patients died after the study period and 12 patients died more than 30 days after the last dose of study drug was administered).

No healthy volunteer or other subject in a phase 1 study died. In the phase 2 and phase 3 studies submitted for review, only one death was reported as being related to MNTX therapy.

Of the 140 MNTX treated patients who died, the reported cause of death was the underlying disease or a complication relating to the underlying disease except in one case which is described below.

Patient 301-19-0007 was a 73 year old Caucasian female hospice patient with Stage IV metastatic breast cancer which was originally diagnosed in 2000 and reoccurred in October of 2003. The patient was randomized and completed the double-blind, single dose period (0.30 mg/kg SC) in study MNTX 301 on 5/27/2004. She entered the open-label phase and initially

received a single dose of MNTX 0.15 mg/kg SC on 5/28/2004. After this dose was given she experienced gastrointestinal cramping and an episode of two small hard stool "pebbles" about one hour post injection. She subsequently received three doses of MNTX 0.30 mg/kg SC from 5/29/2004 unti ——— One hour after the dose was given on ——— the patient complained of mild abdominal pain and had massive diarrhea, nausea and vomiting which caused her to pass out. Vital signs taken during this time revealed a pulse of 60, respirations 18, and a BP of 110/60. The following day she was found dead. An autopsy was not performed. In the Investigator's opinion, causality of the events of severe diarrhea, dehydration, and cardiovascular collapse was probably due to the study drug.

In the DBPC Pool, 18 of 123 (14.6%) placebo-treated patients and 16 of 165 (9.7%) MNTX-treated patient died during a study or within the 30-day follow-up (for those not entering an open-label study).

In the Double-Blind Pool, 18 of 123 (14.6%) placebo-treated patients and 23 of 198 (11.6%) MNTX-treated patients died during a study or within the 30-day follow-up.

Of the 286 patients in the MNTX Pool, 140 (49%) were known to have died during or after one of the studies. One hundred thirty eight of these deaths occurred during a study or within the 30-day follow-up period and two occurred after the 30-day follow-up period..

Medical Reviewer's Comments

- *A Kaplan-Meier analyses based on all causes of mortality showed no meaningful difference in survival between patients who received MNTX throughout the double blind and open label phases and those who initially received placebo in the double-blind and then MNTX in the open-label phase.*
- *The survival data for patients who received only placebo appeared worse than that of patients receiving only MNTX. The estimated median survival time in the placebo group was 43 days and in the MNTX group was 70 days.*

7.1.2 Other Serious Adverse Events

In the DBPC Pool, at least one non-fatal serious adverse event occurred in 11 of the 123 (8.9%) placebo treated patients and two of the 165 (1.2%) MNTX-treated patients. Pain was the only serious adverse event that occurred in more than one patient in either treatment group (1.6% in the placebo-treated patients and none of the MNTX-treated patients). The remaining serious adverse events each occurred in a single patient.

At least one non-fatal serious adverse event occurred in 57 (19.9%) of 286 the MNTX treated patients. The most commonly reported adverse events were nausea, vomiting, and chest pain, each of which occurred in four patients (1.4%). Abdominal pain, dehydration, cancer pain, and delirium each occurred in three (1.0%) patients. Two patients (0.7%) each had constipation, ileus, asthenia, drug withdrawal syndrome (one patient from fentanyl withdrawal and one patient from temazepam withdrawal), peripheral edema, pain, pneumonia, failure to thrive, myalgias,

malignant neoplasm progression, and confusional state. The remaining serious adverse events each occurred in a single patient.

Table 36 is a side-by-side tabulation of the non-fatal serious adverse events from the DBPC Pool and the MNTX Pool.

Table 36 Non-Fatal Serious Adverse Events: DBPC Pool and MNTX Pool

Primary System Organ Class Preferred Term	Placebo-Controlled Pool		MNTX Pool
	Placebo (N=123) n (%)	MNTX (N=165) n (%)	MNTX (N=286) n (%)
Any Preferred Term	11 (8.9)	2 (1.2%)	57 (19.9)
Cardiac Disorders	2 (1.6)	0	2 (0.7)
Cardiac failure congestive	1 (0.8)	0	1 (0.3)
Cyanosis	1 (0.8)	0	0
Myocardial infarction	0	0	1 (0.3)
Gastrointestinal Disorders	3 (2.4)	0	14 (4.9)
Abdominal pain	1 (0.8)	0	3 (1.0)
Constipation	1 (0.8)	0	2 (0.7)
Vomiting	1 (0.8)	0	4 (1.4)
Nausea	0	0	4 (1.4)
Ileus	0	0	2 (0.7)
Diarrhea	0	0	1 (0.3)
Dysphagia	0	0	1 (0.3)
Gastric Ulcer hemorrhage	0	0	1 (0.3)
Esophageal obstruction	0	0	1 (0.3)
General Disorders and Administration Site Conditions	3 (2.4)	1 (0.6)	13 (4.5)
Chest pain	0	0	4 (1.4)
Drug withdrawal syndrome	0	0	2 (0.7)
Asthenia	1 (0.8)	0	2 (0.7)
Edema peripheral	0	0	2 (0.7)
Pain	2 (1.6)	0	2 (0.7)
Concomitant disease progression	0	0	1 (0.3)
Non-cardiac chest pain	0	0	1 (0.3)
Infections and Infestation	2 (1.6)	0	11 (3.8)
Pneumonia	0	0	2 (0.7)
Metabolism and Nutrition Disorders	1 (0.8)	0	6 (0.3)
Dehydration	1 (0.8)	0	3 (1.0)
Failure to thrive	0	0	2 (0.7)
Hypoglycemia	0	0	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	0	0	6 (2.1)
Myalgia	0	0	2 (0.7)
Neoplasms Benign, Malignant and Unspecified	0	0	5 (1.7)
Cancer pain	0	0	3 (1.0)
Malignant neoplasm progression	0	0	2 (0.7)
Nervous System Disorders	1 (0.8)	0	5 (1.7)
Coma	1 (0.8)	0	0

Simple partial seizures	0	0	1 (0.3)
Psychiatric Disorder	0	1 (0.6)	8 (2.8)
Delirium	0	0	3 (1.0)
Confusional state	0	0	2 (0.7)
Suicidal ideation	0	1 (0.6)	1 (0.3)
Renal and Urinary Disorders			1 (0.3)
Renal failure acute	0	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	2 (1.6)	0	5 (1.7)
Dyspnea	1	0	1 (0.3)
Pulmonary congestion	1	0	0
Tracheal stenosis	1	0	0
Lung infiltration	0	0	1 (0.3)
Pleural effusion	0	0	1 (0.3)
Pulmonary edema	0	0	1 (0.3)
Respiratory failure	0	0	1 (0.3)
Vascular Disorders	2 (1.6)	0	3 (1.0)
Hypotension	1 (0.8)	0	1 (0.3)
Peripheral vascular disorder	1 (0.8)	0	0
Hot flush	0	0	1 (0.3)
Thrombosis	0	0	1 (0.3)

Source: Adapted from SCS, Tables 42 and 44, Pages 84 and 89.

Medical Reviewer's Comments

- *The DBPC Pool consisted of 123 patients who received placebo and 165 patients who received MNTX for up to two weeks. The incidence of non-fatal serious adverse events was lower with MNTX than with placebo.*
- *In the MNTX Pool of 286 patients received MNTX in various dosages for up to four months. The most common adverse events were nausea, vomiting and chest pain.*
- *Cardiac related non-fatal, serious adverse events were reported in 2 patients (0.7%) in the MNTX Pool. One 68 year old male (Patient 301-22-0003) with advanced mesothelioma on MNTX 0.30 mg/kg developed congestive heart failure and worsening pneumonia not thought to be related to the study drug. A 72 year old Caucasian female (Patient 302-39-0004) on MNTX 0.30 mg/kg experienced a non-Q wave myocardial infarction from which she later recovered. This event was also not thought to be due to study drug.*
- *Most serious adverse events were thought to be due to the underlying advanced illness.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The number of subjects treated in the DBPC Pool and the MNTX Pool and the reasons for discontinuing a study are given in Table 38.

Within the DBPC Pool, 92.7% of the MNTX-treated group and 86.2% of the placebo-treated group completed a study. Within the DBPC Pool, 2.4% of the placebo-treated patients and 1.2% of the MNTX-treated patients discontinued because of adverse events.

In the MNTX Pool, approximately 59% of the patients were withdrawn from a study prematurely. The most common reason was death (27.6%) followed by patient request to withdraw from the study (12.2%). Withdrawal requests were generally due to a worsening of the patient's underlying condition. Adverse events led to discontinuation in 3.8% of the patients.

Table 37 Patient Disposition: DBPC Pool and MNTX Pool

	DBPC Pool (N=288)		MNTX Pool (N=286)
Category	Placebo (n=123) n (%)	MNTX (n=165) n (%)	MNTX (n=286) n (%)
Number of Patients Completed the Study	106 (86.2)	153 (92.7)	118 (41.3)
Number of Patients Discontinued Prematurely[1]	17 (13.8)	12 (7.3)	168 (58.7)
Number of Patients Died During the Study[2]	18 (14.6%)	16 (9.7)	138 (48.3)
Reasons for Premature Discontinuation			
Administrative/Investigator Decision	0	1 (0.6)	4 (1.4)
Adverse Event	3 (2.4)	2 (1.2)	11 (3.8)
Death on study[3]	4 (3.3)	6 (3.6)	79 (27.6)
Disease progression while on study	0	1 (0.6)	14 (4.9)
Lost to follow-up	1 (0.8)	0	1 (0.3)
Noncompliance	3 (2.4)	1 (0.6)	4 (1.4)
Other	0	0	7 (2.4)
Protocol violation	1 (0.8)	1 (0.6)	1 (0.3)
Unrelated medical condition	0	0	1 (0.3)
Unresponsiveness to treatment	0	0	7 (2.4)
Withdrawal requested by patient	5 (4.1)	0	35 (12.2)
Missing discontinuation reason	0	0	3 (1.0)

[1]Based on information provided by the Investigator from the case report forms
[2]Includes all premature discontinuation and post study deaths
[3]Did not complete double-blind treatment
Source: SCS, Adapted from Table 3 and Table 5, Pages 22 and 24.

7.1.3.2 Adverse events associated with dropouts

In the DBPC Pool, adverse events led to discontinuation of study drug in five (4.1%) placebo-treated patients and five (3.0%) of the MNTX-treated patients. Malignant neoplasm progression led to discontinuation in two patients (1.6%) in the placebo group and two patients (1.0%) in the MNTX group. Two (1.0%) patients in the MNTX group discontinued the study drug due to

abdominal pain. Abdominal pain was the only adverse event that led to discontinuation of more than one patient per group. No other adverse event led to discontinuation in more than one patient per group.

In the MNTX Pool, adverse events led to discontinuation in 23 (8.0%) of 286 MNTX-treated patients. Malignant neoplasm progression was the most common cause of study discontinuation (six patients; 2.1%). Three patients (1.0%) discontinued due to abdominal pain, and two (0.7%) due to vomiting. No other adverse event led to discontinuation in more than one patient. Table 38 summarizes adverse events leading to discontinuation in both analysis pools.

Table 38 Incidence of AEs Leading to Discontinuation: DBPC and MNTX Pool

Primary System Organ Class Preferred Term	DBPC Pool		MNTX Pool
	Placebo (N=123) n (%)	MNTX (N=165) n (%)	MNTX (N=286) n (%)
Any Preferred Term	5 (4.1)	5 (3.0%)	23 (8.0)
Cardiac Disorders	1 (0.8)	0	1 (0.3)
Cyanosis	1 (0.8)	0	0
Cardiac failure congestive	0	0	1 (0.3)
Myocardial infarction	0	0	1 (0.3)
Gastrointestinal Disorders	2 (1.6)	3 (1.8)	7 (2.4)
Abdominal pain	0	2 (1.2)	3 (1.0)
Bowel sounds abnormal	0	1 (0.6)	1 (0.3)
Nausea	1 (0.8)	0	1 (0.3)
Oral mucosal disorder	1 (0.8)	0	0
Vomiting	1 (0.8)	0	2 (0.7)
Flatulence	0	0	1 (0.3)
General Disorders and Administration Site Conditions	0	1 (0.6)	3 (1.0)
Asthenia	0	1 (0.6)	1 (0.3)
Concomitant disease progression	0	0	1 (0.3)
Non-cardiac chest pain	0	0	0
Injection site pain	0	0	1 (0.3)
Injury, Poisoning and Procedural Complications	0	0	1 (0.3)
Intentional overdose	0	0	1 (0.3)
Metabolism and Nutrition Disorders	0	0	1 (0.3)
Hypoglycemia	0	0	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (0.3)
Myalgia	0	0	1 (0.3)
Muscle spasms	0	0	1 (0.3)
Neoplasms Benign, Malignant and Unspecified	0	0	6 (2.1)
Malignant neoplasm progression	0	0	6 (2.1)
Nervous System Disorders	0	0	3 (1.0)
Coma	0	0	1 (0.3)
Syncope	0	0	1 (0.3)
Cerebrovascular accident	0	0	1 (0.3)

Psychiatric Disorder	0	0	2 (0.7)
Delirium	0	0	1 (0.3)
Confusional state	0	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.8)	0	2 (0.7)
Dyspnea	1 (0.8)	0	1 (0.3)
Chronic obstructive pulmonary disease	0	0	1 (0.3)
Vascular Disorders	1 (0.8)	0	0
Hypotension	1 (0.8)	0	0
Skin and Subcutaneous Tissue Disorders	0	0	1 (0.3)
Skin discoloration	0	0	1 (0.3)

Source: Adapted from SCS, Tables 45 and 47. Pages 94 and 98

7.1.3.3 Other significant adverse events

7.1.4 Other Search Strategies

Orthostatic hypotension was observed when MNTX was administered by IV bolus to healthy volunteers at doses ≥0.64 mg/kg in studies performed at the University of Chicago. The data in the integrated database do not reveal an association of orthostatic hypotension with MNTX given SC at doses of 0.15 or 0.30 mg/kg, despite the fact that these patients had advanced illness.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All of the phase 2 and phase 3 trials had similar procedures to evaluate AE data. A standard case report form was used at each subject encounter. Adverse events were solicited at these encounters and were then recorded on the form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All AEs were coded to preferred term and primary SOC using MedDRA, Version 6.0. If an AE was reported more than once for the same subject, the subject was only counted once for the respective AE and assigned the most severe intensity. Treatment-emergent AEs were defined as AEs that occurred after administration of the first dose of study drug (double-blind) through 30 days after the last dose of study drug or AEs that were present at baseline but worsened in severity.

7.1.5.3 Incidence of common adverse events

DBPC Pool

At least one treatment-emergent adverse event occurred in 67.5% of the patients who received placebo and 80.6% of the patients who received MNTX. As shown in Table 39, the incidence of

adverse events was highest within the SOC of Gastrointestinal Disorders in both groups. The rate of adverse events within that SOC was higher in the MNTX group (52.7%) than in the placebo group (35.0%). The only other SOC with rates that were at least 5% greater with MNTX than with placebo was Nervous System Disorders (22.4% versus 15.4%).

MNTX Pool

At least one treatment-emergent adverse event occurred in 97.9% of the patients who received at least one dose of MNTX. As shown in Table 39, the incidence of adverse events was highest within the SOCs of Gastrointestinal Disorders (73.8%) and General Disorders and Administration Site Conditions (54.5%).

7.1.5.4 Common adverse event tables

Table 39 Incidence of Common AEs By System Organ Class: DBPC and MNTX Pool

Primary System Organ Class	DBPC Pool (N=288)		MNTX Pool (N=286)	
	Placebo (n=123) n (%)	MNTX (n=165) n (%)	All MNTX Doses (N=286) n (%)	MNTX 0.15 mg/kg (n=256) n (%)
Any Primary System Organ Class	83 (67.5)	133 (80.6)	280 (97.9)	233 (91.0)
Gastrointestinal Disorders	43 (35.0)	87 (52.7)	211 (73.8)	166 (64.8)
General Disorders and Administration Site Conditions	36 (29.3)	48 (29.1)	156 (54.5)	106 (41.4)
Nervous System Disorders	19 (15.4)	37 (22.4)	132 (46.2)	87 (34.0)
Psychiatric Disorders	25 (20.3)	35 (21.2)	124 (43.4)	73 (28.5)
Respiratory, Thoracic and Mediastinal Disorders	22 (17.9)	32 (19.4)	130 (45.5)	72 (28.1)
Investigations	14 (11.4)	25 (15.2)	73 (25.5)	47 (18.4)
Skin and Subcutaneous Tissue Disorders	16 (13.0)	20 (12.1)	97 (33.9)	63 (24.6)
Musculoskeletal and Connective Tissue Disorders	11 (8.9)	17 (10.3)	74 (25.9)	54 (21.1)
Infections and Infestations	11 (8.9)	14 (8.5)	84 (29.4)	45 (17.6)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	17 (13.8)	13 (7.9)	94 (32.9)	52 (20.3)
Injury, Poisoning and Procedural Complications	14 (11.4)	9 (5.5)	54 (18.9)	20 (11.3)
Metabolism and Nutrition Disorders	13 (10.6)	8 (4.8)	52 (18.2)	33 (12.9)
Cardiac Disorders	10 (8.1)	7 (4.2)	34 (11.9)	23 (9.0)
Vascular Disorders	10 (8.1)	6 (3.0)	43 (15.0)	28 (10.9)

Eye Disorders	1 (0.8)	4 (2.4)	28 (9.8)	15 (5.9)
Renal and Urinary Disorders	6 (4.9)	2 (1.2)	39 (13.6)	20 (7.8)
Blood and Lymphatic System Disorders	2 (1.6)	2 (1.2)	16 (5.6)	9 (3.5)
Ear and Labyrinth Disorders	0	2 (1.2)	4 (1.4)	1 (0.4)
Social Circumstances	0	2 (1.2)	2 (0.7)	1 (0.4)
Reproductive System and Breast Disorders	0	1 (0.6)	9 (3.1)	4 (1.6)
Hepatobiliary Disorders	2 (1.6)	0	1 (0.3)	1 (0.4)

Source: Adapted from SCS, Tables 29, 38 and 40, Pages 51, 70, 76.

Medical Reviewer's Comments

- *In the DBPC Pool, Gastrointestinal Disorders and Nervous System Disorders were the only SOCs with rates at least 5% greater in the MNTX group than in the placebo group.*
- *Although the numbers are small, the incidence of adverse events within the SOC of Cardiac Disorders was higher in the placebo group (8.1%) than in the MNTX group (4.2%).*
- *Adverse events within the SOC of Cardiac Disorders were stratified by the Applicant by the presence or absence of heart failure at baseline for the MNTX Exposure Pool. At least one cardiac event occurred in 20.4% (11/54) of the patients with heart failure at baseline versus 9.9% (23/232) of those without heart failure at baseline.*
- *The frequency of adverse events were slightly less common at the MNTX 0.15 mg/kg dosage level compared to all MNTX dosage levels combined.*

7.1.5.5 Identifying common and drug-related adverse events

The most common adverse events that were related to MNTX therapy and observed in the MNTX Pool are listed in Table 40.

Table 40 Treatment-Emergent AEs That Occurred in >5% of Patients: MNTX Pool

Adverse Reaction	MNTX Pool (N=286)
Abdominal Pain	112 (39.2%)
Malignant neoplasm progression	91 (31.8%)
Nausea	64 (22.4%)
Vomiting	53 (18.5%)
Flatulence	51 (17.8%)
Pain	44 (15.4%)
Anxiety	43 (15.0%)
Peripheral Edema	41 (14.3%)

Hyperhidrosis	38 (13.3%)
Decubitus ulcer	37 (12.9%)
Diarrhea	36 (12.6%)
Confusional state	36 (12.6%)
Dyspnea	35 (12.2%)
Agitation	32 (11.2%)
Rhinorrhea	31 (10.8%)
Restlessness	31 (10.8%)
Asthenia	31 (10.8%)
Tremor	27 (9.4%)
Lethargy	25 (8.7%)
Abdominal Distension	22 (7.7%)
Urinary tract infection	22 (7.7%)
Back Pain	21 (7.3%)
Fall	20 (7.0%)
Fatigue	19 (6.6%)
Dysphagia	18 (6.3%)
Chest pain	18 (6.3%)
Concomitant disease progression	18 (6.3%)
Muscle spasms	17 (5.9%)
Headache	17 (5.9%)
Depressed level of consciousness	16 (5.6%)
Somnolence	16 (5.6%)
Delirium	16 (5.6%)
Depression	16 (5.6%)
Pyrexia	15 (5.2%)
Dehydration	15 (5.2%)
Coma	15 (5.2%)
Insomnia	15 (5.2%)

Source: Adapted from SCS, Pages 72-74

The adverse events listed in Table 41 were the most common. Most of these were described as either mild or moderate in intensity.

Table 41 Incidence of Gastrointestinal Adverse Events by Severity: DBPC Pool

Preferred Term	Maximum Severity	Placebo (N=123) n (%)	MNTX All Doses (N=165) n (%)

Abdominal Pain	Mild Moderate Severe Life Threatening	5 (4.1%) 4 (3.3%) 3 (2.4%) 0	26 (15.8%) 18 (10.9%) 3 (1.8%) 0
Flatulence	Mild Moderate Severe Life Threatening	5 (4.1%) 2 (1.6%) 0 0	20 (12.1%) 2 (1.2%) 0 0
Nausea	Mild Moderate Severe Life Threatening	1 (0.8%) 2 (1.6%) 3 (2.4%) 0	12 (7.3%) 5 (3.0%) 2 (1.2%) 0
Diarrhea	Mild Moderate Severe Life Threatening	0 3 (2.4%) 0 0	6 (3.6%) 3 (1.8%) 0 0
Dizziness	Mild Moderate Severe Life Threatening	2 (1.6) 1 (0.8) 0 0	10 (6.1) 2 (1.2) 0 0

Source: Information Relating to Pharmacovigilance, Page 18

Medical Reviewer's Comments

- *In the DBPC Pool, the most common adverse events occurring in the MNTX group which occurred at least twice that in the placebo group were abdominal pain, flatulence, nausea, diarrhea and dizziness. These gastrointestinal adverse events are not surprising for a drug that acts on the bowel by increasing motility and drug transit time. The increased dizziness may be due to vasovagal reactions from straining at stool.*
- *Abdominal pain tended to decrease in frequency after the first few doses of MNTX as the passage of stool became easier.*
- *The gastrointestinal adverse reactions identified for MNTX are not generally severe nor life threatening*
- *The severity of the above common adverse incidence did not differ significantly from those in subjects taking placebo.*
- *During the open-label extension period, there was one death in which it was reported that severe diarrhea contributed to the demise of a patient with metastatic breast cancer (See Section 7.1.1).*
- *The orthostatic hypotension seen in healthy volunteers taking higher doses of MNTX was not seen in the placebo-controlled studies.*
- *Adverse event profiles were similar irrespective of age or sex.*
- *There were too few non-Caucasian patients to determine if ethnic or racial differences affected adverse event profiles.*

7.1.5.6 Additional analyses and explorations

In order to ensure that MNTX administration did not interfere with analgesia, the daily use of opioid medications (morphine equivalents) was summarized using descriptive statistics. Doses of opioid medication were converted to oral morphine equivalents using information from

approved product labels or published literature. All opioid use from 12:01 am on the day that double-blind medication was administered until midnight of the dosing day was summarized and used to represent the baseline opioid data. Values for the 24 hours following dosing were similarly summarized. The median number of morphine equivalents used in the 24-hour period after dosing was generally similar for each treatment group.

The potential for MNTX to cause central effects of opioid antagonism was also assessed by pain scores based on the Modified Himmelsbach scale. The MNTX and placebo groups had essentially no change from baseline to the end of the double-blind period in withdrawal symptoms as assessed using the Modified Himmelsbach scale.

Medical Reviewer's Comments

- *Treatment with MNTX did not generally result in increased opioid withdrawal symptoms. There were no apparent trends across treatment groups in the incidence of AEs associated with the Modified Himmelsbach Opioid Withdrawal Scale.*
- *MNTX treatment did not result in meaningful increases in pain scores. Opioid doses taken by the patients were converted to oral morphine equivalents for the purpose of analysis. The median morphine equivalents per day showed no consistent pattern of change in either the placebo or MNTX group. In the MNTX Pool, which allowed tracking of the opioid use over a period of months, an increase in opioid use was noted after approximately two months of treatment however this was probably due to the expected progression of the underlying disease.*

7.1.6 Less Common Adverse Events

There were no less common AEs (AEs occurring in <1% of subjects) that were of note or significance among all the reported AEs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Descriptive statistics were used to summarize laboratory values at baseline, at post-baseline evaluations during treatment and at termination. Treatment emergent abnormal values were defined as values that met the National Cancer Institute (NCI) Common Terminology Criteria for Grade 3 or higher adverse events at sometime after baseline, but had been Grade 2 or lower at baseline.

Laboratory Assessments included serum chemistry (ALT, AST, albumin, alkaline phosphatase, total bilirubin, bicarbonate, total protein, glucose, sodium, potassium, chloride, calcium, creatinine, and blood urea nitrogen.

Hematology included a complete blood count (CBC) with differential consisting of WBC, RBC, hematocrit, hemoglobin, and differential (neutrophils, basophils, monocytes, eosinophils,

lymphocytes, platelets, and pregnancy tests for women (urine or serum) of childbearing potential.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Analyses were based on the submitted primary clinical trials.

7.1.7.3 Standard analyses and explorations of laboratory data

DBPC Pool
The mean changes in clinical laboratory tests that occurred in the MNTX treated patients were small and generally similar to the placebo treated patients. The highest rate of shift in the MNTX group was from within the normal range to below the normal range for percent lymphocytes (8.0% in MNTX group to 1.3% in the placebo group). The mean changes in absolute lymphocyte counts however were small and comparable in both the MNTX and placebo groups. Other hematological and serum chemistry parameters did not show significant shift differences.

The incidence of adverse events related to abnormal laboratory test results was low in the placebo-controlled, double-blind studies. The only laboratory-related adverse events that occurred in more than one patient per group were anemia (0.8% in the placebo group versus 1.2% in the MNTX group), serum alkaline phosphatase increased (1.6% versus 0%), and hyperglycemia (0% versus 1.2%).

MNTX Pool
The only treatment emergent abnormal laboratory value that occurred in 5.0% or more of the patients was a 12.3% decrease in lymphocytes. Abnormal liver function tests occurred in <2.0% of the patients.

Of patients who had normal percent lymphocyte values at baseline, 20 of 199 (10.1%) had abnormally low decreases at the final visit. This was the only abnormal shift in the hematological or clinical chemistry parameters.

Medical Reviewer's Comments

- *Many of the patients began these studies with lymphopenia and many of the patients had received steroids or chemotherapeutic agents. No clinical correlation of the lymphopenia was reported. There were no clinically meaningful changes over time with respect to other hematologic parameters.*
- *There were also no clinically meaningful changes over time with respect to liver function, renal function, or other clinical laboratory tests that were associated with MNTX therapy.*

7.1.7.4 Additional analyses and explorations

None were performed or indicated.

7.1.7.5 Special assessments

None were performed or indicated.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were obtained at screening, at each study visit and at the study termination visits.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Analyses were based on the submitted primary clinical trials.

7.1.8.3 Standard analyses and explorations of vital signs data

DBPC Pool
Blood pressure, pulse rate, respiration rate, and temperature were recorded before dose administration on Day 1 and several times during the four hours after administration. Values were also recorded on Days 7, 9 (if the dose was escalated), and 14 in MNTX 302. The mean changes that occurred during the placebo-controlled double-blind treatment were small in both treatment groups and were not clinically meaningful.

MNTX Pool
The mean changes in vital signs that occurred during MNTX treatment were small and were not clinically meaningful.

As shown in Table 39, 11.9% of all MNTX-treated patients had at least one adverse event within the SOC of Cardiac Disorders. The most commonly reported cardiac disorders were tachycardia, which occurred in 4.5% of the patients, bradycardia, which occurred in 1.4% of the patients, and arrhythmia and palpitations which occurred in 0.7% of the patients. At least one adverse event within the SOC of Vascular Disorders occurred in 15.0% of all MNTX treated patients. These were hypotension, the most commonly reported vascular disorder, which occurred in 4.5% of the patients, orthostatic hypotension, which occurred in 1.7% of the patients, and hypertension which occurred in 0.7% of the patients. Other adverse events that may have been related to vital signs generally occurred in fewer than 2.0% of the patients.

7.1.8.4 Additional analyses and explorations

Since there were no significant differences in important vital signs, there were no additional analyses and explorations performed.

Medical Reviewer's Comment

- *There were no clinically significant changes over time with respect to vital signs or physical examinations that were associated with MNTX therapy.*

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing other than in Study MNTX 1106 (Effects of MNTX on ECG parameters and cardiac repolarization) were not performed in the phase 2 and phase 3 clinical trials.

The Applicant originally submitted Study MNTX 1106 as the definitive QT/QTc clinical cardiac repolarization study. The study was found to be inadequate with respect to design and sensitivity. The Applicant was then asked to conduct a suitably designed IV "Thorough QT Study" to assess the QT prolongation potential of MNTX. The study submitted was a single-center, randomized, double-blind, placebo and moxifloxacin controlled, open label 4-period crossover study in which 56 healthy subjects were administered either 0.3 mg/kg MNTX, 0.64 mg/kg MNTX or placebo as a 20-minute IV infusion. Subjects also received a single oral dose of moxifloxacin 400 mg . This study was submitted to the Agency on 12/7/2007 and was reviewed by the Interdisciplinary Review Team for QT Studies. In a report dated 2/2/2008, the review team concluded that. the second study submitted was adequately designed and conducted to detect an effect on the QT interval. After review, the team determined that no significant effect of MNTX on QT/QTc interval was detected.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No analyses were performed for overall drug control comparisons.

7.1.9.3 Standard analyses and explorations of ECG data

No ECG analyses were performed in the phase 2 and phase 3 studies..

7.1.9.4 Additional analyses and explorations

No additional ECG analyses were performed.

7.1.10 Immunogenicity

MNTX is not a protein. Immunogenicity studies were not performed.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not performed.

7.1.12 Special Safety Studies

Phase 1 studies MNTX 1105 and MNTX 1107 enrolled subjects with renal impairment and hepatic impairment, respectively. In these studies, each subject received a single SC dose of MNTX 0.30 mg/kg.

In MNTX 1105, two of eight subjects with mild renal impairment had adverse events (fatigue in Subject 1105-0002-0103 and paresthesia in Subject 1105-0002-0104). One of eight subjects with moderate renal impairment had adverse events (diarrhea, dyspepsia, and injection site stinging in Subject 1105-0001-0002). One of eight subjects with severe renal impairment had adverse events (dyspepsia, headache, hot flush, and vomiting in Subject 1105-0002-0105). All of the adverse events were mild or moderate in intensity.

Medical Reviewer's Comment

- *There was no consistent pattern of increasing rates of adverse events as the degree of renal dysfunction increased. Neither any gastrointestinal disorder nor diarrhea occurred more frequently in MNTX-treated patients with moderate or severe renal impairment than those with normal renal function or mild renal impairment.*

In MNTX 1107, three of eight subjects with mild hepatic impairment had headaches (1107-0002-0804, 1107-0003-0801, 1107-0003-0802), one subject had ALT increased and AST increased (1107-0001-0803), and one subject had injection site burning (1107-0003-0801). Two of the eight subjects with moderate hepatic impairment had headaches (1107-0001-0805, 1107-0002-0803) and one subject each had diarrhea (1107-0002-0805), dysgeusia (1107-0003-0805), flushing (1107-0002-0803), and injection site burning (1107-0003-803). All events were mild in intensity.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena and abuse potential were not addressed in this NDA. MNTX is an opioid antagonist with no agonist properties. Based on this pharmacological property, there is no reason to suspect that MNTX has abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of MNTX in pregnant women therefore the potential for teratogenic effects of SC MNTX on a human fetus are unknown.

Reproduction studies have been performed in pregnant rats and rabbits and no effects on fetal development at intravenous dosages of up to 25 mg/kg/day (38 times the exposure AUC in humans at a SC dose of 0.15 mg/kg) were reported. In lactating rats, MNTX has been shown to be excreted in breast milk but it is not known if MNTX is excreted in human milk.

Medical Reviewer's Comments

- *The Applicant has designated MNTX as Pregnancy Category B: Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.*
- *There were no pregnant patients in the MNTX development program.*

7.1.15 Assessment of Effect on Growth

MNTX was not studied in the pediatric population. No assessment of the effect on growth has been done.

7.1.16 Overdose Experience

A study conducted by Investigators under the University of Chicago IND identified orthostatic hypotension as the dose-limiting toxicity at a dose of 0.64 mg/kg IV bolus given over 10 minutes to healthy volunteers. The maximum tolerated dose by that route of administration was found to be 0.32 mg/kg.

In the phase 1 study, MNTX 1106, one cohort of healthy volunteers received single SC doses of 0.50 mg/kg with a safety profile that was similar to cohorts receiving either 0.15 mg/kg or 0.30 mg/kg. In the phase 2 study in patients with post-operative ileus (MNTX 203), MNTX was administered IV at a dose of 0.30 mg/kg every six hours for up to one week with a safety profile similar to that of placebo.

The phase 2 and phase 3 studies conducted with SC MNTX did not define a dose level that would result in overdose.

Medical Reviewer's Comment

- *In the primary studies that were reviewed, there were no MNTX overdoses described.*

7.1.17 Postmarketing Experience

MNTX is a new molecular entity so has never been approved or marketed in the United States or in any foreign country. Therefore, there is no postmarketing experience with this drug..

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety base is composed of the following trials:

- two phase 3 clinical trials enrolling 288 evaluable subjects
- one phase 2 clinical trial enrolling 33 evaluable subjects

- four phase 1 clinical trials enrolling 269 subjects

7.2.1.1 Study type and design/patient enumeration

Table 42 Safety Base from Phase 1, Phase 2 and Phase 3 Studies

Study	Number of Subjects Evaluable for Safety	Dosage Regimen	Duration of Treatment	Terminally Ill vs. Healthy
Phase 2 and Phase 3 Studies				
MNTX 301 (Phase 3)	154	MNTX 0.15 mg/kg (n=47), 0.30 mg/kg (n=55) or placebo (n=52) SC followed by Open-Label starting at MNTX 0.15 mg/kg SC with dose adjustments to 0.075 or 0.30 mg/kg QD PRN	Single dose QD PRN up to 1 month	Terminally ill with opioid induced constipation
MNTX 301EXT (Phase 3)	21	Minimum dose of MNTX 0.075 mg/kg SC with maximum dose of mg/kg 0.30 mg/kg SC PRN QD	Additional 3 months QD PRN (total drug exposure = 4 months)	Terminally ill with opioid induced constipation
MNTX 302 (Phase 3)	134	MNTX 0.15 mg/kg (n=63) or placebo (n=71) SC QOD x 1 week followed by 0.15 mg/kg or 0.3. mg/kg or placebo SC QOD for one week	Single dose QOD PRN for 2 weeks	Terminally ill with opioid induced constipation
MNTX 302EXT (Phase 3)	82	Starting dose of MNTX 0.15 mg/kg to 0.75 mg/kg or 0.30 mg/kg SC QOD PRN	Additional 3 months QOD PRN (total drug exposure = 3½ months)	Terminally ill with opioid induced constipation
MNTX 251 (Phase 2)	33	MNTX 1 (n=10), 5 (n=7), 12.5 (n=10) or 20 mg (n=6) SC QOD for 1 week then 5-20 mg SC QOD PRN for 3 weeks	Single dose QOD PRN for 4 weeks	Terminally ill with opioid induced constipation
Phase 1 Studies				
MNTX 103 (Crossover study to determine plasma pharmacokinetics and urinary excretion)	6	Dose 1: 0.30 mg/kg IV Dose 2: 0.10 mg/kg SC Dose 3: 0.30 mg/kg SC Dose 4: 0.45 mg/kg SC	Single dose x 4	Healthy male volunteers 18-45 years of age
MNTX 1105 (Pharmacokinetics in patients with renal impairment)	32	0.30 mg/kg SC	Single dose	Healthy patients with normal renal function (n=8) Patients with mild renal impairment (n=8), moderate renal impairment (n=8), and severe renal impairment (n=8)
MNTX 1106 (Effects of MNTX on ECG and cardiac repolarization)	207	0.15 mg/kg SC (n=40) 0.30 mg/kg SC (n=39) 0.50 mg/kg SC (n=41) Placebo SC (n=44)	Single dose	Healthy male and female volunteers 18-45 years of age

		Moxifloxacin 400 mg PO (n=43)		
MNTX 1107 (Pharmacokinetics in patients with hepatic impairment)	24	0.30 mg/kg SC	Single dose	Healthy patients with normal hepatic function (n=8), mild hepatic impairment (n=8), and moderate hepatic impairment (n=8)

Source: Adapted from Summary of Clinical Safety (SCS), Table 2, Pages 12-16

Medical Reviewer's Comments

- *The longest study submitted to this NDA is MNTX 301/301EXT which is 16 weeks in duration. The label should state that there is no safety data collected for MNTX beyond 16 weeks of treatment.*
- *Study MNTX 1107 did not include patients with severe hepatic impairment. This should be stated in the label.*

7.2.1.2 Demographics

Of the 286 patients in the MNTX Pool, 144 (50.3%) were male and 142 (49.7%) were female. The majority of the patients in the study were Caucasian (87.1%). Of the 286 patients, 124 (43.4%) were between 18 and 64 years of age, 70 (24.5%) were between 65 and 74 years of age, and 92 (32.2%) were 75 years or older. The demographic characteristics of the patients treated with MNTX in the DBPC Pool were similar to those of the patients in the MNTX Pool.

Table 43 Patient Demographics: MNTX Pool

	MNTX (N=286)
Sex, n (%)	
Female	142 (49.7)
Male	144 (50.3)
Race, n (%)	
Asian	3 (1.0)
Black	21 (7.3)
Caucasian	249 (87.1)
Hispanic	12 (4.2)
Other	1 (0.3)
Age Group, n (%)	
<40	13 (64.0)
40-64	111 (38.8)
65-74	70 (24.5)
≥75	92 (32.2)
Age (Years)	

Mean	66
Median	68
Minimum	20
Maximum	100
Weight, n (%)	
Mean	67.8
Median	67.3
Minimum	29
Maximum	189

Source: SCS, Adapted from Table 26, Page 48

Medical Reviewer's Comment

- *The incidence and the severity of the adverse events recorded in the MNTX Pool were independent of the sex and age of the patients.*

7.2.1.3 Extent of exposure (dose/duration)

Safety data from the DBPC and the Double-Blind Pools were analyzed according to the dose in the double-blind studies (0.15 or 0.3 mg/kg), and the fixed doses (0.075, 0.15, or 0.30 mg/kg) used in the open-label and extension studies. Patients in these pools received MNTX or placebo as a single dose, QOD for one week, or QOD for two weeks.

In the MNTX Pool, 286 patients received at least one dose of MNTX and 95 (33.9%) were treated for one month or more. Nearly 50% of the patients in the MNTX Pool received seven or more doses of MNTX and 34% received 10 or more doses. The median number of doses per patient was seven and the median interval of time between doses was 2.6 days.

MNTX 301 included only one double-blind dose of study drug. Therefore, 52 placebo-treated patients and 102 MNTX-treated patients in the placebo-controlled, double-blind studies received a maximum of one dose and had a maximum duration of exposure of one day.

MNTX 302 was the only study in which patients received more than one double-blind dose of placebo. The maximum possible number of double-blind doses in MNTX 302 was seven. Because these doses were administered QOD, the first dose was given on Day 1 and the last dose on Day 13. Therefore, the maximum duration of exposure to study drug in this study was 13 days.

The maximum number of double-blind doses in MNTX 251 was three, so an additional 33 MNTX-treated patients received a maximum of three doses. There was no placebo group in this study however.

The longest duration of drug exposure in a single study was four months in MNTX 301/301EXT however only nine subjects of 27 (33%) completed this study. The maximum duration of open-label treatment was three months in MNTX 302EXT, and three weeks in MNTX 251.

Dosing in all open-label phases of the phase 2 and phase 3 studies was PRN per investigator discretion with a maximum frequency of one dose per 24 hours.

Table 44 Cumulative Number of Doses Received: MNTX Pool

Cumulative MNTX Doses	MNTX (N=286) N (%)
≥ 1 dose	286 (100)
≥ 7 dose	136 (47.6)
≥ 10 dose	97 (33.9)
≥ 20 dose	38 (13.3)
≥ 30 dose	16 (5.6)
≥ 40 dose	11 (3.8)
≥ 50 dose	7 (2.4)
≥ 60 dose	3 (1.0)

Source: SCS, Table 16, Page 36

Medical Reviewer's Comment

- *One MNTX-treated patient in MNTX 302 (302-0002-0003) had more than 13 days of exposure because the patient deviated from the protocol-specified dosing schedule.*

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical sources were used to evaluate safety for this NDA review.

7.2.2.1 Other studies

Other studies were not used to evaluate safety for this NDA review.

7.2.2.2 Postmarketing experience

MNTX is a new molecular entity and has never been marketed so there is no postmarketing experience with this drug.

7.2.2.3 Literature

A review of the current medical literature regarding MNTX was conducted.

7.2.3 Adequacy of Overall Clinical Experience

As agreed to by the Division and the Applicant during the IND phase of development, the overall clinical experience is adequate for the specific population for which the drug is indicated.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in-vitro testing was indicated or required.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing for this NDA was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction workup performed for this NDA were adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No specific recommendations for future study are applicable.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data submitted for this NDA was judged by this Reviewer to be adequate and acceptable.

7.2.9 Additional Submissions, Including Safety Update

There were no additional major clinical submissions to the NDA. A Four-Month Safety Update (30 June 2006-1 February 2007) was submitted.

No new studies of SC MNTX for the indication specified in this NDA had been initiated at the time of the safety update. The safety information available to date from these current studies does not alter the conclusions reached from data submitted with the original NDA submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The standard parameters were used to evaluate the overall safety of MNTX for the indication proposed. All deaths, serious adverse events, adverse events leading to discontinuation from the primary clinical trials, and most common adverse events were analyzed. Vital signs, chemistry

labs, hematology labs, the effects of MNTX on pain control and possible opioid withdrawal symptoms were also reviewed.

The one reported study death that was probably related to MNTX therapy was due to dehydration and diarrhea. The patient's underlying terminal breast cancer however may have played a confounding role.

The incidence of non-fatal, serious adverse events was lower in the MNTX arm than in the placebo arm. Most of these adverse events were related to the gastrointestinal system and, more specifically, most were probably related to MNTX effects on the obstipated colon.

Four of the five most common adverse events in the MNTX Pool (abdominal pain, nausea, vomiting and flatulence) were also related to the gastrointestinal tract. The fifth event was malignant neoplasm progression which was not unexpected in this patient population.

Among the MNTX treated patients there were no clinically significant changes over time with respect to liver function, renal function or hematologic test results. The only laboratory parameter associated with MNTX use was a mild lymphopenia that was present in 20/199 (10.1%) of the patients. The mean changes in absolute lymphocyte counts were small (-0.1 x 10^9/L). The clinical significance of this change is uncertain.

Pain scores from both the DBPC and MNTX Pools showed no meaningful change with MNTX treatment demonstrating that MNTX did not appreciably interfere with the central opioid analgesic effect of administered pain medications.

As measured by the Modified Himmelsbach Opioid Withdrawal scale, MNTX did not induce the symptoms of opioid withdrawal in the patients studied.

This Reviewer's overall conclusion is that MNTX, in doses of 8 mg and 12 mg (both of which roughly correspond to the 0.15 mg/kg dose used in the three primary studies) are safe and well tolerated in the treatment of OIC in patients receiving terminal care.

7.4 General Methodology

The standard parameters were used to evaluate the overall safety of the MNTX. All serious adverse events, adverse events leading to discontinuation from the study, and most common adverse events were analyzed. Vital signs, hematology, and serum chemistries were obtained at baseline, during the studies, and at study termination.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The safety data was pooled across the three primary studies where applicable.

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

No explorations were done.

7.4.2.1 Explorations for dose dependency for adverse findings

No explorations were done.

7.4.2.2 Explorations for time dependency for adverse findings

No explorations were done.

7.4.2.3 Explorations for drug-demographic interactions

The data collected from the primary clinical studies revealed the following regarding drug-demographic interactions:

- There was no consistent pattern of increasing rates of adverse events as the age of the patients increased.
- The overall rate of adverse events was similar for male and females.
- There was no consistent pattern of increasing rates of adverse events as the degree of renal dysfunction decreased.

7.4.2.4 Explorations for drug-disease interactions

No explorations were done.

7.4.2.5 Explorations for drug-drug interactions

No explorations were done.

7.4.3 Causality Determination

No explorations were done.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The clinical dosing of MNTX proposed by the Applicant is weight related. Eight mg SC is recommended for patients weighing between 84 and 136 pounds (38 to 61 kg) and 12 mg SC for patients weighing between 136 to 251 pounds (62 to 114 kg). Both of these fixed dosage levels

are similar to the studied weight-based dose of MNTX 0.15 mg/kg. For patients whose weight falls outside these ranges (< 38 kg or > 114 kg), dosing at 0.15 mg/kg is recommended. The proposed label states that MNTX is administered no more frequently than one dose in a 24-hour period.

Medical Reviewer's Comment

- *The instructions in the Dosing and Administration section of the proposed label do not state that the drug should only be taken as needed.*

Table 45 Doses Proposed for Two Body Weight Bands and Corresponding AUC

Body Weight (kg)	MNTX Dose (mg)	MNTX Dose (mg/kg)	AUC (ng.h/mL)	AUC (ng.h/mL) Fixed MNTX 0.15 mg/kg Dose Used in Clinical Studies
38-61	8	0.21-0.13	194-148	
62-114	12	0.19-0.11	220-169	
38-114				139-240

Source: Adapted from Reports of Analysis of Data, Fixed Dose Justification, NDA 21-964, Page 10

Medical Reviewer's Comments

- *Based on the pharmacokinetic data obtained from healthy subjects, the Applicant has concluded that there is an effect of body weight on MNTX mg/kg dose-adjusted exposure (AUC). The clearance of MNTX per kg body weight decreases as body weight increases. Therefore, a slightly higher or lower mg/kg dose can be given to patients with body weights at the lower and higher extremes and still result in a relatively consistent drug exposure. The Applicant uses this pharmacokinetic property of MNTX to justify the weight-band based dose adjustments that are being proposed for clinical use.*
- *No significant effect of body weight on C_{max} was detected in the pharmacokinetic studies submitted.*
- *The 8 and 12 mg doses for the proposed weight bands correspond to mean AUC estimates ranging from 148 to 220 ng.h/mL, while the mean AUC estimates using 0.15 mg/kg weight based dose adjustment varies from 139 to 240 ng.h/mL over the body weight ranges of 38-114 kg.*
- *The AUC estimates at doses of 8 and 12 mg for their respective weight bands are comparable to those obtained with the 0.15 mg/kg for the given population with body weights of 38 to 114 kg.*
- *The mean AUC found in 39 healthy volunteers following a 0.15 mg/kg SC dose of MNTX was 175 ng.h/mL.*
- *The Applicant points out that the two weight band based dose adjustments will simplify the preparation and administration of this drug and this would help prevent dosing errors.*

8.2 Drug-Drug Interactions

Preclinical studies suggested no induction or inhibition of CYP_{450} isozymes by MNTX in humans with the exception of some competitive inhibition of $CYP_{450}2D6$ activity. The clinical relevance of this interaction in humans was studied in MNTX 1108. No statistically-significant changes in the metabolism of dextromethorphan, a $CYP_{450}2D6$ substrate, were observed when SC or IV MNTX was administered concurrently. Therefore, MNTX has a low probability for drug-drug interactions that would complicate concomitant use of other medications.

There is evidence in humans (MNTX 102, MNTX 103) that there is a selective active tubular excretion of MNTX. Therefore, drugs that may impair this tubular function may be a potential source of concern in patients taking this drug.

8.3 Special Populations

There were no factors identified that altered exposure to MNTX which would require a dose adjustment except for the factors of severe renal impairment and body weight.

In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone, renal impairment had a marked effect on the renal excretion of MNTX. Severe renal impairment (creatinine clearance less than 30 mL/min) decreased the renal clearance of MNTX by 8- to 9- fold. However, this resulted in only a 2-fold increase in total MNTX exposure (AUC). C_{max} was not significantly changed (MNTX 1105). No dose adjustment is required in patients with mild or moderate renal impairment. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Medical Reviewer's Comments

- *The Applicant recommends a 50% reduction in dose for patients with severe renal impairment and no dose reduction for patients with mild to moderate renal impairment.*
- *It should be stated in the label that no studies were performed in patients with end-stage renal impairment requiring dialysis.*
- *Patients with severe hepatic impairment were not studied.*

The effect of body weight on AUC was studied from data derived from 137 healthy subjects. It was noted that AUC per 1 mg/kg dose increased as body weight increased which suggested that MNTX clearance per mg/kg body weight decreases as body weight increases.

Medical Reviewer's Comment

- *The Applicant believes that a slightly higher or lower mg/kg dose can be given to patients with body weights at the lower and higher ranges respectively and that this will still maintain a relatively consistent exposure to MNTX.*

The data collected from study MNTX 1107 showed no meaningful effect of mild to moderate hepatic impairment on the AUC or C_{max} of MNTX. No studies were performed in patients with severe hepatic impairment.

Medical Reviewer's Comment

- *No dosage adjustment is recommended for patients with mild to moderate hepatic impairment.*

8.4 Pediatrics

The youngest patient enrolled across the phase 2 and phase 3 primary studies was 20 years of age. This was a patient with Sickle Cell Disease. The Applicant states that the practicality of studying MNTX in the pediatric population would be challenging from many aspects and has therefore requested a deferral for pediatric studies. It is their intention in the future however to develop a pediatric clinical plan for the study of MNTX SC for the treatment of OIC in pediatric patients with advanced illness.

Medical Reviewer's Comment

- *A specific pediatric plan was not provided within the submission.*

8.5 Advisory Committee Meeting

No Advisory Committee meeting was indicated or held.

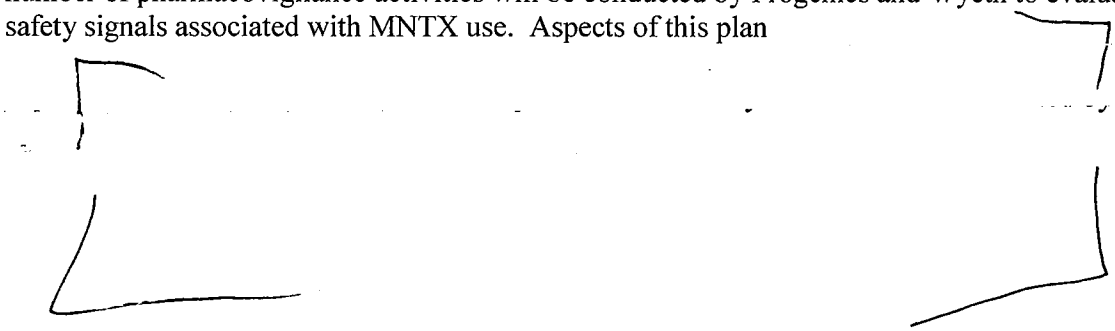
8.6 Literature Review

A review of relevant medical literature regarding μ-opioid receptor antagonists was conducted.

8.7 Postmarketing Risk Management Plan

The major adverse events observed in the clinical trials of SC MNTX were those effects related to its pharmacodynamic mechanism of action, specifically the gastrointestinal side effects. Other potential risks that may be associated with the use of this drug are its off-label use, possible medicating errors and the possibility of misuse of the drug by those abusing opioid substances.

The Applicant has submitted a postmarketing plan that will be primarily based on the surveillance of adverse event reports in the AERs data base.. However, in addition to this, a number of pharmacovigilance activities will be conducted by Progenics and Wyeth to evaluate safety signals associated with MNTX use. Aspects of this plan



8.8 Other Relevant Materials

There were no other special materials that were relevant for the review of this NDA.

9 OVERALL ASSESSMENT

9.1 Conclusions

The NDA 21-964 submission is complete and adequate for clinical review. Based on the clinical review of the data included in the NDA submission, the Medical Reviewer's conclusion is that SC MNTX is safe and effective for the treatment of opioid-induced constipation in patients receiving terminal care.

9.2 Recommendation on Regulatory Action

The Medical Reviewer recommends that SC MNTX in the 8 and 12 mg dosages be approved for the following indication: treatment of opioid-induced constipation in patients receiving terminal care.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Constipation is a major adverse effect of opioid use thus the potential exists for MNTX to be used off-label in patients taking opioids for non-malignant chronic pain. In addition, this drug will be used in hospice type facilities or even for home care so that errors in administration or incorrect dosing of MNTX may occur. During the clinical trials, no cases of MNTX overdose were reported.

The major adverse events observed to date in clinical studies of MNTX SC are those adverse effects related to its mechanism of action, specifically gastrointestinal side effects which include abdominal pain, flatulence, nausea, and diarrhea.

Medical Reviewer's Comments

- *The Applicant plans*
- *In addition, the Applicant is planning*

9.3.2 Required Phase 4 Commitments

No specific phase 4 commitments are recommended for the indications being sought.

9.3.3 Other Phase 4 Requests

No specific phase 4 requests are recommended for the indications being sought.

9.4 Labeling Review

9.5 Comments to Applicant

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

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Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review

NDA	21964
Brand Name	Relistor
Generic Name	methylnaltrexone (MOA-728)
Sponsor	Progenics Pharmaceuticals, Inc.
Indication	Treatment of Opioid Induced Constipation in patients receiving Palliative care
Dosage Form	IV solution
Drug Class	Peripheral Opioid Antagonist
Therapeutic Dose	0.30 mg/kg and 0.64 mg/kg IV infusion
Duration of Therapeutic Use	Acute and chronic
Application Submission Date	12/07/2007
Review Classification	TQT Study report in Standard NDA
Date Consult Received	12/11/2007
Clinical Division	DGP / HFD 180
PDUFA Date	4/30/2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant effect of methylnaltrexone was detected in this 'thorough QT' study. The largest upper limits of the two-sided 90% CI for the mean difference between the two doses of methylnaltrexone (0.3 mg/kg and 0.64 mg/kg IV infusion) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

The study was a single-center, randomized, double-blind, placebo- and moxifloxacin-(open label) controlled 4-period crossover study in which 56 healthy subjects were administered 0.3 mg/kg, methylnaltrexone 0.64 mg/kg, placebo as a single 20-minute IV infusion. Subjects also received a single oral dose of moxifloxacin 400-mg. Overall findings are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MOA-728 (0.3 mg/kg and 0.64 mg/kg) and the Largest Lower Bound for Moxifloxacin

Treatment	Time (hour)	ΔΔQTcN (ms)	90% CI (ms)
MOA-728 0.30 mg/kg	0.67	0.05	(-1.8, 1.9)
MOA-728 0.64 mg/kg	2	0.8	(-1.1, 2.6)
Moxifloxacin*	2	9.4	(6.7, 12.0)

* Multiple time points are adjusted with 3 post -baseline time points.

The largest lower bound of the two-sided 90% CI for the ΔΔQTcN for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

The methylnaltrexone doses evaluated in this study are acceptable. The mean peak plasma concentration from the supratherapeutic dose (0.64 mg/kg IV) is 9-fold and 2.3-fold greater than those observed from the SC therapeutic dose (0.15 mg/kg SC) and IV therapeutic dose (24 mg). There are no known intrinsic or extrinsic factors that can increase exposure to methylnaltexone greater than what was observed following the supratherapeutic IV dose (Clinical Pharmacology Table, section 6.1).

We note that blood samples were not analyzed for the metabolites of methylnalterexone; therefore, the exposure to metabolites with the supratherapeutic dose was not evaluated.

2 PROPOSED LABEL

The present statement regarding the effect of methylnaltrexone on cardiac repolarization in the label (Section 12.3) reads

Reviewer's comments: The study was not found adequate with respect to design and sensitivity and sponsor was asked to conduct a suitably designed IV study to assess the QT prolonging potential of methylnaltrexone. The following recommendations are only our suggestions for labeling. We defer all final labeling decisions to the review divisions.

In a randomized, double blind placebo - and (open-label) moxifloxacin - controlled 4 - period crossover study, 56 healthy subjects were administered RELISTOR 0.3 mg/kg and RELISTOR 0.64 mg/kg by IV infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At both the 0.3 mg/kg and 0.64 mg/kg RELISTOR doses, no significant effect on the QTc interval was detected.

3 BACKGROUND

Methylnaltrexone (MNTX) is a quaternary ammonium derivative of the opioid antagonist naltrexone in which methyl group has been added to the amine ring of the parent compound. Compared with naltrexone, MNTX has greater polarity and lower lipid solubility, decreasing its access to the central nervous system. The sponsor believes that MNTX can reverse opioid-induced constipation without diminishing centrally mediated opioid analgesia.

3.1 MARKET APPROVAL STATUS

Not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: IB

"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 IC50 for MNTX was > 1000 µM, whereas the IC50 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 ms (18%), 54 ms (24%), and 49 ms (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."

3.3 Previous Clinical Experience

Source: IB

As of 31 Dec 2006, over 724 subjects or patients have received MNTX through participation in such studies. These trials have enrolled patients with advanced illness, POI patients, patients with compromised hepatic or renal function and healthy volunteers. Most studies used double-blind placebo-controlled designs. Results were summarized based on pooled data from clinical studies of SC MNTX in 2 analysis population pools: subjects in double-blind phase 2/3 studies and all MNTX-treated subjects in phase 2/3 studies.

The most commonly (>20%) reported AEs with MNTX were abdominal pain (39.2%), malignant neop1asm progression (31.8%), and nausea (22.4%).

Of the 286 patients in the MNTX exposure pool, 140 (49.0%) died. There was no statistical difference between the survival rates of patients who received MNTX and those who received placebo. The rates of deaths in the phase 2/3 studies are not surprising given the serious nature of the patients' underlying illnesses, the duration of exposure, and the fact that the patients could be enrolled if the investigators considered their life expectancies to be as short as 1 month. In the healthy volunteer pool, there were no deaths, SAEs, or discontinuations due to AEs among the healthy volunteers who received SC MNTX or placebo in the pooled phase 1 studies.

3.4 Clinical Pharmacology

Appendix 6.1 summarizes the key features of methlynaltrexone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 Overview

4.2 TQT Study

The sponsor submitted a thorough QT study and the associated electronic data sets. Digital ECGs were submitted to the ECG warehouse.

4.2.1 Title

A Randomized, Double-Blind, Placebo- and Moxifloxacin (Open label)-Controlled, 4-Period Crossover Study Of The Effects Of A Single Dose Of MOA-728 Infused Intravenously On Cardiac Repolarization In Healthy Subjects.

4.2.2 Protocol Number

3200L2-104-US

4.2.3 Study Dates

The study started in August 2007 and ended in October 2007.

4.2.4 Objectives

To assess the effect of MOA-728 after a single IV infusion of either 0.3 mg/kg or 0.64 mg/kg on cardiac repolarization as assessed by the corrected QT interval (QTc) in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, placebo- and moxifloxacin- (open label) controlled 4-period crossover study of the effects of a single dose of MOA-728 infused intravenously on cardiac repolarization in 56 healthy subjects at a single study site.

The following 4x4 crossover design was conducted.

Period 1	Period 2	Period 3	Period 4
H	M	L	P
M	P	H	L
L	H	P	M
P	L	M	H

H: MOA-728 0.64 mg/kg
L: MOA-728 0.3 mg/kg
P: Placebo
M: Moxifloxacin

4.2.5.2 Controls

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

4.2.5.3 Blinding

With the exception of the moxifloxacin treatment, this is a double blind trial. The investigators and the study subjects will remain blinded to the treatment assignments throughout the trial. The PK analyst, biostatistician, and Clinical Data Management project representatives may be unblinded to analyze PK/PD data or to provide descriptive statistics for safety and/or PD variables during the course of the study.

The readers were blinded to subject identifiers, treatment, treatment sequence, and time of ECG.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

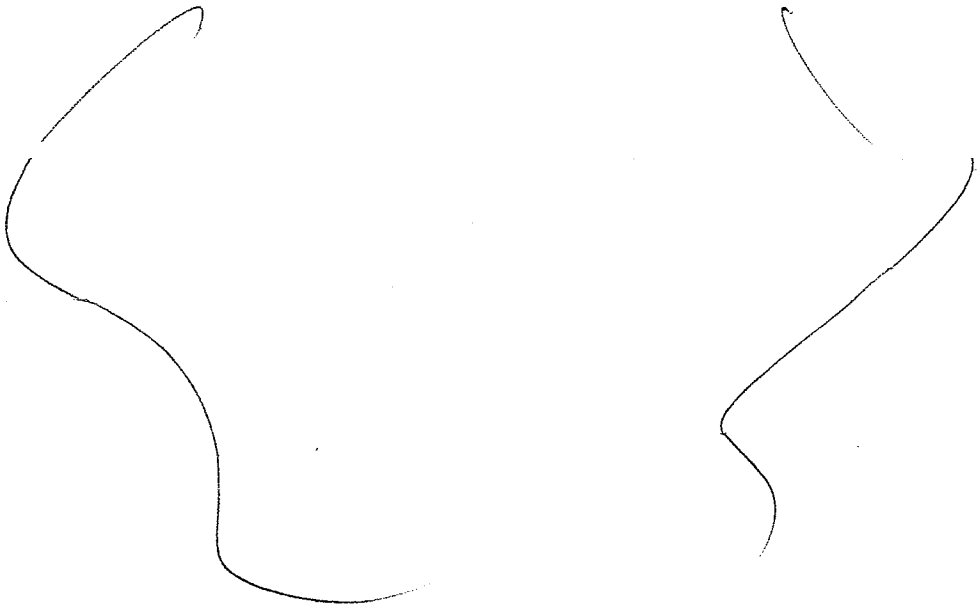
Subjects will receive each of the following treatments in a random sequence:

- 0.3 mg/kg of MOA-728 administered as a 20-minute IV infusion
- 0.64 mg/kg of MOA-728 administered as a 20-minute IV infusion
- Placebo MOA-728 administered as a 20-minute IV infusion
- 400 mg of moxifloxacin (single 400-mg tablet) [open-label]

Reviewer's comments: The single dose QT study performed by the sponsor seems to be reasonable. There was no appreciable accumulation of methylnaltrexone following multiple SC dose (R=1.07 as determined based on simulation) or multiple 20 min IV infusions (R=1.19 following 5 doses q6h at 0.45 mg/kg, Study MNTX 1108) or multiple 24 mg fixed dose (R=1.2 following 17 doses q6h, MNTX 1303). According to study MNTX 102, less than 10% of methylnaltrexone was recovered as metabolites after IV administration. Also, based on study MNTX 1303, it was shown that there was accumulation of 2-3 fold for methylnaltrexone's metabolites after 17 doses. However, it was shown in this study that the disposition of all the metabolites was formation rate limited and the accumulation factor (which was estimated based on the AUC_{6h} ratio of 17^{th} dose to first dose) may be overestimated because of incomplete formation of the metabolites after first dose.

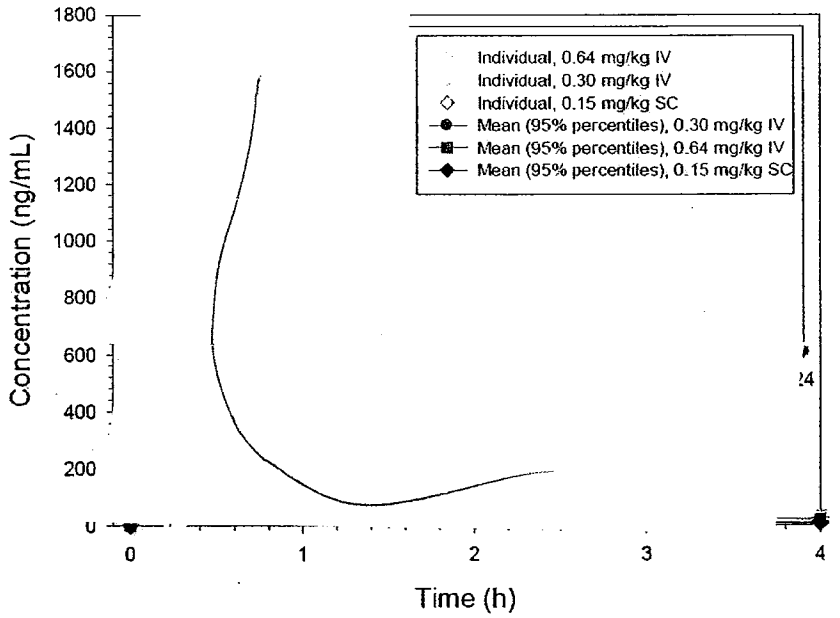
4.2.6.2 Sponsor's Justification for Doses

According to sponsor,



Reviewer's comments: The sponsor has reasonably justified the choice of therapeutic and supratherapeutic doses of methylnaltrexone to support the therapeutic SC dose and the ongoing clinical development program of methylnaltrexone IV [redacted] Sponsor compared the exposures of therapeutic SC and IV doses to facilitate the use of the QTc results to support the 0.15 mg/kg SC dose. Results from the study MNTX 1106 show that mean (±SD) C_{max} values were 117±33 ng/ml at SC dose of 0.15 mg/kg (the recommended therapeutic dose) and 392±148 ng/ml at 0.5 mg/kg SC dose (the corresponding supratherapeutic dose). These C_{max} values were lower than those of IV dose of 0.3 mg/kg (462±82 ng/ml) by factors of 4 and 1.2 respectively, and by factors of 9.1 and 2.7 when compared to IV dose of 0.64 mg/kg (1062±258 ng/ml). In context of justifying the doses with respect to IV therapeutic dose, it was unclear why sponsor used only subjects with GFR of ≥50 mL/min/1.73 m^2 for simulations when it was shown in the study MNTX 1105 that exposures doubled and there was 1.2 fold increase in mean C_{max} values in subjects with severe renal impairment. Considering the overall findings, the supratherapeutic dose of 0.64 mg/kg IV covers the peak concentrations possible in worst case scenario following therapeutic IV or SC dose. The figure below compares the exposures following IV and SC dose administration.

Figure 1. Comparison of methylnaltrexone Plasma Concentration–Time Profiles following IV Infusions at 0.3 and 0.64 mg/kg, and SC administration at 0.15 mg/kg



(Source: Summary of Clinical Study Report: Study 3200L2-104-US; Figure 5-19, page 26)

4.2.6.3 Instructions with Regard to Meals

Not Applicable

4.2.6.4 ECG and PK Assessments

Table 1. ECG and PK Sampling Schedule

Study Day	-2, -1	1	2-4
Intervention	No treatment (Baseline)	Single dose	No treatment
12-Lead ECGs	Day -2, Day -1 (0.33, 0.67, 1, 2, 3, 4, 6, 9, 12 h)*	Predose (-2 h), 0.33, 0.67, 1, 2, 3, 4, 6, 9, 12, 24 hours post dose)	Day 4 (72 h)*
PK Samples for drug	None collected	Predose (-2 h), 0.33, 0.67, 1, 2, 3, 4, 6, 9, 12, 24 hours post dose)	None collected†

* Day -2 and Day 4 were 12- Lead ECGs (single) measurements while all other measurements were in triplicate

† No PK sample was collected at 72 h post dose

4.2.6.5 Baseline

Time-matched baselines were used in the study.

4.2.7 ECG Collection

Triplicate ECGs were obtained on day -1 and day 1 at the time points specified above. Triplicate ECGs were performed 1 to 2 minutes apart. Subjects rested in the supine position for at least 5 minutes before the ECG recording is started. The clinic's staff attempted to maintain the subject's resting state so that the subject has a stable heart rate before ECG recordings.

The ECGs were stored electronically and sent to a central laboratory for a manual assessment of rhythm, and RR, PR, QRS, QT, and corrected QT (QTc) intervals. The central ECG laboratory used in this study was

readers were blinded to subject identifiers, treatment, treatment sequence, and time of ECG. At the conclusion of the study, conducted a 2% quality assurance read and provided inter- and intra- variability for this study to the sponsor.

Safety twelve (12)-lead ECGs were collected at the time points specified in the flow chart (screening, day 4 in each period and at the final study evaluation). The investigator reviewed the initial ECGs on day -1 at least 4 to 6 times over the 24-hour period, before dose administration, and near the times of maximum observed concentration (tmax) of MOA-728 and moxifloxacin (immediately after the start of the infusion to approximately 4 hours after dose administration). The investigator was responsible for providing the overall interpretation of ECGs.

Reviewer's Comment: Waveforms submitted to the ECG warehouse were reviewed. ECG acquisition and interpretation appears acceptable.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

The study population consisted of 47 healthy men and 9 healthy women aged 20 to 48 years with normal baseline ECG and BMI between 19.87 and 29.76 kg/m^2. All 56 subjects completed the study and none were replaced.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the average of the tracings' change from baseline in QTcN for the MOA-728 treatment groups. For each dose of MOA-728, a 90% CI (equivalent to a one-sided 95% CI) for the baseline-adjusted difference in QTcN at each of the timepoints between the active treatment and placebo was computed (presented in Table 2).

Table 2: QTcN Interval Differences from Placebo in Change From Baseline for MOA-728 Treatments

Drug Name	Timepoint (hr)	N	QTcN Mean (msec)	QTcN 90% CI (msec)
MOA 0.30 mg/kg	0.33	56	-1.6	(-3.4, 0.3)
	0.67	56	-0.2	(-2.0, 1.7)
	1	56	-0.6	(-2.4, 1.3)
	2	56	-0.3	(-2.2, 1.6)
	3	56	-0.5	(-2.4, 1.3)
	4	56	-0.9	(-2.7, 1.0)
	6	56	-0.3	(-2.1, 1.6)
	9	56	-0.7	(-2.6, 1.1)
	12	56	-0.9	(-2.8, 0.9)
	24	56	-0.3	(-2.1, 1.6)
MOA 0.64 mg/kg	0.33	56	-3.2	(-5.0, -1.3)
	0.67	56	-0.2	(-2.1, 1.7)
	1	56	-0.5	(-2.4, 1.4)
	2	56	0.5	(-1.4, 2.4)
	3	56	-0.9	(-2.8, 0.9)
	4	56	-1.9	(-3.7, -0.0)
	6	56	0.1	(-1.8, 1.9)
	9	56	-0.1	(-2.0, 1.7)
	12	56	0.3	(-1.6, 2.2)
	24	56	0.4	(-1.4, 2.3)

Abbreviations: N= Number of subjects; MOA = MOA-728; QTcN = Linear study population correction.

(Source: Clinical Study Report: Study 3200L2-104-US; Table 9-1, page 45)

To evaluate assay sensitivity, a positive control (400 mg moxifloxacin) was compared to placebo using baseline-adjusted QTcN at timepoints near expected tmax. This was conducted by comparing the lower and upper bounds of the 90% CIs for the QTcN change from baseline difference compared to placebo with 0 ms. and 10 ms. for timepoints of 1, 2 and 3 hours postdose. It was pre-specified that the timepoint with the largest geometric mean plasma concentration would be considered the primary timepoint to assess assay sensitivity. This timepoint was 2 hours postdose.

Table 3: QTcN Interval Differences From Placebo in Change From Baseline for Moxifloxacin 400 mg at Pre-Specified Timepoints

Drug Name	Timepoint (hr)	N	QTcN Mean (msec)	QTcN 90% CI (msec)
MOXI 400 mg	1	56	7.9	(6.0, 9.7)
	2	56	9.2	(7.4, 11.1)
	3	56	8.3	(6.5, 10.2)

Abbreviations: N= Number of subjects; MOXI = Moxifloxacin; QTcN = Study population (linear regression) correction.

(Source: Clinical Study Report: Study 3200L2-104-US: Table 9-2, page 46)

Reviewer's comments: The sponsor proposed a statistical model which adjusts carryover effect, and results are similar to those without adjusting a carryover effect. This reviewer also examined the carryover effect and found out that the carryover effect is not real (see the details in the following statistical assessment section).

4.2.8.2.2 Categorical Analysis

A categorical analysis was done summarize QTc intervals of >450, >480 and >500 ms as well as QTc changes from time-matched baseline of ≥30 and ≥60 ms. All categorical summaries were based on the average of replicates within a time point.

No subjects had postdose QTcN intervals above 450 ms in any of the treatment groups. Categorical assessments using QT intervals, and QTc values based on Fridericia's correction and Bazett's correction were consistent with that using the QTcN intervals. The largest postdose QTcN interval change from baseline is summarized in Table 4. No subjects had QTcN interval changes from baseline of ≥ 30 ms after receiving placebo or either of the two MOA-728 doses, while 12.5% (7 out of 56) of the subjects had changes from baseline of ≥ 30 ms after receiving moxifloxacin.

Table 4: Categorical QT Change From Baseline Summary Using Study Population (Linear Regression) Correction

Endpoint	Drug Name	<30 msec Number / Total (Percent)	≥30 msec Number / Total (Percent)	≥60 msec Number / Total (Percent)
QTcN Interval (msec)	MOA 0.30 mg/kg	56/56 (100.0%)	0/56 (0.0%)	0/56 (0.0%)
	MOA 0.64 mg/kg	56/56 (100.0%)	0/56 (0.0%)	0/56 (0.0%)
	MOXI 400 mg	49/56 (87.5%)	7/56 (12.5%)	0/56 (0.0%)
	Placebo	56/56 (100.0%)	0/56 (0.0%)	0/56 (0.0%)

Abbreviations: MOXI = Moxifloxacin; QTcN = Study population (linear regression) correction.

(Source: Clinical Study Report: Study 3200L2-104-US: Table 9-3, page 56)

4.2.8.2.3 Additional Analyses

The average change from baseline in QT interval corrected by Fridericia's formula was analyzed as a secondary endpoint. The QTcF interval analysis was similar to the QTcN interval analysis.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study. There were no discontinuations due to AEs Overall, 38 (67.9%) subjects experienced at least one TEAE during the study. All TEAEs were considered by the investigator as either mild or moderate. The most frequent TEAEs were Skin and Tissue Disorders (contact dermatitis, 11 subjects, 19.6%; papular

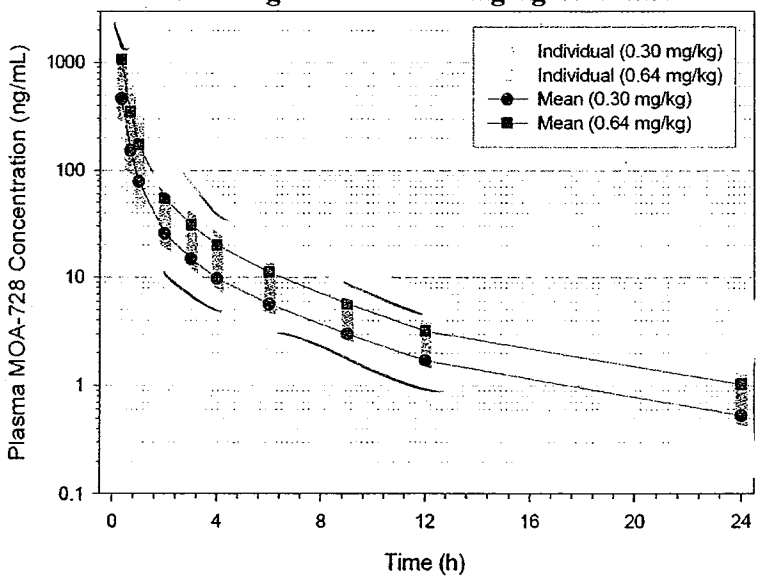
rash, 6 subjects, 10.7%). Other frequent TEAEs included headache (9 subjects, 16.1%) and nausea (6 subjects, 10.7%).
One subject experienced vasovagal syncope following venipuncture *prior* to receiving MOA 728 (0.64 mg/kg).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean plasma concentration-time profiles of methylnaltrexone after 20 min IV infusion at the two doses is shown in Figure 2. Summary statistics of the pharmacokinetics of methylnaltrexone at these two doses is provided in Table 5. The mean C_{max} and AUC_{∞} at supratherapeutic dose (0.64 mg/kg) were 2.3 and 2.2 fold respectively when compared to therapeutic dose (0.3 mg/kg). *(Refer to section 4.2.6.2 for comparison of exposures at the 0.3 and 0.64 mg/kg IV dose to therapeutic SC dose).*

Figure 2. Mean and individual methylnaltrexone plasma concentration profiles following 0.30 and 0.64 mg/kg IV infusion



(Source: Clinical Study Report: Study 3200L2-104-US; Figure 8-1, page 43)

Table 5. Summary statistics of methylnaltrexone's PK parameters following 0.3 and 0.64 mg/kg IV infusion (Values are expressed as median (min, max) or otherwise as mean ± SD (95% CI for mean))

Parameter	0.30 mg/kg (n=56)		0.64 mg/kg (n=56)	
C_{max} (ng/mL)	462 ± 82	(440 – 484)	1062 ± 258	(993 – 1131)
t_{max} (h)[a]	0.37	(0.35, 0.43)	0.37	(0.35, 0.68)
AUC_t (ng.h/mL)	335 ± 50	(322 – 349)	739 ± 139	(701 – 776)
AUC_∞ (ng.h/mL)	340 ± 52	(326 – 354)	748 ± 142	(711 – 786)
$t_{1/2}$ (h)	5.52 ± 0.86	(5.29 – 5.75)	5.61 ± 2.25	(5.01 – 6.22)
CL (mL/h/kg)	901 ± 125	(868 – 935)	885 ± 170	(840 – 931)
V_{SS} (mL/kg)	2054 ± 425	(1941–2168)	1951 ± 1048	(1670– 2231)

(Source: Clinical Study Report: Study 3200L2-104-US; Table 8-1, page 44)

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not perform exposure response analysis.

Reviewer's Comments: See reviewer's assessments for exposure response analysis (Section 5.2)

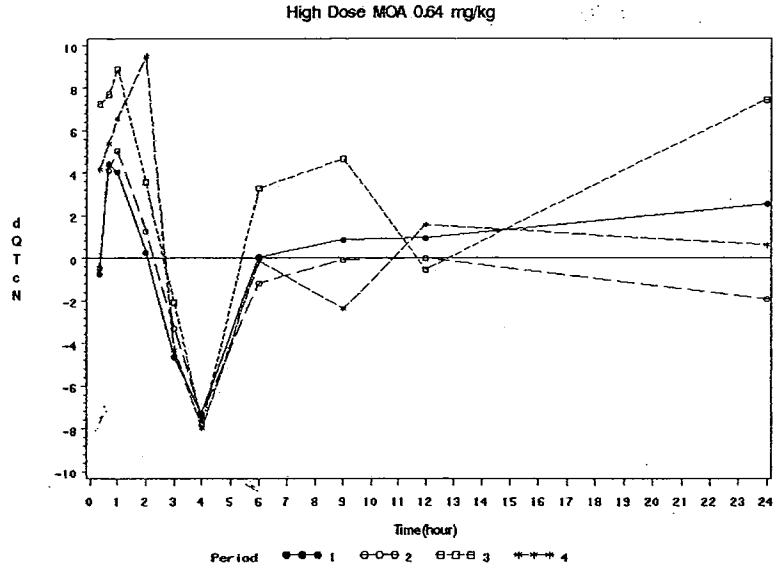
5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

This statistical reviewer performed an independent analysis based on the electronically submitted ECG data.

The carryover effect of the study was assessed by comparing the baseline corrected QTcN values from periods 2, 3, and 4 with those in period 1. We conclude that the carryover effect is not real. However, as demonstrated in the following figure, for the high dose treatment group MOA-728 0.64 mg/kg, baseline corrected QTcN values at multiple time points 0.33, 0.67, 1, 6, 9 and 24 hours in period 3, are higher than those in period 1, which makes the overall baseline corrected QTcN intervals statistically significant different for the high dose between period 3 and period 1. We do not believe this is the carryover effect. Based on the study design, at period 3, the high dose MOA-728 0.64 mg/kg was given after placebo. This difference could due to the variability of the study or the period effect subject to that subgroup administered the high dose of the study drug in period 3.

Figure 3: Time Course of Mean Changes from Baseline in ΔQTcN



Since there was a possibility of period effect on ECG data at period 3 for the high dose MOA-728 0.64 mg/kg, we conducted both analyses with and without period 3 data. The results by eliminating data in period 3 are very similar to those based on the full data set. For demonstration purpose, we only list the results based on the full data set.

As showed in Table 6, for both MOA-728 0.30 mg/kg and MOA 0.64 mg/kg groups, the upper bounds of the 2-sided 90% CIs are below 10 ms. This reviewer also performed the same analysis using QTcF and QTcI, and the results are very similar to those results using QTcN.

Table 6: Upper boundary of the one-sided 95% ANOVA model based CI for the placebo and baseline corrected values (delta delta analysis) of QTcN

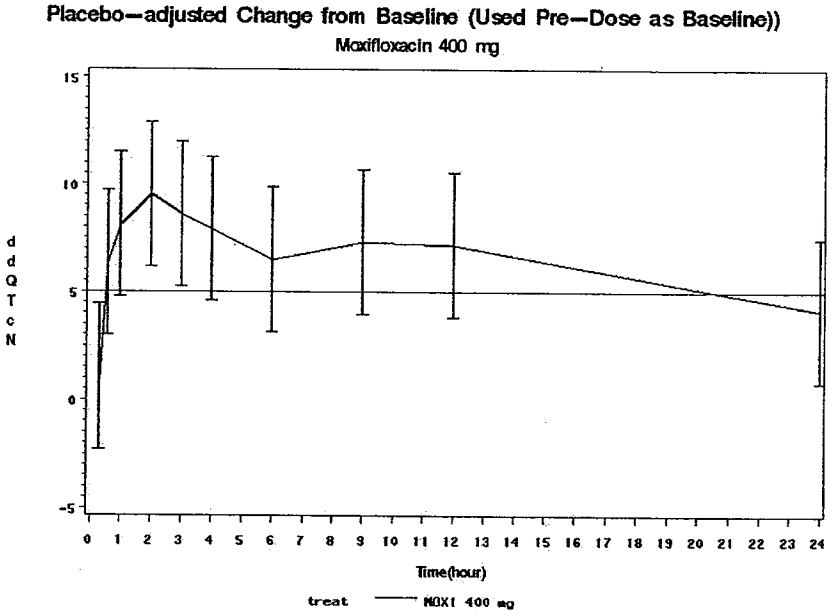
Time post-dose (hrs)	Least Square Means			Treatment Difference		95% One-sided Upper Limit	
	MOA-728 0.30 mg/kg (n = 56)	MOA-728 0.64 mg/kg (n = 56)	Placebo (n = 56)	MOA-728 0.30 mg/kg - Placebo	MOA-728 0.64 mg/kg - Placebo	MOA-728 0.30 mg/kg - Placebo	MOA-728 0.64 mg/kg - Placebo
0.33	3.2	1.7	4.5	-1.3	-2.9	0.5	-1.0
0.67	4.0	4.0	3.9	0.05	0.1	1.9	2.0
1	4.3	4.4	4.6	-0.3	-0.2	1.5	1.6
2	-0.4	0.4	-0.3	-0.1	0.8	1.8	2.6
3	-4.1	-4.4	-3.8	-0.3	-0.6	1.5	1.2
4	-4.6	-5.5	-3.9	-0.6	-1.6	1.2	0.3
6	0.4	0.8	0.4	-0.03	0.4	1.8	2.2
9	4.3	5.0	4.8	-0.5	0.2	1.3	2.0
12	-2.1	-0.8	-1.4	-0.7	0.6	1.2	2.5
24	0.6	1.3	0.6	-0.03	0.7	1.8	2.6

Table 7 summarizes the results of the mean difference between moxifloxacin and placebo in QTcN with multiple adjustments at pre-specified timepoints. With multiple endpoint adjustment, the largest lower bound is 5.7 ms at 2 hour. Figure 4 presents the time-course of QTcN for moxifloxacin.

Table 7: Placebo-Adjusted, Mean QTcN Change From Baseline for Moxifloxacin 400 mg at Pre-Specified Timepoints

Timepoint		Mean	Bonferroni Corrected 90% CI (ms)	
(hr)	# of Obs	(ms)	Lower Bound	Upper Bound
1	56	8.2	5.6	10.9
2	56	9.4	6.7	12.0
3	56	8.9	6.3	11.5

Figure 4: Time Course of Mean Changes in ΔΔQTcN for Moxifloxacin



For categorical analysis, we confirmed that no subject had an absolute QTcN interval above 450 ms post treatment. There were one subject, 4 subjects, 2 subjects and 20 subjects who had an increase from baseline between 30 and 60 ms in MOA-728 0.30 mg/kg , MOA-728 0.64 mg/kg group, placebo and moxifloxacin groups, respectively. No subject had an increase in QTcN from baseline of more than 60 ms. Similar results were reached for QTcF.

Table 8: Frequency for Delta QTcN: 30~60 ms.

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
MOA-728 0.30 mg/kg	56	1	1.8%	1,680	2	0.1%
MOA-728 0.64 mg/kg	56	4	7.1%	1,680	6	0.4%
Placebo	56	2	3.6%	1,680	2	0.1%
Moxifloxacin 400 mg	56	20	35.7%	1,680	40	2.4%

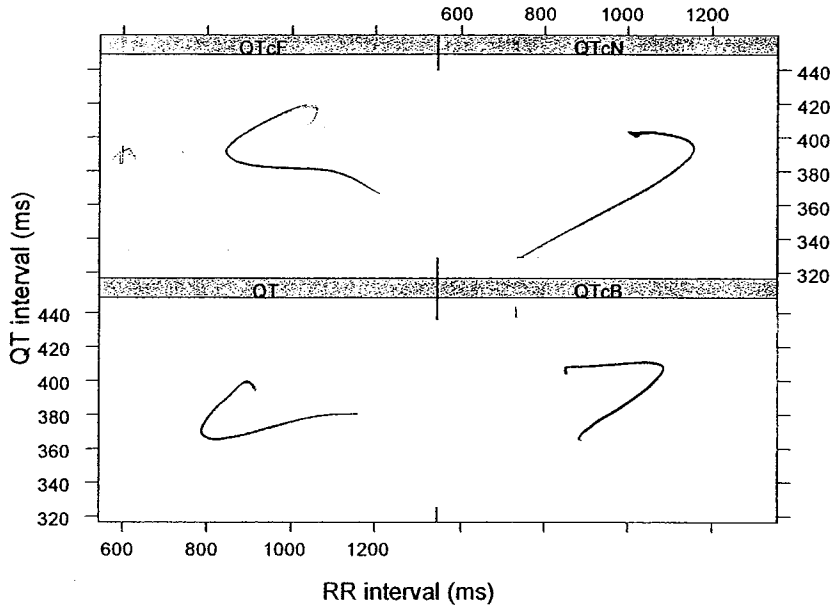
Reviewer's conclusions:

- Using pre-dose as a baseline, the upper bounds of the 2-sided 90% CIs in QTcN between both dose of MOA (0.30 mg/kg and 0.64 mg/kg) and placebo in change from baseline-and placebo-corrected at each extracted time point were less than 10 ms, thus satisfying the criteria for a negative thorough QT/QTc study.
- Assay sensitivity of the study has been established.
- For all treatments, no subjects developed a QTcN greater than 480 ms or a change from baseline QTcN greater than 60 ms.

5.2 Clinical Pharmacology Assessments

The relationship between QT and RR using two different correction methods is illustrated in Figure 5. The Fridericia's correction method was found to be reasonable for further analysis.

Figure 5. QT (Raw QT measurements, Bazzet's and Fridericia's corrected QT)-RR interval relationship



The time course of mean ΔΔQTcF for therapeutic (0.3 mg/kg), supratherapeutic (0.64 mg/kg), and moxifloxacin (400 mg) is illustrated in Figure 6 and Figure 7. It is evident that there is no dose dependency on QTcF and neither of the studied doses prolongs the QT interval. The mean (Upper CI) effect at mean C_{max} (1061.6 ng/ml) after supratherapeutic dose is 3.2 ms (5.44).

Figure 6: Time course of mean ΔΔQTcF

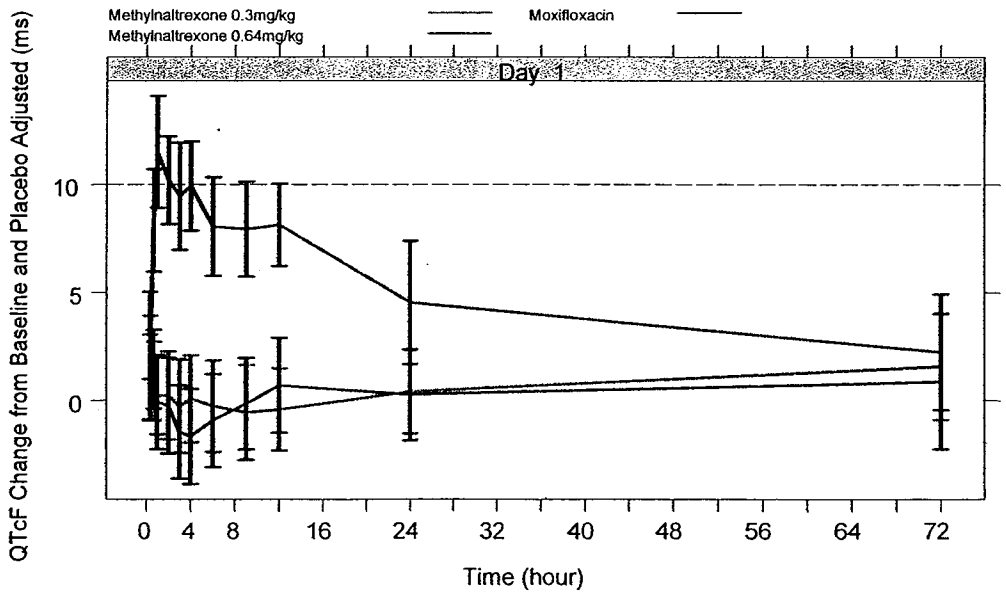
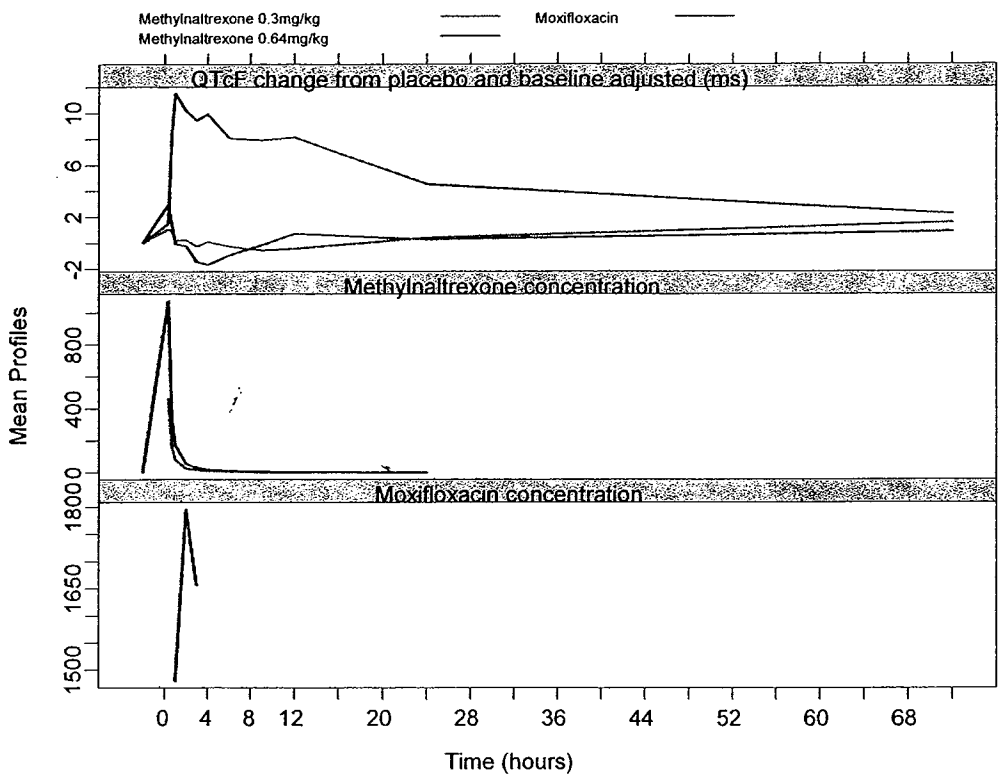


Figure 7: Time course of mean ΔΔQTcF and concentrations



Additional evidence based on Concentration-QTcF modeling from

Appears This Way
On Original

Figure 8, shows that methylnaltrexone does not prolong QT interval at the studied doses.

Appears This Way
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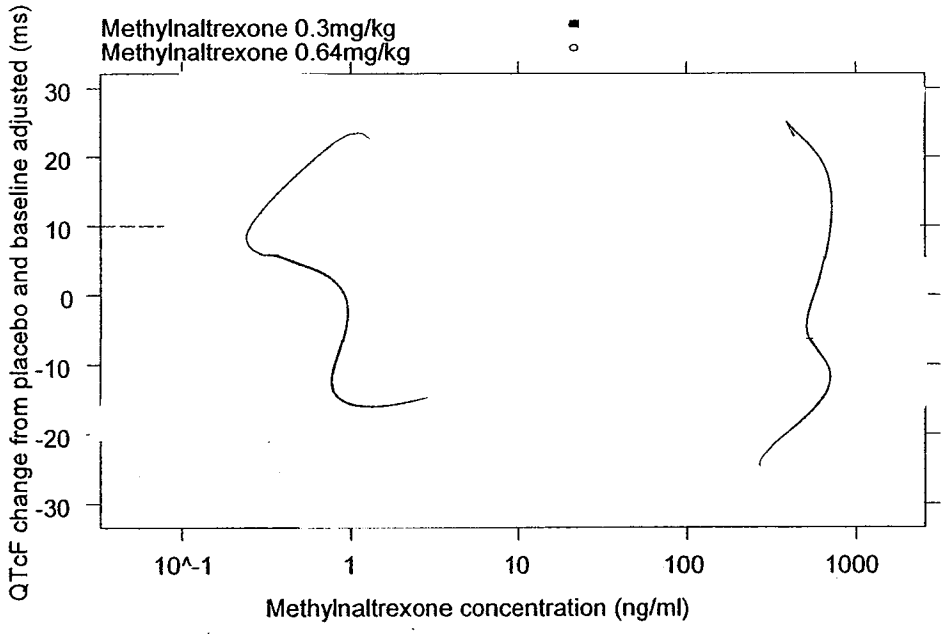
Figure 8: Log Concentration-ΔΔQTcF relationship



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.

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/s/

Joanne Zhang
2/12/2008 03:52:32 PM
BIOMETRICS
This is the revised version of the IRT QT study report for NDA 21964 dated on 2/4/2008.

Kate L Dwyer
2/12/2008 04:01:13 PM
BIOMETRICS

Christine Garnett
2/25/2008 02:18:42 PM
BIOPHARMACEUTICS

Suchitra Balakrishnan
2/25/2008 03:39:00 PM
MEDICAL OFFICER

Norman Stockbridge
2/25/2008 03:46:36 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review

NDA	21964
Brand Name	Relistor
Generic Name	methylnaltrexone (MOA-728)
Sponsor	Progenics Pharmaceuticals, Inc.
Indication	Treatment of Opioid Induced Constipation in patients receiving Palliative care
Dosage Form	IV solution
Drug Class	Peripheral Opioid Antagonist
Therapeutic Dose	0.30 mg/kg and 0.64 mg/kg IV infusion
Duration of Therapeutic Use	Acute and chronic
Application Submission Date	12/07/2007
Review Classification	TQT Study report in Standard NDA
Date Consult Received	12/11/2007
Clinical Division	DGP / HFD 180
PDUFA Date	4/30/2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant effect of methylnaltrexone was detected in this 'thorough QT' study. The largest upper limits of the two-sided 90% CI for the mean difference between the two doses of methylnaltrexone (0.3 mg/kg and 0.64 mg/kg IV infusion) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

The study was a single-center, randomized, double-blind, placebo- and moxifloxacin-(open label) controlled 4-period crossover study in which 56 healthy subjects were administered 0.3 mg/kg, methylnaltrexone 0.64 mg/kg, placebo as a single 20-minute IV infusion. Subjects also received a single oral dose of moxifloxacin 400-mg. Overall findings are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MOA-728 (0.3 mg/kg and 0.64 mg/kg) and the Largest Lower Bound for Moxifloxacin

Treatment	Time (hour)	ΔΔQTcN (ms)	90% CI (ms)
MOA-728 0.30 mg/kg	24	0.7	(-1.5, 2.9)
MOA-728 0.64 mg/kg	24	0.3	(-1.9, 2.4)
Moxifloxacin*	2	9.4	(5.7, 13.0)

* Multiple time points are adjusted with 3 post –baseline time points.

The largest lower bound of the two-sided 90% CI for the ΔΔQTcN for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

The methylnaltrexone doses evaluated in this study are acceptable. The mean peak plasma concentration from the supratherapeutic dose (0.64 mg/kg IV) is 9-fold and 2.3-fold greater than those observed from the SC therapeutic dose (0.15 mg/kg SC) and IV therapeutic dose (24 mg). There are no known intrinsic or extrinsic factors that can increase exposure to methylnaltexone greater than what was observed following the supratherapeutic IV dose (Clinical Pharmacology Table, section 6.1).

We note that blood samples were not analyzed for the metabolites of methylnalterexone; therefore, the exposure to metabolites with the supratherapeutic dose was not evaluated.

2 PROPOSED LABEL

The present statement regarding the effect of methylnaltrexone on cardiac repolarization in the label (Section 12.3) reads

Reviewer's comments: The study was not found adequate with respect to design and sensitivity and sponsor was asked to conduct a suitably designed IV study to assess the QT prolonging potential of methylnaltrexone. The following recommendations are only our suggestions for labeling. We defer all final labeling decisions to the review divisions.

In a randomized, double blind placebo - and (open-label) moxifloxacin - controlled 4 - period crossover study, 56 healthy subjects were administered RELISTOR 0.3 mg/kg and RELISTOR 0.64 mg/kg by IV infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At both the 0.3 mg/kg and 0.64 mg/kg RELISTOR doses, no significant effect on the QTc interval was detected.

3 BACKGROUND

Methylnaltrexone (MNTX) is a quaternary ammonium derivative of the opioid antagonist naltrexone in which methyl group has been added to the amine ring of the parent compound. Compared with naltrexone, MNTX has greater polarity and lower lipid solubility, decreasing its access to the central nervous system. The sponsor believes that MNTX can reverse opioid-induced constipation without diminishing centrally mediated opioid analgesia.

3.1 MARKET APPROVAL STATUS

Not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: IB

"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 IC50 for MNTX was > 1000 μM, whereas the IC50 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 ms (18%), 54 ms (24%), and 49 ms (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."

3.3 Previous Clinical Experience

Source: IB

As of 31 Dec 2006, over 724 subjects or patients have received MNTX through participation in such studies. These trials have enrolled patients with advanced illness, POI patients, patients with compromised hepatic or renal function and healthy volunteers. Most studies used double-blind placebo-controlled designs. Results were summarized based on pooled data from clinical studies of SC MNTX in 2 analysis population pools: subjects in double-blind phase 2/3 studies and all MNTX-treated subjects in phase 2/3 studies.

The most commonly (>20%) reported AEs with MNTX were abdominal pain (39.2%), malignant neop1asm progression (31.8%), and nausea (22.4%).

Of the 286 patients in the MNTX exposure pool, 140 (49.0%) died. There was no statistical difference between the survival rates of patients who received MNTX and those who received placebo. The rates of deaths in the phase 2/3 studies are not surprising given the serious nature of the patients' underlying illnesses, the duration of exposure, and the fact that the patients could be enrolled if the investigators considered their life expectancies to be as short as 1 month. In the healthy volunteer pool, there were no deaths, SAEs, or discontinuations due to AEs among the healthy volunteers who received SC MNTX or placebo in the pooled phase 1 studies.

3.4 Clinical Pharmacology

Appendix 6.1 summarizes the key features of methlynaltrexone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 Overview

4.2 TQT Study

The sponsor submitted a thorough QT study and the associated electronic data sets. Digital ECGs were submitted to the ECG warehouse.

4.2.1 Title

A Randomized, Double-Blind, Placebo- and Moxifloxacin (Open label)-Controlled, 4-Period Crossover Study Of The Effects Of A Single Dose Of MOA-728 Infused Intravenously On Cardiac Repolarization In Healthy Subjects.

4.2.2 Protocol Number

3200L2-104-US

4.2.3 Study Dates

The study started in August 2007 and ended in October 2007.

4.2.4 Objectives

To assess the effect of MOA-728 after a single IV infusion of either 0.3 mg/kg or 0.64 mg/kg on cardiac repolarization as assessed by the corrected QT interval (QTc) in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, placebo- and moxifloxacin- (open label) controlled 4-period crossover study of the effects of a single dose of MOA-728 infused intravenously on cardiac repolarization in 56 healthy subjects at a single study site.

The following 4x4 crossover design was conducted.

Period 1	Period 2	Period 3	Period 4
H	M	L	P
M	P	H	L
L	H	P	M
P	L	M	H

H: MOA-728 0.64 mg/kg
L: MOA-728 0.3 mg/kg
P: Placebo
M: Moxifloxacin

4.2.5.2 Controls

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

4.2.5.3 Blinding

With the exception of the moxifloxacin treatment, this is a double blind trial. The investigators and the study subjects will remain blinded to the treatment assignments throughout the trial. The PK analyst, biostatistician, and Clinical Data Management project representatives may be unblinded to analyze PK/PD data or to provide descriptive statistics for safety and/or PD variables during the course of the study.

The readers were blinded to subject identifiers, treatment, treatment sequence, and time of ECG.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects will receive each of the following treatments in a random sequence:

- 0.3 mg/kg of MOA-728 administered as a 20-minute IV infusion
- 0.64 mg/kg of MOA-728 administered as a 20-minute IV infusion
- Placebo MOA-728 administered as a 20-minute IV infusion
- 400 mg of moxifloxacin (single 400-mg tablet) [open-label]

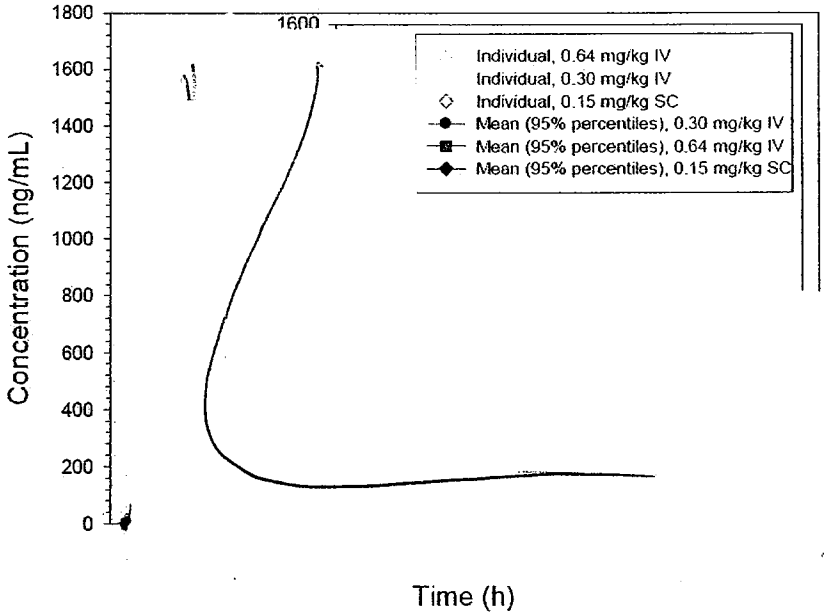
Reviewer's comments: The single dose QT study performed by the sponsor seems to be reasonable. There was no appreciable accumulation of methylnaltrexone following multiple SC dose (R=1.07 as determined based on simulation) or multiple 20 min IV infusions (R=1.19 following 5 doses q6h at 0.45 mg/kg, Study MNTX 1108) or multiple 24 mg fixed dose (R=1.2 following 17 doses q6h, MNTX 1303). According to study MNTX 102, less than 10% of methylnaltrexone was recovered as metabolites after IV administration. Also, based on study MNTX 1303, it was shown that there was accumulation of 2-3 fold for methylnaltrexone's metabolites after 17 doses. However, it was shown in this study that the disposition of all the metabolites was formation rate limited and the accumulation factor (which was estimated based on the AUC_{6h} ratio of 17^{th} dose to first dose) may be overestimated because of incomplete formation of the metabolites after first dose.

4.2.6.2 Sponsor's Justification for Doses

According to sponsor,

Reviewer's comments: The sponsor has reasonably justified the choice of therapeutic and supratherapeutic doses of methylnaltrexone to support the therapeutic SC dose and the ongoing clinical development program of methylnaltrexone IV at [redacted] Sponsor compared the exposures of therapeutic SC and IV doses to facilitate the use of the QTc results to support the 0.15 mg/kg SC dose. Results from the study MNTX 1106 show that mean (±SD) C_{max} values were 117±33 ng/ml at SC dose of 0.15 mg/kg (the recommended therapeutic dose) and 392±148 ng/ml at 0.5 mg/kg SC dose (the corresponding supratherapeutic dose). These C_{max} values were lower than those of IV dose of 0.3 mg/kg (462±82 ng/ml) by factors of 4 and 1.2 respectively, and by factors of 9.1 and 2.7 when compared to IV dose of 0.64 mg/kg (1062±258 ng/ml). In context of justifying the doses with respect to IV therapeutic dose, it was unclear why sponsor used only subjects with GFR of ≥50 mL/min/1.73 m^2 for simulations when it was shown in the study MNTX 1105 that exposures doubled and there was 1.2 fold increase in mean C_{max} values in subjects with severe renal impairment. Considering the overall findings, the supratherapeutic dose of 0.64 mg/kg IV covers the peak concentrations possible in worst case scenario following therapeutic IV or SC dose. The figure below compares the exposures following IV and SC dose administration.

Figure 1. Comparison of methylnaltrexone Plasma Concentration–Time Profiles following IV Infusions at 0.3 and 0.64 mg/kg, and SC administration at 0.15 mg/kg



(Source: Summary of Clinical Study Report: Study 3200L2-104-US; Figure 5-19, page 26)

4.2.6.3 Instructions with Regard to Meals

Not Applicable

4.2.6.4 ECG and PK Assessments

Table 1. ECG and PK Sampling Schedule

Study Day	-2, -1	1	2-4
Intervention	No treatment (Baseline)	Single dose	No treatment
12-Lead ECGs	Day -2, Day -1 (0.33, 0.67, 1, 2, 3, 4, 6, 9, 12 h)*	Predose (-2 h), 0.33, 0.67, 1, 2, 3, 4, 6, 9, 12, 24 hours post dose)	Day 4 (72 h)*
PK Samples for drug	None collected	Predose (-2 h), 0.33, 0.67, 1, 2, 3, 4, 6, 9, 12, 24 hours post dose)	None collected†

* Day -2 and Day 4 were 12- Lead ECGs (single) measurements while all other measurements were in triplicate

† No PK sample was collected at 72 h post dose

4.2.6.5 Baseline

Time-matched baselines were used in the study.

4.2.7 ECG Collection

Triplicate ECGs were obtained on day -1 and day 1 at the time points specified above. Triplicate ECGs were performed 1 to 2 minutes apart. Subjects rested in the supine position for at least 5 minutes before the ECG recording is started. The clinic's staff attempted to maintain the subject's resting state so that the subject has a stable heart rate before ECG recordings.

The ECGs were stored electronically and sent to a central laboratory for a manual assessment of rhythm, and RR, PR, QRS, QT, and corrected QT (QTc) intervals. The central ECG laboratory used in this study was

readers were blinded to subject identifiers, treatment, treatment sequence, and time of ECG. At the conclusion of the study, conducted a 2% quality assurance read and provided inter- and intra- variability for this study to the sponsor.

Safety twelve (12)-lead ECGs were collected at the time points specified in the flow chart (screening, day 4 in each period and at the final study evaluation). The investigator reviewed the initial ECGs on day -1 at least 4 to 6 times over the 24-hour period, before dose administration, and near the times of maximum observed concentration (tmax) of MOA-728 and moxifloxacin (immediately after the start of the infusion to approximately 4 hours after dose administration). The investigator was responsible for providing the overall interpretation of ECGs.

Reviewer's Comment: Waveforms submitted to the ECG warehouse were reviewed. ECG acquisition and interpretation appears acceptable.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

The study population consisted of 47 healthy men and 9 healthy women aged 20 to 48 years with normal baseline ECG and BMI between 19.87 and 29.76 kg/m^2. All 56 subjects completed the study and none were replaced.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the average of the tracings' change from baseline in QTcN for the MOA-728 treatment groups. For each dose of MOA-728, a 90% CI (equivalent to a one-sided 95% CI) for the baseline-adjusted difference in QTcN at each of the timepoints between the active treatment and placebo was computed (presented in Table 2).

Table 2: QTcN Interval Differences from Placebo in Change From Baseline for MOA-728 Treatments

Drug Name	Timepoint (hr)	N	QTcN Mean (msec)	QTcN 90% CI (msec)
MOA 0.30 mg/kg	0.33	56	-1.6	(-3.4, 0.3)
	0.67	56	-0.2	(-2.0, 1.7)
	1	56	-0.6	(-2.4, 1.3)
	2	56	-0.3	(-2.2, 1.6)
	3	56	-0.5	(-2.4, 1.3)
	4	56	-0.9	(-2.7, 1.0)
	6	56	-0.3	(-2.1, 1.6)
	9	56	-0.7	(-2.6, 1.1)
	12	56	-0.9	(-2.8, 0.9)
	24	56	-0.3	(-2.1, 1.6)
MOA 0.64 mg/kg	0.33	56	-3.2	(-5.0, -1.3)
	0.67	56	-0.2	(-2.1, 1.7)
	1	56	-0.5	(-2.4, 1.4)
	2	56	0.5	(-1.4, 2.4)
	3	56	-0.9	(-2.8, 0.9)
	4	56	-1.9	(-3.7, -0.0)
	6	56	0.1	(-1.8, 1.9)
	9	56	-0.1	(-2.0, 1.7)
	12	56	0.3	(-1.6, 2.2)
	24	56	0.4	(-1.4, 2.3)

Abbreviations: N= Number of subjects; MOA = MOA-728; QTcN = Linear study population correction.

(Source: Clinical Study Report: Study 3200L2-104-US; Table 9-1, page 45)

To evaluate assay sensitivity, a positive control (400 mg moxifloxacin) was compared to placebo using baseline-adjusted QTcN at timepoints near expected tmax. This was conducted by comparing the lower and upper bounds of the 90% CIs for the QTcN change from baseline difference compared to placebo with 0 ms. and 10 ms. for timepoints of 1, 2 and 3 hours postdose. It was pre-specified that the timepoint with the largest geometric mean plasma concentration would be considered the primary timepoint to assess assay sensitivity. This timepoint was 2 hours postdose.

Table 3: QTcN Interval Differences From Placebo in Change From Baseline for Moxifloxacin 400 mg at Pre-Specified Timepoints

Drug Name	Timepoint (hr)	N	QTcN Mean (msec)	QTcN 90% CI (msec)
MOXI 400 mg	1	56	7.9	(6.0, 9.7)
	2	56	9.2	(7.4, 11.1)
	3	56	8.3	(6.5, 10.2)

Abbreviations: N= Number of subjects; MOXI = Moxifloxacin; QTcN = Study population (linear regression) correction.

(Source: Clinical Study Report: Study 3200L2-104-US: Table 9-2, page 46)

Reviewer's comments: The sponsor proposed a statistical model which adjusts carryover effect, and results are similar to those without adjusting a carryover effect. This reviewer also examined the carryover effect and found out that the carryover effect is not real (see the details in the following statistical assessment section).

4.2.8.2.2 Categorical Analysis

A categorical analysis was done summarize QTc intervals of >450, >480 and >500 ms as well as QTc changes from time-matched baseline of ≥30 and ≥60 ms. All categorical summaries were based on the average of replicates within a time point.

No subjects had postdose QTcN intervals above 450 ms in any of the treatment groups. Categorical assessments using QT intervals, and QTc values based on Fridericia's correction and Bazett's correction were consistent with that using the QTcN intervals. The largest postdose QTcN interval change from baseline is summarized in Table 4. No subjects had QTcN interval changes from baseline of ≥ 30 ms after receiving placebo or either of the two MOA-728 doses, while 12.5% (7 out of 56) of the subjects had changes from baseline of ≥ 30 ms after receiving moxifloxacin.

Table 4: Categorical QT Change From Baseline Summary Using Study Population (Linear Regression) Correction

Endpoint	Drug Name	< 30 msec Number / Total (Percent)	≥ 30 msec Number / Total (Percent)	≥ 60 msec Number / Total (Percent)
QTcN Interval (msec)	MOA 0.30 mg/kg	56/56 (100.0%)	0/56 (0.0%)	0/56 (0.0%)
	MOA 0.64 mg/kg	56/56 (100.0%)	0/56 (0.0%)	0/56 (0.0%)
	MOXI 400 mg	49/56 (87.5%)	7/56 (12.5%)	0/56 (0.0%)
	Placebo	56/56 (100.0%)	0/56 (0.0%)	0/56 (0.0%)

Abbreviations: MOXI = Moxifloxacin; QTcN = Study population (linear regression) correction.

(Source: Clinical Study Report: Study 3200L2-104-US: Table 9-3, page 56)

4.2.8.2.3 Additional Analyses

The average change from baseline in QT interval corrected by Fridericia's formula was analyzed as a secondary endpoint. The QTcF interval analysis was similar to the QTcN interval analysis.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study. There were no discontinuations due to AEs Overall, 38 (67.9%) subjects experienced at least one TEAE during the study. All TEAEs were considered by the investigator as either mild or moderate. The most frequent TEAEs were Skin and Tissue Disorders (contact dermatitis, 11 subjects, 19.6%; papular

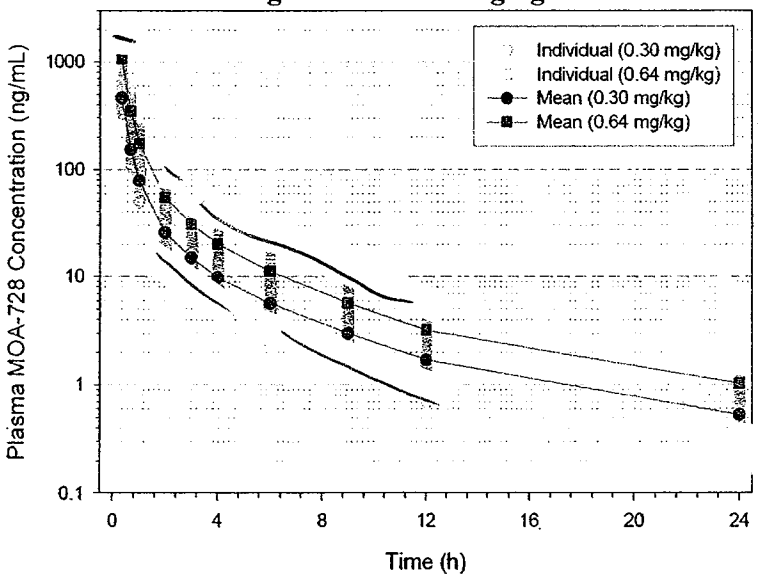
rash, 6 subjects, 10.7%). Other frequent TEAEs included headache (9 subjects, 16.1%) and nausea (6 subjects, 10.7%).
One subject experienced vasovagal syncope following venipuncture *prior* to receiving MOA 728 (0.64 mg/kg).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean plasma concentration-time profiles of methylnaltrexone after 20 min IV infusion at the two doses is shown in Figure 2. Summary statistics of the pharmacokinetics of methylnaltrexone at these two doses is provided in Table 5. The mean C_{max} and AUC_{∞} at supratherapeutic dose (0.64 mg/kg) were 2.3 and 2.2 fold respectively when compared to therapeutic dose (0.3 mg/kg). *(Refer to section 4.2.6.2 for comparison of exposures at the 0.3 and 0.64 mg/kg IV dose to therapeutic SC dose).*

Figure 2. Mean and individual methylnaltrexone plasma concentration profiles following 0.30 and 0.64 mg/kg IV infusion



(Source: Clinical Study Report: Study 3200L2-104-US: Figure 8-1, page 43)

Table 5. Summary statistics of methylnaltrexone's PK parameters following 0.3 and 0.64 mg/kg IV infusion (Values are expressed as median (min, max) or otherwise as mean ± SD (95% CI for mean))

Parameter	0.30 mg/kg (n=56)		0.64 mg/kg (n=56)	
C_{max} (ng/mL)	462 ± 82	(440 – 484)	1062 ± 258	(993 – 1131)
t_{max} (h)[a]	0.37	(0.35, 0.43)	0.37	(0.35, 0.68)
AUC_t (ng.h/mL)	335 ± 50	(322 – 349)	739 ± 139	(701 – 776)
AUC_∞ (ng.h/mL)	340 ± 52	(326 – 354)	748 ± 142	(711 – 786)
$t_{1/2}$ (h)	5.52 ± 0.86	(5.29 – 5.75)	5.61 ± 2.25	(5.01 – 6.22)
CL (mL/h/kg)	901 ± 125	(868 – 935)	885 ± 170	(840 – 931)
V_{SS} (mL/kg)	2054 ± 425	(1941–2168)	1951 ± 1048	(1670– 2231)

(Source: Clinical Study Report: Study 3200L2-104-US; Table 8-1, page 44)

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not perform exposure response analysis.

Reviewer's Comments: See reviewer's assessments for exposure response analysis (Section 5.2)

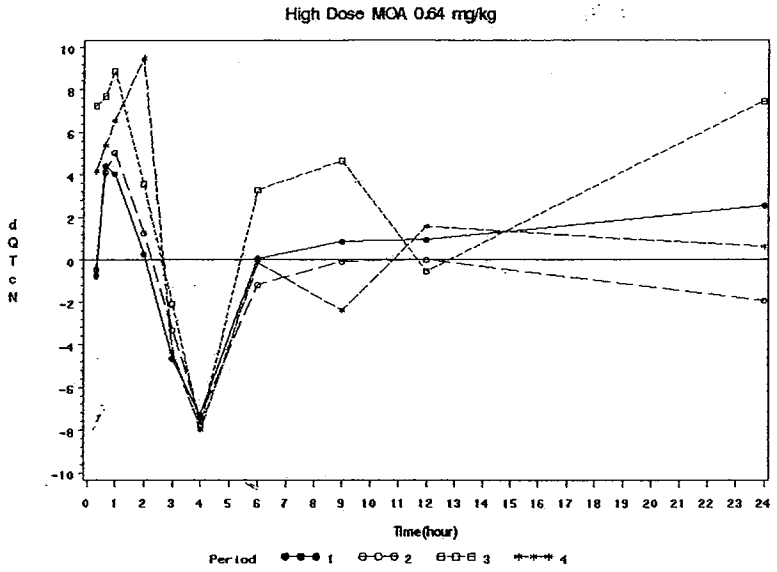
5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

This statistical reviewer performed an independent analysis based on the electronically submitted ECG data.

The carryover effect of the study was assessed by comparing the baseline corrected QTcN values from periods 2, 3, and 4 with those in period 1. We conclude that the carryover effect is not real. However, as demonstrated in the following figure, for the high dose treatment group MOA-728 0.64 mg/kg, baseline corrected QTcN values at multiple time points 0.33, 0.67, 1, 6, 9 and 24 hours in period 3, are higher than those in period 1, which makes the overall baseline corrected QTcN intervals statistically significant different for the high dose between period 3 and period 1. We do not believe this is the carryover effect. Based on the study design, at period 3, the high dose MOA-728 0.64 mg/kg was given after placebo. This difference could due to the variability of the study or the period effect subject to that subgroup administered the high dose of the study drug in period 3.

Figure 3: Time Course of Mean Changes from Baseline in ΔQTcN



Since there was a possibility of period effect on ECG data at period 3 for the high dose MOA-728 0.64 mg/kg, we conducted both analyses with and without period 3 data. The results by eliminating data in period 3 are very similar to those based on the full data set. For demonstration purpose, we only list the results based on the full data set.

As showed in Table 6, for both MOA-728 0.30 mg/kg and MOA 0.64 mg/kg groups, the upper bounds of the 2-sided 90% CIs are below 10 ms. This reviewer also performed the same analysis using QTcF and QTcI, and the results are very similar to those results using QTcN.

Table 6: Upper boundary of the one-sided 95% ANOVA model based CI for the placebo and baseline corrected values (delta delta analysis) of QTcN

Time post-dose (hrs)	Least Square Means			Treatment Difference		95% One-sided Upper Limit	
	MOA-728 0.30 mg/kg (n = 56)	MOA-728 0.64 mg/kg (n = 56)	Placebo (n = 56)	MOA-728 0.30 mg/kg - Placebo	MOA-728 0.64 mg/kg - Placebo	MOA-728 0.30 mg/kg - Placebo	MOA-728 0.64 mg/kg - Placebo
0.33	3.6	2.6	4.9	-1.6	-3.6	0.6	-1.5
0.67	5.0	5.4	3.7	-0.5	-1.0	1.7	1.2
1	6.1	6.1	5.3	-0.2	-0.8	1.9	1.3
2	2.0	3.7	2.0	-1.3	-0.4	0.9	1.8
3	-3.3	-3.6	-3.4	-0.1	-1.4	2.1	0.8
4	-7.0	-7.6	-6.7	-1.1	-1.9	1.1	0.2
6	-0.5	0.5	-1.3	-0.5	-0.4	1.6	1.8
9	0.0	0.8	0.1	-1.6	-1.4	0.6	0.8
12	-0.7	0.5	-0.4	-0.5	-0.6	1.6	1.5
24	1.0	2.2	0.9	0.7	0.3	2.9	2.4

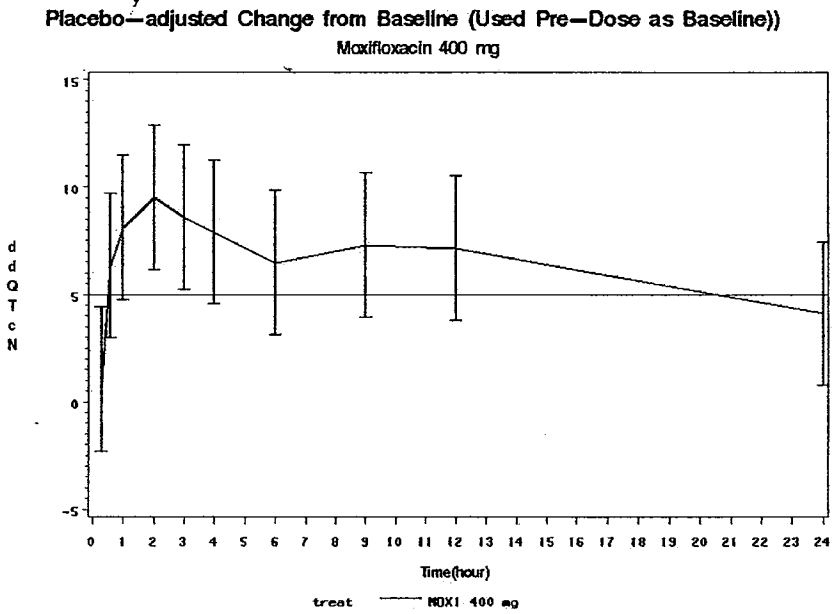
Table 7 summarizes the results of the mean difference between moxifloxacin and placebo in QTcN with multiple adjustments at pre-specified timepoints. With multiple endpoint

adjustment, the largest lower bound is 5.7 ms at 2 hour. Figure 4 presents the time-course of QTcN for moxifloxacin.

Table 7: Placebo-Adjusted, Mean QTcN Change From Baseline for Moxifloxacin 400 mg at Pre-Specified Timepoints

Timepoint (hr)	# of Obs	QTcN Mean (ms)	QTcN 90% CI (ms) Lower Bound	Upper Bound
1	56	8.2	4.6	11.9
2	56	9.4	5.7	13.0
3	56	8.9	5.3	12.5

Figure 4: Time Course of Mean Changes in ΔΔQTcN for Moxifloxacin



For categorical analysis, we confirmed that no subject had an absolute QTcN interval above 450 ms post treatment. There were one subject, 4 subjects, 2 subjects and 20 subjects who had an increase from baseline between 30 and 60 ms in MOA-728 0.30 mg/kg , MOA-728 0.64 mg/kg group, placebo and moxifloxacin groups, respectively. No subject had an increase in QTcN from baseline of more than 60 ms. Similar results were reached for QTcF.

Table 8: Frequency for Delta QTcN: 30~60 ms.

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
MOA-728 0.30 mg/kg	56	1	1.8%	1,680	2	0.1%
MOA-728 0.64 mg/kg	56	4	7.1%	1,680	6	0.4%
Placebo	56	2	3.6%	1,680	2	0.1%
Moxifloxacin 400 mg	56	20	35.7%	1,680	40	2.4%

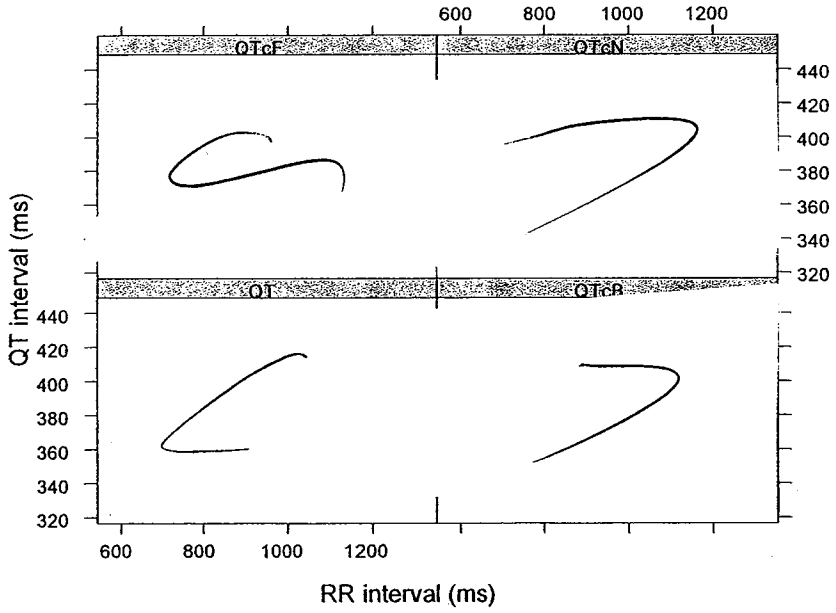
Reviewer's conclusions:

- Using pre-dose as a baseline, the upper bounds of the 2-sided 90% CIs in QTcN between both dose of MOA (0.30 mg/kg and 0.64 mg/kg) and placebo in change from baseline-and placebo-corrected at each extracted time point were less than 10 ms, thus satisfying the criteria for a negative thorough QT/QTc study.
- Assay sensitivity of the study has been established.
- For all treatments, no subjects developed a QTcN greater than 480 ms or a change from baseline QTcN greater than 60 ms.

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between QT and RR using two different correction methods is illustrated in Figure 5. The Fridericia's correction method was found to be reasonable for further analysis.

Figure 5. QT (Raw QT measurements, Bazzet's and Fridericia's corrected QT)-RR interval relationship



The time course of mean ΔΔQTcF for therapeutic (0.3 mg/kg), supratherapeutic (0.64 mg/kg), and moxifloxacin (400 mg) is illustrated in Figure 6 and Figure 7. It is evident that there is no dose dependency on QTcF and neither of the studied doses prolongs the QT interval. The mean (Upper CI) effect at mean C_{max} (1061.6 ng/ml) after supratherapeutic dose is 3.2 ms (5.44).