

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-964

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

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-964

REVIEWER: Insook Kim, Ph.D.

E. Dennis Bashaw, Pharm.D.

GENERIC NAME: Methyl-Naltrexone

OCPB DIVISION: DCP-3

TRADE NAME: RELISTOR

CLINICAL DIVISION: Division of

Gastroenterology and In-born Errors of
Metabolism

FORMULATIONS: SC Injection

APPLICANT: Progenics Laboratories

SUBMISSION DATES: Orig 3/30/2007

Amend:| 5/17/07 | 8/3/07 | 8/17/07 | 8/28/07 |
9/7/07 | 9/28/07 | 10/17/07 |11/5/07 | 11/6/07 |
11/8/07 | 11/30/07 | 12/7/07

Executive Summary

The sponsor is seeking an approval for methylnaltrexone (Relistor®, NDA 21-964). In December 2007, the general clinical pharmacology review closed with one outstanding issue regarding QT prolongation (see clinical pharmacology review DFS dated 12/12/2007). Briefly, in certain toxicology studies in dogs, MNTX was associated with QTc prolongation at doses that exceeded the highest proposed SC clinical dose. The question of QT prolongation potential could not be further addressed because a thorough QTc (TQT) clinical study of SC MNTX (MNTX 1106) conducted in humans was found to be deficient by the FDA IRT/QT team in a number of areas including the failure of the positive control arm to perform as expected in a number of areas. Thus the TQT study remained an unresolved issue at the time of general clinical pharmacology review closure.

Subsequently, it was agreed between the sponsor and the Agency to incorporate the results of an IV MNTX study (sponsored by their development partner Wyeth under IND 64583) into this NDA as a major amendment to address this issue. The amendment 0014 was submitted with the QTc clinical study report and summary (3200L2-104 US) on December 7, 2007 and resulted in a 90 day clock extension in the PDFUA date for the application.

The FDA IRT/QT team has reviewed the study report and concluded that there was no significant effect of methylnaltrexone on QT prolongation detected in the study (see the following excerpt from the IRT/QT team review, the IRT/QT review has been placed in DFS).

Excerpt from the IRT/QT team review for the new TQT study report conducted at 0.3 mg/kg and 0.64 mg/kg IV MNTX.

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)	$\Delta\Delta\text{QTcN}$ (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.

Conclusion and Recommendation

With the successful closure of the QT issue by the FDA IRT/QT team, there are no outstanding issues from a clinical pharmacology standpoint for this NDA.

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

/s/

Insook Kim
3/11/2008 02:50:28 PM
BIOPHARMACEUTICS

Dennis Bashaw
3/11/2008 02:59:45 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-964

REVIEWER: Insook Kim, Ph.D.
E. Dennis Bashaw, Pharm.D.

GENERIC NAME: Methyl-Naltrexone
TRADE NAME: RELISTOR

OCBP DIVISION: DCP-3
CLINICAL DIVISION: Division of
Gastroenterology and In-born Errors of
Metabolism

FORMULATIONS: SC Injection

APPLICANT: Progenics Laboratories

SUBMISSION DATES: Orig 3/30/2007 Amend:| 5/17/07 | 8/3/07 | 8/17/07 | 8/28/07 |
9/7/07 | 9/28/07 | 10/17/07 |11/5/07 | 11/6/07 |
11/8/07 | 11/30/07 | 12/7/07

DRAFT REVIEW: 12/3/2007

REVIEW for DFS: 12/12/2007

TABLE OF CONTENTS:

1. Executive Summary	
1.1 Recommendation	1
1.2 Phase 4 Commitments	2
1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings	2
2. Question Based Review	
2.1 General Attributes	5
2.2 General Clinical Pharmacology	7
2.3 Intrinsic Factors (sex, race, age, renal and hepatic impairment)	21
2.4 Extrinsic Factors (drug interactions).	27
2.5 General Biopharmaceutics	29
2.6. Analytical Section	29
3. Clinical Pharmacology Labeling Recommendations	32
Appendices	
1. Individual Study Reviews	34
2. Original Proposed Labeling	78

1. Executive Summary

1.1 Recommendation

At this time (Dec. 2007) the clinical pharmacology studies submitted in support of this NDA are incomplete as the required TQT (thorough QT study) is un-evaluable due to methodological difficulties related to the failure of the positive control to produce the necessary QT prolongation for comparison (*see Summary of Clinical Pharmacology Findings*). In communications with the Agency in Nov. 2007 the sponsor committed to providing the results of a TQT study with the IV formulation to support the approval of the SC product in this NDA on an accelerated timeline:

- November 30th Submission of summary cardiology report containing final QTc results and conclusions and SAS datasets for ECG

- December 7 Submission of full clinical study report for study 104, including PK and other safety information, in addition to the QTc results by or before.
- December 11 Submission (approximately of individual waveforms sent/uploaded to the data warehouse by, if necessary).

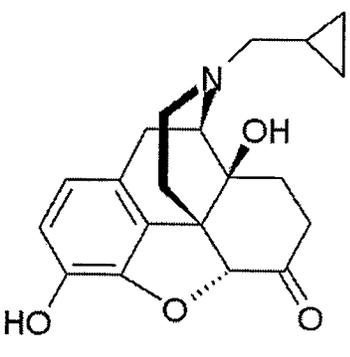
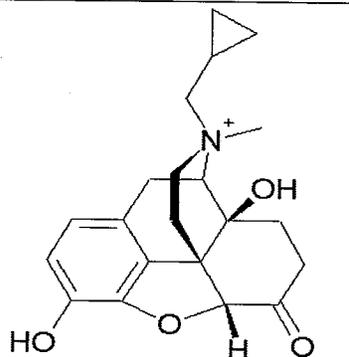
As this would result in a major amendment to the NDA, with the attendant 90 day clock extension, a decision was made to close out all pending reviews and in the case of Clinical Pharmacology issue a second review that would capture the new TQT study with regards to its affect on the safety calculus. As such it is the recommendation of the Clinical Pharmacology Review Team that this issue should be addressed prior to full approval for this drug. Otherwise, from a clinical pharmacology stand point, the sponsor has adequately addressed the requirements of 21 CFR 320. Final labeling negotiations will be deferred until the new TQT study has been reviewed.

1.2 Phase 4 Commitments

None at this time.

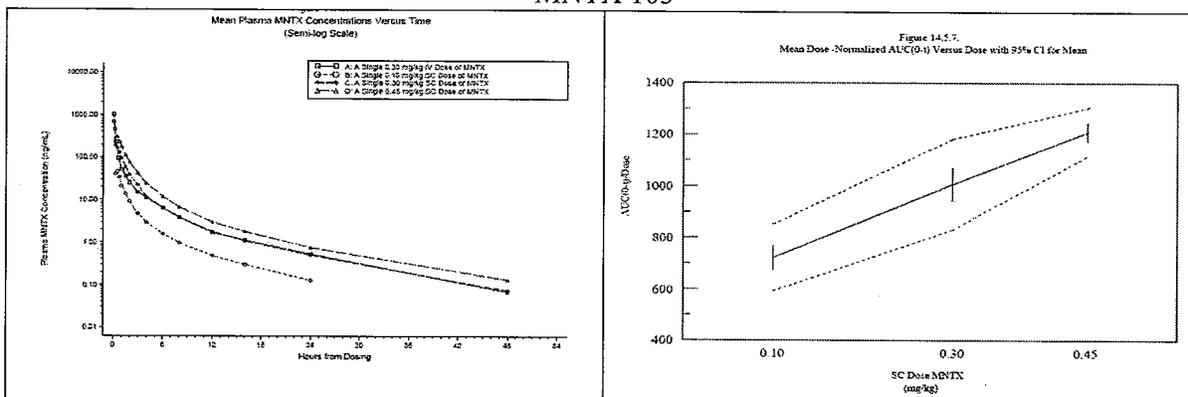
1.3 Summary of Clinical Pharmacology Findings

Palliative administration of opioid medication is widely regarded as a primary approach for the treatment of pain associated with serious medical illness, such as cancer and AIDS. Chronic opioid use may be complicated by a number of adverse effects, including constipation. The laxatives that are currently available to patients with advanced illness (that is, patients with life expectancies of less than six months) receiving palliative opioid treatment have many disadvantages in this population. The onset of effect is variable and will also depend on the type of laxative and the dose. Methylnaltrexone bromide (MNTX), a selective μ -opioid receptor antagonist, is a quaternary derivative of the opioid antagonist, naltrexone.

Naltrexone	Methyl-Naltrexone
17-(cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one	17-(Cyclopropylmethyl)-17-methyl-4,5-epoxy-3,14-dihydroxymorphinanium-6-one
	

The addition of a methyl group at the ring nitrogen forms a quaternary amine and the permanent positive charge provides the compound with greater polarity and lower lipid solubility. These

MNTX 103



This finding was generally confirmed in study MNTX1106 (the TQT study) where dose proportionality was demonstrated in 119 subjects receiving SC doses of 0.15, 0.3, or 0.5mg/kg in a parallel fashion (see section 2.2.5).

	0.30 mg/kg IV	0.10 mg/kg SC	0.30 mg/kg SC	0.45 mg/kg SC
	Mean (SD)			
C_{max} (ng/mL)	1006 (190)	47.5 (12.3)	197.0 (47.0)	317.0 (82.0)
AUC_t (ng/mL)*h	378.6 (52.3)	72.1 (10.4)	301.9 (42.5)	544.0 (33.9)
AUC_∞ (ng/mL*h)	379.8 (52.9)	73.3 (10.6)	303.2 (43.14)	545.7 (34.6)
t_{max} (h)	0.06 (0.01)	0.45 (0.21)	0.30 (0.11)	0.45 (0.11)
t_{1/2} (h)	7.81 (1.17)	6.14 (0.88)	8.04 (1.67)	8.83 (0.85)
Cl (L/h/kg)	0.80 (0.11)	-	-	-
Cl/F (L/h/kg)	-	1.39 (0.21)	1.00 (0.14)	0.83 (0.05)
V (L/kg)	9.05 (1.81)	-	-	-
V/F (L/kg)	-	12.3 (2.1)	11.7 (2.9)	10.5 (1.1)
F	-	0.60 (0.07)	0.82 (0.08)	0.99 (0.14)
f_R (%)	43.5 (7.1)	25.6 (4.0)	24.3 (4.2)	50.5 (4.1)
Cl_R (mL/min)	401.6 (88.6)	397.5 (84.0)	270.6 (44.8)	469.5 (59.3)

Data source: Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4

As can be seen in the data above, appearance of drug in the plasma is rapid with concentrations being detected in the plasma at 15min, with peak levels occurring at 30min, followed by a multi-compartmental elimination profile with an overall T_{1/2} in the range of 6-9hrs. A cross-study evaluation of the pharmacokinetic data from the NDA did not reveal any significant impact of either race or gender on the pharmacokinetics of MNTX. A similar examination was made on age, however, the data in this NDA was collected in a healthy adult population with only 1 subject older than 60, so no conclusions with regards to age effects in the elderly can be drawn nor have there been any studies conducted in children to date with the SC formulation.

1.3.1.2 BE of Clinically Studied vs. To-Be-Marketed

All of the clinical pharmacology studies except for MNTX-3200KI-103, were conducted with the original formulation. This study (3200KI-103) was an open-label, single-dose, randomized, 2-period crossover, bioequivalence study between the clinically studied and to-be-marketed formulations in normal subjects. This study was conducted against the advice of the FDA clinical pharmacology reviewer at that time as under both the regulations and SUPAC principles neither of the changes being made could be considered as changes that would result in an alteration of absorption for a SC administered product. The results of this trial are more completely discussed in the appendix, however, the tabular results of this trial are reproduced in the following table:

As one would expect, given the minor formulation changes (see section 2.1.1 below), the variability seen was minimal and the plasma level concentration profiles (as shown in the appendix) essentially lie on top of each other. On the basis of the observed results the two formulations can be considered equivalent.

Formulation	C _{max} (ng/mL)	AUC _t (ng·h/mL)	AUC _∞ (ng·h/mL)	t _{1/2} (h)	t _{max} (h)
Current					
Mean ± SD (Min, Max)	119 ± 33 (62.6, 197)	221 ± 36 (163, 333)	223 ± 36 (168, 335)	9.2 ± 2.5 (7.0, 19.4)	0.41 (0.08, 1.0)
New					
Mean ± SD (Min, Max)	127 ± 34 (82.9, 188)	218 ± 37 (165, 333)	220 ± 37 (172, 335)	8.4 ± 1.4 (6.4, 13.8)	0.34 (0.08, 1.0)
Ratios of geometric LS means and 90% confidence intervals ^a					
Ratio of geometric LS Means	107%	98.6%	98.4%	-	-
90% Log- transformed CI	98.1 – 117%	96.2 – 101%	95.9 – 101%	-	-

1.3.2 Special population (Renal and Hepatic Insufficiency)

The effects of renal impairment on the pharmacokinetics of MNTX were evaluated in subjects with mild, moderate and severe renal impairment (see section 2.3 Intrinsic Factors). Total exposure (AUC_∞) increased as a function of the renal impairment, and was approximately doubled in the severe renal impairment group (89% increase) while mean C_{max} was varied among groups. As such the cumulative quantity excreted unchanged (F_R (%)) declined from 45.2% in the normal subjects to 10.3% in the subjects with severe renal impairment. In that situation the sponsor is recommending a halving of the dose. For mild and moderate renal insufficiency no dose reduction is being recommended by the sponsor based on both the lack of a dose response and the demonstrated safety of the compound in the clinical studies. On the other hand, the mild and moderate hepatic impairment resulted in only modest changes in the pharmacokinetics of MNTX. As such no dose adjustment is recommended for patients with hepatic insufficiency.

1.3.3. Drug-drug interaction

Based on in vitro testing (see section 2.4.2) MNTX was identified as a potential inhibitor of CYP2D6 with an IC₅₀ value of 15.92 µM. In order to evaluate this further the sponsor conducted a study of the effect of a single SC dose or five IV doses of MNTX on CYP2D6 activity. This study included paroxetine as a positive control and used changes in the urine dextromethorphan/free dextrophan ratio as the endpoint. Compared to baseline values, the mean change in dextromethorphan/free dextrophan urinary ratio was not statistically significant when the MNTX-treated groups were compared to placebo (p>0.8402), but were highly significant when the paroxetine group was compared to placebo (p =0.0107). The observed change in urinary metabolic ratio are not suggestive of an effect of MNTX on CYP2D6,

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physico-chemical properties of methyl-naltrexone and the final to-be-marketed product

The proposed commercial formulation of Methyl-naltrexone Bromide Injection, 20 mg/mL, consists of 20 mg/mL MNTX, — mg/mL edetate calcium disodium (CaEDTA), \ mg/mL glycine hydrochloride and # mg/mL sodium chloride in water for injection.

Phase 1-3 clinical studies evaluated refrigerated formulations of 2-40 mg/mL MNTX in saline solution. Phase 3 clinical trials were conducted on a 20 mg/mL and a 40 mg/mL subcutaneously administered formulation of MNTX in saline solution.

The clinical formulation had three main MNTX degradation products:

The re-formulated product is stable at room temperature storage conditions. An overfill of / mL (total fill volume, / mL) is included in the vials to allow delivery of 0.6 mL with a syringe. The drug product vial is intended for single-use only, and therefore a preservative was not considered for evaluation in formulation development. A summary of formulations used in clinical development is provided below:

Formulation Comparison-Phase 3 Clinical Trials (Commercial) Formulation of MNTX

Component	Refrigerated (Phase 3)	Room Temperature
Vial glass	Apiber	Clear
Stopper		
Methyl-naltrexone bromide	20 mg/mL	20 mg/mL
CaEDTA	Not used	mg/mL
Glycine HCl	Not used	ng/mL
NaCl	7 mg/mL	ng/mL
pH	3.5 - 7.0	3.0 - 5.0
Fill volume		
Maximum volume of injection	1.0 mL	0.6 mL

2.1.2 What is the proposed mechanism of action of methyl-naltrexone

As a locally acting opiate antagonist, MNTX works at the level of the peripheral opiate receptors found throughout the GI tract. By antagonizing the effect of opiates at these peripheral sites GI motility can be increased resulting in improved bowel function and alleviation of opiate induced constipation associated with the use of opiates in palliative care.

2.1.3 What is the proposed indication?

The proposed indication is for the treatment of opioid-induced constipation in patients receiving palliative care. In this setting palliative care is defined as a life expectancy of six months or less.

2.1.4 What are the proposed dosing regimens for methyl-naltrexone?

The proposed dose of MNTX SC is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb).

Patient Weight		Injection Volume	Dose	Dose mg/kg (low range)*	Dose mg/kg (high range)*
Pounds	Kilograms				
84 to less than 136	38 to less than 62	0.4 mL	8 mg	0.21	0.129
136 to 251	62 to 114	0.6 mL	12 mg	0.19	0.105

*range based on the the proposed extremes of patient body weight

Patients whose weight falls outside of the ranges in the table should be dosed at 0.15 mg/kg. The injection volume for these patients should be calculated using one of the following:

- Multiply the patient weight in pounds by 0.0034 and round the volume to the nearest 0.1 mL
- Multiply the patient weight in kilograms by 0.0075 and round the volume to the nearest 0.1 mL

The dosing strategy as proposed by the sponsor is thus somewhat variable. For example, a patient who upon admission to hospice weighs 63kg would receive under this dosing strategy a dose of 0.19mg/kg. A week later, their weight could fall to 60kg, now they would receive 0.133mg/kg, a dosage change of ~30% ($0.0545/0.19 * 100$) for a less than 5% change in body weight. The clinical studies were done with a dosage regimen that was primarily based on straight mg/kg and not fixed doses (see section 2.2.1). Even so, the drug has been shown to safe in clinical studies in the target patient population and lacking evidence of a dose response for either safety or efficacy, there is no apparent justification to strict dosing control (ie mg/kg vs. fixed doses) thus, the proposed dosing regimen appears acceptable.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the sponsor is recommending a dose reduction by one-half, (see section 2.3.2.5).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

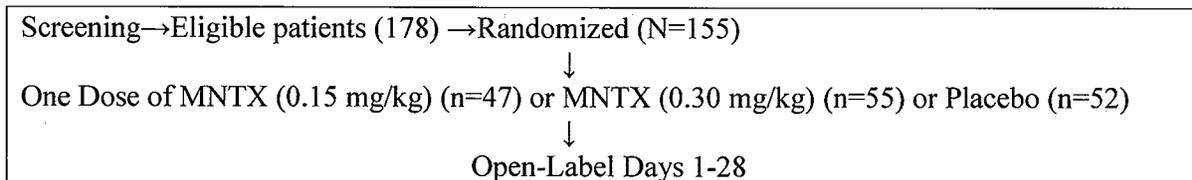
The efficacy of SC MNTX was evaluated in two double-blind, randomized, placebo-controlled phase 3 studies (MNTX 302 and MNTX 301) and one double-blind, randomized, dose-ranging phase 2 study (MNTX 251). These represent all of the studies conducted by the Sponsor to evaluate the efficacy of SC MNTX in the treatment of patients with advanced illness who were receiving both palliative opioid therapy for pain associated with their illness and background laxative regimens for opioid-induced constipation. The doses used ranged from 0.02 mg/kg to 0.3 mg/kg as a single dose once-daily.

The important differences in the above studies are:

- The duration of double-blind treatment was one day (one dose) in MNTX 301, two weeks (seven doses) in MNTX 302 and one week (three doses) in MNTX 251.
- The duration of open-label treatment following completion of the double-blind period was three weeks in MNTX 251, three months in MNTX 302/302EXT, and four months in MNTX 301/301EXT. Although the primary goal of long-term treatment was to evaluate safety, efficacy was also assessed.
- MNTX 251 was a dose-ranging study that included a subtherapeutic MNTX dose (1 mg) but not a placebo group.

As an example of the design and clinical response of MNTX in these patients, the results of Study MNTX 301 are briefly covered below and in the following section, as excerpted from Dr. Orleans (Medical Officer) efficacy review:

Study Design MNTX 301



Patient Demographics for Study MTNX 301

Characteristics	Category	Placebo (N=52)	MNTX 0.15 (N=47)	MNTX 0.30 (N=55)
Age (years)	Mean	64.7	65.9	65.3
	Median	62.5	67.0	68.0
Sex (%)	Male	53.8	53.2	56.4
	Female	46.2	46.8	43.6
Race (%)	Caucasian	82.7	80.9	83.6
	Black	5.8	10.6	7.3
	Hispanic	9.6	6.4	7.3
	Asian	1.9	2.1	0
Weight (kg)	Mean	67.1	70.4	65.5
Primary Diagnosis (%)	Cancer	82.7	78.7	81.2

	Cardiovascular	3.8	8.5	5.2
	HIV/AIDS	0	2.1	0.6
	Other	13.5	10.6	13.0
Oral Morphine Equivalents (mg/day)	Mean	617.3	3289.8	1220.4
	Median	150.0	207.0	188.0
Current Pain Score (1-10)	Mean	3.2	3.2	3.1
Constipation Distress (%)	None	8.2	8.7	7.4
	Somewhat	20.4	19.6	24.1
	Very Much	16.3	26.1	20.4
Number of Laxatives Taken by Generic Term	Mean	2.1	1.9	2.0

2.2.2 What is the basis for selecting the response endpoints?

The response endpoints used varied by trial and trial design but were centered on laxation and included the following measures in study MNTX-301:

Primary Efficacy Endpoint:

Laxation response within 4 hours of double-blind dosing with study drug. The proportion of patients with positive laxation response was the basis for point estimates of efficacy for each treatment group.

Laxation Response by Treatment Group after 4 Hours MNTX 301 Double-Blind

Time	Placebo (n=52)	0.15 mg/kg (n=47)	0.30 mg/kg (n=55)
Number of Patients with Rescue-Free Laxation Response within the Time Interval			
4 Hours	7 (13.5%)	29 (61.7%)	32 (58.2%)
P-Value [1]		<0.0001	<0.0001
Number of Patients with Laxation Response within the Time Interval (with or without Rescue)			
4 Hours	7 (13.5%)	30 (63.8%)	32 (58.2%)
P-Value [1]		<0.0001	<0.0001

[1] P-values are the nominal p-value in the pairwise comparison of each MNTX dose with placebo. Because of the interim analysis and comparison of each dose with placebo, p-values <0.0249 are considered statistically significant.

Secondary efficacy endpoints (Study MNTX 301):

- 1) Laxation response within 24 hours of treatment.
- 2) Changes in constipation distress scale.
- 3) Changes in bowel movement consistency.
- 4) Changes in bowel movement difficulty.
- 5) Changes in pain ratings.
- 6) Changes in opioid withdrawal symptoms (using a Modified Himmelsbach scale)
- 7) Global clinical impression of change (GCIC) ratings (patient and clinician).

While other endpoints were used, they are all related to laxation and bowel movement consistency. For most, if not all secondary endpoints there was a marked improvement in bowel function following dosing with MNTX.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, see Mass-Balance (section 2.2.5.5) and Analytical (section 2.6) for details on these issues.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Clinical dose-response relationships were explored using a theoretical approach supplemented with data from phase 3 clinical trials MNTX-251, MNTX-301, and MNTX-302 (For details, see **Clinical review on these studies**). It should be noted that no PK data was collected from patients and exposure data was estimated by the sponsor based on the linear relationships between AUC and dose established from MNTX1106. In study MNTX-251, fixed doses of 1, 5, 12.5 and 20 mg were administered to 6-10 patients at each dose and then converted to a weight-based dose based on one body weight of 60 kg *not based on the actual body weight of patients*. In addition, it should be noted that there was no placebo arm in study MNTX251.

The study MNTX-251 showed that dose-response relationship does not exist although 1 mg MNTX was less effective than doses greater than 5 mg such that 43% (3/7), 60% (6/10) and 33% (2/6) patients had laxation response within 4 h after a single dose of 5 mg, 12.5 mg, and 20 mg MNTX respectively, whereas 10% (1/10) patients at 1 mg MNTX dose had laxation response within 4 h (Table 1). Similarly in the study MNTX 301/302, there was no increase in efficacy with dose increase such that 62% (29/47) and 58% (32/55) of patients had laxation response following single dose of 0.15 mg/kg and 0.3 mg/kg MNXT, respectively while patients on placebo had 13% laxation response within 4 h. Doses less than 0.15 mg/kg were not studied in studies MNTX301/302 for efficacy and two doses 0.15 mg/kg and 0.3 mg/kg were studied in MNTX301 while in MNTX302 only one dose 0.15 mg/kg was studied (Table 2 and 3).

Table 1: Number of Patients (% with Laxation on Days 1, 3 and 5 of Total Remaining in Study MNTX-251 and No Prior Laxation Response) with Laxation Response after Four Hours on Dosing Days: Double-Blind Phase

Dosing Day	MNTX Dose Level (mg/kg conversion based on 60 kg body weight)				
	1 mg/0.02 mg/kg	5 mg/0.08 mg/kg	12.5 mg/0.2 mg/kg	20 mg/0.33 mg/kg	>5 mg/0.8 mg/kg Combined
Four-hour response					
1	1/10 (10%)	3/7 (43%)	6/10 (60%)	2/6 (33%)	11/23 (48%)
3	2/9 (22%)	4/6 (67%)	5/7 (71%)	2/4 (50%)	11/17 (65%)
5	0/7 (0%)	4/5 (80%)	4/7 (57%)	3/4 (75%)	11/16 (69%)

Table 2: Laxation Response within Four Hours of Single Double-Blind Dose of MNTX SC

Dose group	Rescue-Free Laxation Within Four Hours of Dosing		Total	P-Value (vs. placebo)
	No	Yes		
Placebo	45 87%	7 13%	52	
0.15 mg/kg	18 38%	29 62%	47	<0.0001
0.30 mg/kg	23 42%	32 58%	55	<0.0001
Total	86	68	154	

Table 3: Laxation Response Within Four Hours of the First Double-Blind Dose of Placebo and MNTX SC

	Placebo (71)			MNTX (62)			P-Value ^a
	Patients Dosed	Patients with Laxation Response	Percentage of Responders (95% CI)	Patients Dosed	Patients with Laxation Response	Percentage of Responders (95% CI)	
Laxation within 4 hours on Day 1	71	11	15.5 (7.1 - 23.9)	62	30	48.4 (35.9 - 60.8)	p<0.0001
At least 2 Laxations within 4 hours over the first 4 doses	71	6	8.5 (2.0 - 14.9)	62	32	51.6 (39.2 - 64.1)	p<0.0001

^a A Double-Blind, Phase 3, Two-Week, Placebo Controlled Study of Methylnaltrexone Bromide (MNTX) for the Relief of Constipation Due to Opioid Therapy in Advanced Medical Illness, Progenics Study MNTX 302 (11).

The sponsor provided dose-response relationship based on the combined efficacy data in MNTX 251 and MNTX301/302 in the following table:

Table 5: Observed Efficacy (Patients Response to Laxation Within Four Hours [%]) at Various First Double-Blind MNTX Doses Administered in Studies MNTX-251, MNTX-301, and MNTX-302 Compared with Peak (C_{max}) and Total (AUC₂₄) Exposures Simulated for Each Dose.

MNTX Study	N	First Double Blind Dose (mg/kg)	C _{max} ^b (mg/mL)	AUC ₂₄ ^b (mg/mL*hr)	Patient Response Laxation Within Four Hours (%)
301/302	123	Placebo	0	0	15
251 ^a	10	0.02	16	23	10
251	7	0.08	63	94	43
301/302	110	0.15	118	176	54
251	10	0.20	157	235	60
301	55	0.30	236	352	58
251	6	0.33	260	388	33

^a There was no placebo arm in MNTX-251.

^b Estimated using data from MNTX-1106.

It is inadequate to combine study results especially when MNTX251 did not have a placebo arm and the number of subjects at each treatment arm was largely unbalanced between studies. Therefore, there are only two doses studied for dose-response relationship and no further increase in response rate was observed at tested high dose, 0.3 mg/kg. Of note, Cmax may possibly be correlated with the efficacy. The Cmax is achieved approximately at 0.5-0.45 h and it appears to correspond to the median time to laxation response following MNTX dosing, which ranged 0.42 to 0.73 h regardless of number of doses in study MNTX 302EXT (Table 5).

Table 5. The Median time to rescue-free laxation response from MNTX 302EXT (copied from the submission)

Table 11: Median time to rescue-free laxation response (analysis set: safety)

Dose	Number of Patients with Laxation Response ^a	Median Time to Laxation (hours)	Range (Hours)
1	37	0.60	0.0-2.9
2	32	0.43	0.0-2.2
3	31	0.42	0.0-4.0
4	30	0.54	0.0-4.0
5	30	0.48	0.0-2.5
6	27	0.52	0.0-3.5
7	21	0.42	0.0-4.0
8	20	0.50	0.0-3.0
9	21	0.50	0.0-2.3
10	20	0.63	0.1-3.3
11	23	0.58	0.0-4.0
12	18	0.54	0.0-3.8
13	23	0.50	0.0-4.0
14	17	0.50	0.0-3.0
15	18	0.48	0.0-1.5
16-29	21	0.73	0.0-2.2
30+	8	0.71	0.4-1.6

Reference: Section 14.2, Table 14.2.2.1 and Section 16.2, Listing 16.2.6.1

^a Laxation response=rescue-free laxation within 4 hours after the dose.

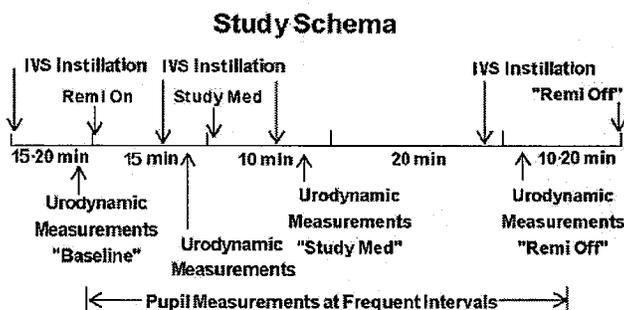
2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

At this time the overall safety evaluation of the clinical data is still underway. One of the concerns associated with this product is the potential for the MNTX to cross the blood-brain-barrier and cause central opiate blocking, an effect that would negate therapeutic pain control. To evaluate the potential of MNTX to enter the CNS, the sponsor has conducted a urodynamic study that also incorporated tests of pupillary response as a marker for any central opioid blocking effect. From a dynamic point of view the study was designed to test the hypothesis that a significant proportion of opioid-induced changes in bladder function, (measurable as detrusor pressure [Pdet] or maximal force of bladder contraction), are due to activation of peripheral opioid receptors and can be reversed by MNTX.

This was designed as a single-center, double-blind, randomized, placebo and active comparator-controlled phase 1 pilot study of the urodynamic effects of the opioid antagonists MNTX and naloxone in healthy male volunteers who had received a short acting opioid, remifentanyl (REMI). It should be noted that this study *was not done* with the to-be-marketed subcutaneous formulation, but with the IV formulation

It is included in this NDA package as part of the demonstration, on a mechanistic basis, of the relative selectivity of MNTX for peripheral opiate receptors as outlined above.

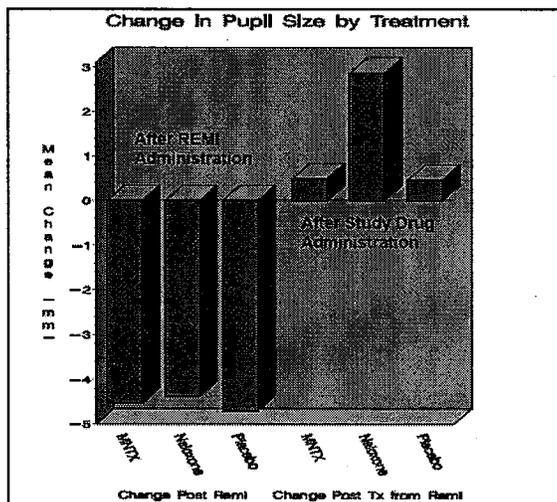
Figure 1: Schema of timepoints for urodynamic (P_{det}) measurements



The urodynamic effects component of this study is contained in the ISR for study MNTX 206 in the appendix.

Pupillary Effects

Eye pupil size reversal was defined as a change 10 minutes post-study drug. Across all subjects, REMI administration caused a mean pupillary constriction of 4 to 5 mm. Following administration of study drug 30 to 60 minutes post-baseline, all subjects receiving naloxone (100%) showed an increase in pupil size, while subjects receiving MNTX and placebo showed no significant increase, suggesting that MNTX did not cross into the CNS and thus was unable to reverse the REMI induced effects. By 160 minutes, all three groups showed pupil size returned to baseline levels



Infusion of the μ -type opioid, REMI, produced ocular miosis in 21 of 21 sessions (100%), and urinary retention in 18 of 25 sessions (72%). While the pure opioid antagonist naloxone successfully reversed all opioid-induced miosis in all sessions, neither placebo nor MNTX had any significant effect on miosis, demonstrating that MNTX does not cross into the CNS in any appreciable amounts.

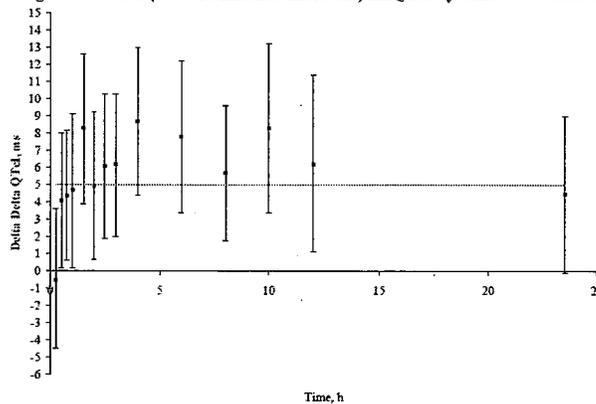
2.2.4.3 Does this drug prolong the QT or QTc interval?

In certain toxicology studies in dogs, MNTX was associated with QTc prolongation at doses that exceeded the highest proposed SC clinical dose. According to the sponsor, several nonclinical cardiovascular safety pharmacology studies showed a mild lengthening of the QTc interval (QT interval corrected for heart rate). Additional changes affecting the cardiovascular organ system were observed in hemodynamic and repeat dose toxicity studies of MNTX. Histopathological examinations in rats and dogs in repeated-dose toxicity studies found signs of altered circulatory function. Per the sponsor, no changes were seen upon histopathological examination of the heart and there were no effects on ionic channel current or action potential duration in cardiac-related tissues. Studies of MNTX in models of cardiac function that test mechanisms associated with torsades de pointes and QT prolongations were also negative. Potassium current through hERG channels was not affected by MNTX exposure in two studies, yet low concentrations of the positive-control substances cisapride and terfenadine produced strong reductions in current.

A thorough QTc (TQT) clinical study of SC MNTX was conducted (MNTX 1106), however, upon evaluation by the FDA IRT/QT team the study was found to be deficient in a number of areas, but most importantly in the failure of the positive control arm to perform as expected in a number of areas:

- 1.) The positive control, a single oral dose of 400 mg moxifloxacin, failed to have the expected effect on the QTc; at no time was the mean effect on the QTc greater than 5 ms as evidenced by a lower 90% confidence interval ≥ 5 ms. Therefore, the study lacked assay sensitivity, i.e. the ability to detect a mean effect of methylnaltrexone on the QTc of about 5 ms had it been present.

Figure 1: Mean (90% Confidence Intervals) $\Delta\Delta$ QTcI by Time for Moxifloxacin



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

3.) The confidence intervals for the placebo corrected mean change in QTc of moxifloxacin and MNTX are wide and overlapping indicating large variability in the study. This large variability may be due in part to the use of a parallel group design instead of a crossover design, which limits variability by using each subject as their own control.

In addition to the issues related to the positive control arm, both an unusually large number of subjects had an increase from baseline in QTc between 30 and 60 ms (over 50% among all the treatment groups) and several subjects had un-interpretable ECGs due to “technical problems,” which also suggests problems in the overall conduct of the study.

At this time the conclusion of the IRT/QT team is that the study is un-interpretable for these reasons which raise the question of risk-benefit to the patient population. This issue is at the time of this review (Nov. 2007) an outstanding issue. The Agency is having discussions with the sponsor about the feasibility of the incorporating of the results of an on-going IV MNTX study (sponsored by their development partner Wyeth under IND ~~_____~~), into this NDA as a major amendment to address this issue. This study is a multi-arm 4 way crossover study that represents a more powerful study design than the one utilized in this NDA. The Agency is expecting final submission of the ECG datasets in mid Dec. Given the nature of the study, the size of the data, and its impact on labeling it is likely that this submission will be recorded as a major amendment, extending the clock 90 days from Jan 30th, to approximately the first week in May. A new TQT study review will be placed into DFS at that time that will hopefully address these issues.

2.2.5 Pharmacokinetic characteristics

2.2.5.1 What are the single dose and multiple dose PK parameters?

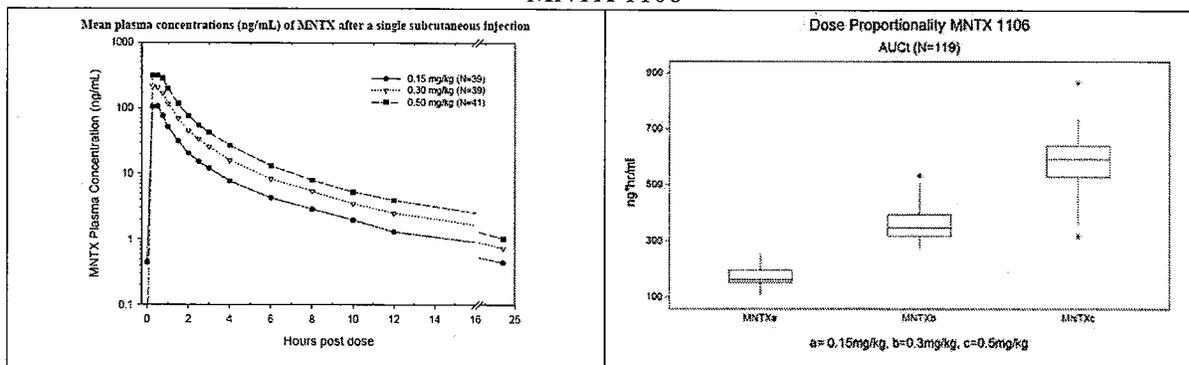
The following table summarizes the single dose pk data from the dose proportionality trial MNTX 103, and the MNTX arms of the TQT study MNTX 1106. While the validity of the QT portion of 1106 may be in question (see section 2.2.4.3) the pk data generated from this trial are generally in agreement with the values from the other studies and represents the largest single database in this NDA with 119 subjects data for the MNTX arm (representing almost ½ of the total pk data available).

Combined Summary Data Table MNTX 103 and 1106

STUDY	Objectives	Design/ Treatment Groups/N	C _{max} (ng/mL)	t _{max} (h)	AUC _t (ng•h/mL)	AUC _∞ (ng•h/mL)	t _{1/2} (h)	Cl or CLF (L/h/kg)	V or V/F (L/kg)	Comments
MNTX-103	PK in plasma and urine Absolute bioavailability	4-way crossover N = 6 males; 5 completed								F = 0.82 at 0.3 mg/kg
		0.10 mg/kg SC	47.5 (12.3)	0.45 (0.21)	72.1 (11)	73 (11)	6.14 (0.89)	1.39 (0.21)	12.3 (2.1)	
		0.30 mg/kg SC	197 (46.7)	0.30 (0.11)	302 (43)	303 (43)	8.04 (1.67)	1.00 (0.14)	11.7 (2.98)	
		0.45 mg/kg SC	317 (81.7)	0.45 (0.11)	544 (34)	546 (35)	8.83 (0.85)	0.83 (0.05)	10.5 (11.1)	
		0.30 mg/kg IV	1006 (190)		379 (52)	380 (53)	7.81 (1.17)	0.80 (0.11)	9.05 (1.81)	
MNTX-1106	QTc	Parallel N = 206 completed; 199 for QTc, 119 for PK								PK Linearity Established
		MNTX 0.15 mg/kg SC	117 (32.7)	0.50 (0.25-0.75)	175 (37)					
		MNTX 0.30 mg/kg SC	239 (62.2)	0.50 (0.25-0.75)	362 (63.8)					
		MNTX 0.50 mg/kg SC	392 (148)	0.50 (0.25-0.75)	582 (111.2)					

As noted in the introduction to the single dose pk data in section 1.3.1, study 1106, the data from this study was also used to demonstrate dose proportionality between the different doses of MNTX. In general the pharmacokinetics of MNTX are linear with a multi-phasic elimination phase with a half-life of approximately 8hrs as shown below:

MNTX 1106



However, it should always be understood that this data was generated in healthy adult subjects. In clinical practice, this drug will be used in a population that is both nutritionally depleted, been subject to both radiation and chemotherapy, and have altered disposition due to these therapies. The use of pk data to design dosage regimens for a patient population that is likely to be very heterogeneous in nature should be done with caution as the extrapolation from healthy subjects to subjects in an end-of-life setting is markedly different.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

As noted previously the clinical pharmacology studies were done in healthy adult subjects. No end-stage or palliative care patients were enrolled in the trial and based on ethical issues of quality of life (and the expected high pharmacokinetic variability in this population) it is highly unlikely that any studies will be done in this population.

2.2.5.3 What are the characteristics of drug absorption?

MTX is administered in this application as a SC injection; as such absorption is relatively rapid with peak levels occurring routinely in less than one half hour.

2.2.5.4 What are the characteristics of drug distribution?

Free MNTX is generally well distributed throughout the tissues with minimal protein binding (<20%). In study MNTX 102, following an IV dose 0.30 mg/kg (99.975 μ Ci) dose of 14 C-MNTX in six healthy adult male subjects the reported volume of distribution, expressed as V_{area} , was 7.92 ± 1.54 L/kg. By comparison following repeated IV infusions of 0.45mg/Kg in study MNTX-1108 the volume of distribution, expressed as V_{ss} , was 1.07 ± 0.21 L/kg.

2.2.5.5 Mass Balance Study

The sponsor conducted a mass balance study using an IV dose 0.30 mg/kg (99.975 μ Ci) dose of 14 C-MNTX in six healthy adult male subjects. Pharmacokinetic metrics for both unchanged MNTX and total radioactivity in plasma, and for total radioactivity in whole blood, were estimated following non-compartmental analysis of data. Mass balance was determined from total recovered radioactivity in urine, feces, and exhaled 14 CO₂. Identification and quantification of metabolites by LC/MS was undertaken, using selected urine and fecal samples. Metrics for unchanged MNTX in plasma and total radioactivity in plasma and in whole blood are given in the following table:

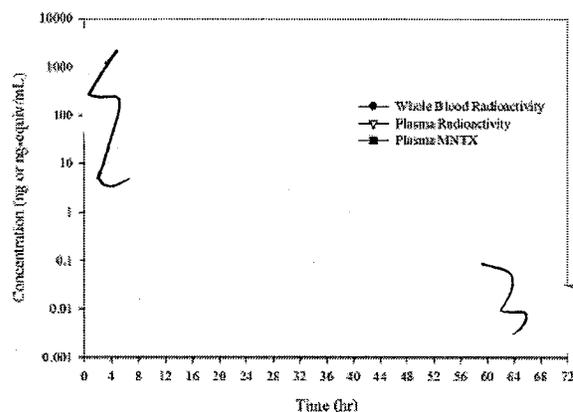
Summary of Mean (SD)^a Pharmacokinetic Metrics for MNTX and Total Radioactivity in Plasma and Whole Blood

Metric	Units	Plasma MNTX	Plasma 14 C	Blood 14 C
C_{max}	(ng/mL) ^c	1151 (305)	1183 (260)	646 (139)
t_{max}	(hr)	0.0500 (0.0500, 0.100)	0.0500 (0.0500, 0.100)	0.0500 (0.0500, 0.100)
AUC ₁₂	(ng·hr/mL) ^b	368 (44)	622 (47)	NA
AUC ₁	(ng·hr/mL) ^b	393 (52)	652 (84)	301 (31)
AUC _∞	(ng·hr/mL) ^c	394 (52)	748 (103)	392 (42)
% AUC _∞ Extrapolated	(%)	0.335 (0.119)	12.7 (1.8)	23.3 (2.1)
λ	(1/hr)	0.0822 (0.0179)	0.125 (0.041)	0.130 (0.027)
$t_{1/2}$	(hr)	8.89 (2.59)	6.15 (2.27)	5.51 (0.97)
V_{area}	(L/kg)	7.92 (1.54)	2.84 (0.68)	4.98 (0.83)
Cl	(mL/min/kg)	10.5 (1.5)	5.55 (0.81)	10.5 (1.2)
Cl _R	(mL/min/kg)	6.37 (3.00)	3.01 (0.54)	NA

^a Median (min, max) shown for t_{max}

^b Units for 14 C-MNTX are ng-equivalents rather than ng

After intravenous administration of MNTX, concentrations of both unchanged drug and total radioactivity in plasma and blood declined in a polyexponential manner, with a relatively rapid distribution phase followed by a slower terminal phase. In all subjects total radioactivity in both matrices declined to below the limit of quantification after 24 hours post dose. Concentrations of MNTX were still detectable in most subjects at 48 hours.



Concentration versus time profiles of MNTX and total radioactivity in plasma and whole blood

2.2.5.6 What are the characteristics of methyl-naltrexone metabolism?

Using the data collected as part of study MTNX 102, the mean plasma AUC₀₋₁₂ ratio of unchanged MNTX to total radioactivity was 0.59. Overall, approximately 50% of the recovered radio-label was present as unchanged MNTX.

Relative abundance of methyl-naltrexone metabolites in urine and feces

MNTX/Metabolite ^a	Percent of Dose		
	Urine 0-24 Hours Post dose	Feces 0-168 Hours Post dose	Total ^c
Mean (\pm SD) Radiodose Excreted	43.9 \pm 17.2	17.3 \pm 6.2	61.2
Methyl-naltrexone (MNTX)	37.1	11.4	48.5
M1 (Methyl-6-naltrexol Sulfate)	0.14	ND	0.14
M2 (Methyl-naltrexone Sulfate)	1.26	ND	1.26
M3 (Dihydroxy-methyl-6-naltrexol)	0.04	ND	0.04
M4 (Methyl-6-naltrexol Isomer)	4.25	0.83	5.08
M5 (Methyl-6-naltrexol Isomer)	0.74	0.24	0.98
Total ^b	43.5	12.5	56.0 ^c

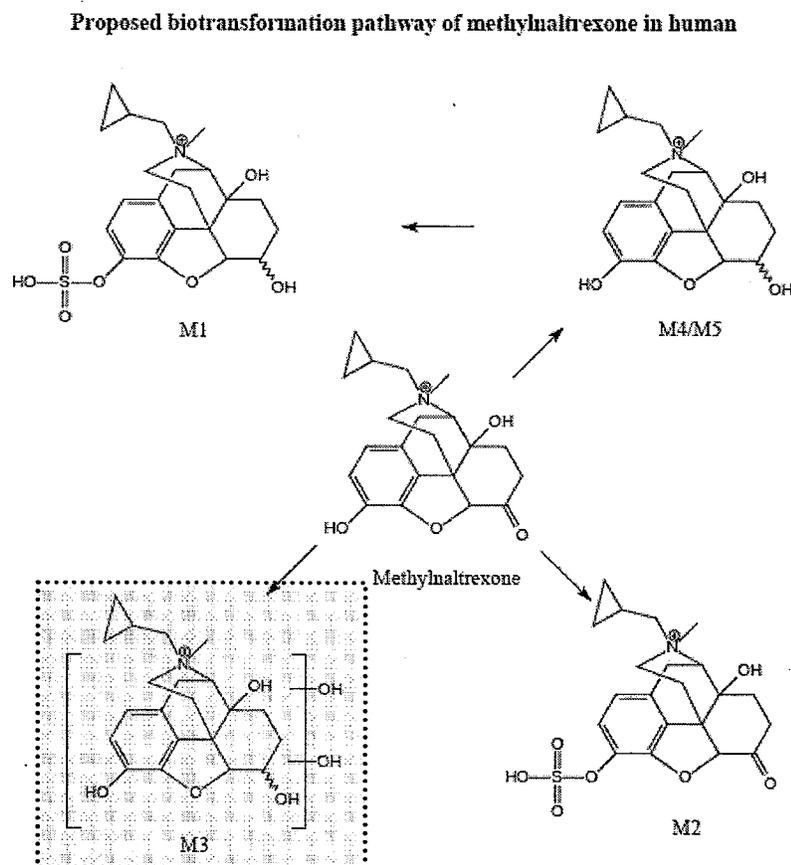
ND Not detected.

a Tentatively identified by LC/MS analysis.

b Recovered radiodose for 0-24 hour urine and selected feces samples over 0-96 hour post dose.

c Includes Subject 03 (incomplete collections)

Based on the results of study MNTX 102, the following metabolic scheme was proposed for MNTX.



MNTX is primarily eliminated in the urine as unchanged drug with lesser amounts of radioactivity being excreted into the feces. Approximately 60% of the administered radioactivity was recovered with 5 distinct metabolites being resolved, none of which being detected in amounts over 6% of total. Of the metabolites 1 of them (M3) was only detected in 1 subject and then a very low amounts only. Limitations of this study include the lack of complete recovery of the radioactivity and the potential impact of depletion of sub-cutaneous fat stores in end stage cancer/AIDS patients and its potential impact on SC absorption. This latter issue is not so much a limitation of the study itself but in the ethical issues of doing such a study.

2.2.5.7 What are the characteristics of methyl-naltrexone excretion?

The excretion profile of MNTX and metabolites in 0-24 h post-dose urine samples from the mass balance study was generally consistent across subjects and consisted primarily of unchanged methylnaltrexone (33.0%-53.3% of administered radioactivity), along with six low abundance metabolites. As noted above, the most abundant metabolites, 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.

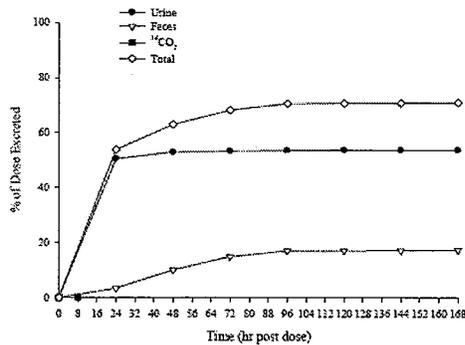


Figure 3: Mean Percent of Administered Radioactivity Excreted in Urine, Feces, and as ¹⁴C₂

Note: Subject 3 excluded from urine and total recovery due to incomplete urine collection.

Urine excretion profiles at later time points showed lower amounts of methyl-naltrexone relative to metabolites suggesting that the pharmacokinetics of the metabolites may differ from that of the parent drug.

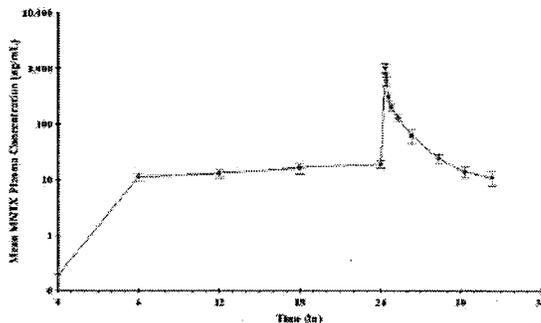
2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the methyl-naltrexone dose-concentration relationship?

As demonstrated previously in the section on single dose pk parameters MNTX has shown dose proportionality.

2.2.5.9 How do methyl-naltrexone pharmacokinetic parameters change with time following chronic dosing?

Unknown as at this time as chronic dosing has not been studied with the SC dosage form. In the Cyp2D6 mediated drug-drug interaction study (MNTX 1108) MNTX 0.45 mg/kg was administered IV as a 20-minute infusion every six hours for five doses. It resulted in an accumulation factor (R) of 1.19

Trough Concentrations (C_{55,min}) and the Profile Following Dose 5 (Mean ± SD)



It would be expected that SC dosing, having a somewhat lower relative bioavailability would have a lower accumulation factor, and simulations done by the sponsor suggest an R value of 1.07 or minimal accumulation, which is what would be expected based on the IV data.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers, and what are the major causes of variability.

In the largest single dose trial done (MNTX 1106) the inter-individual CVs associated with the data for AUC and Cmax were on the order of between 20-30%, with Cmax having CVs toward the higher estimate. Given the route of administration, these are not evidence of excessive variability. As for intra-individual, the majority of the studies are underpowered to provide a meaningful estimate of intra-individual CVs as, for example, the N in study MNTX 103 was six. As study MNTX 1106 was a parallel study, an estimate of intra-individual CV was not possible for MTNX. Again, as mentioned previously, given the target population, it is likely that the inter- and intra-subject variability seen in these subjects would exceed the variability seen here due to the differences inherent in this patient population.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure or response to methyl-naltrexone? What is the impact of these factors on exposure and response?

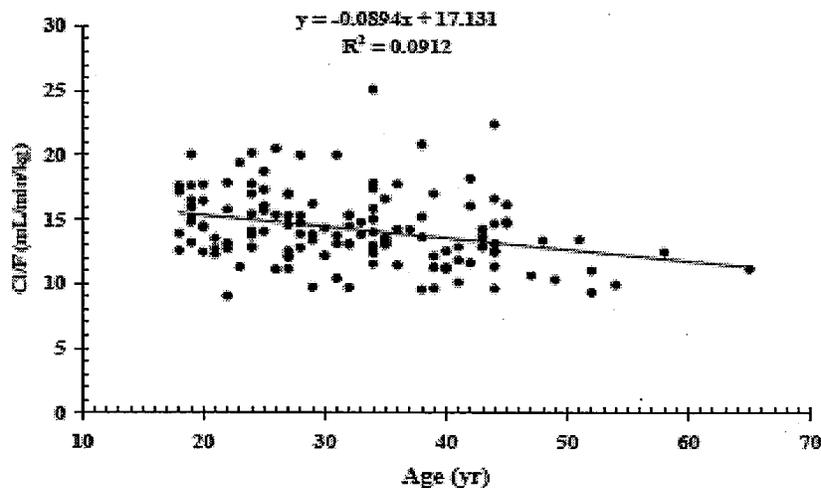
No intrinsic factor has been identified that would require dose adjustment beyond renal function.

2.3.2 Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

2.3.2.1 Elderly

As noted previously, the clinical pharmacology dataset was composed of healthy adults. Thus the number of subjects aged 65 or more is insufficient to draw conclusions on. The sponsor did, however, conduct a linear regression of Cl/F vs. Age to look at general trends in the dataset|

**Linear Regression Analysis of Cl/F vs Age Using the Pooled SC MNTX
Doses 0.15 to 0.50 mg/kg**



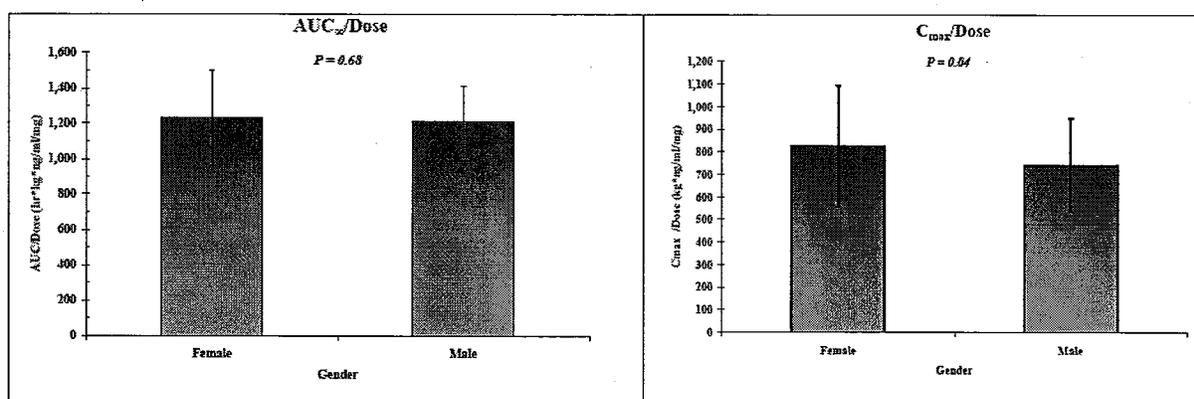
Age was found to have a *statistically-significant* but clinically-irrelevant effect on the following four metrics: AUC_{∞} , Cl/F, $t_{1/2}$, and MRT. However, given the limitations in the data (6 subjects over the age of 50), whether or not this is a true effect of age on MNTX pharmacokinetics is unknown and the magnitude itself is does not lend itself to a modification of the dosing regimen.

2.3.2.2 Pediatric Patients

No studies have been done to date in pediatric patients.

2.3.2.3 Gender

The sponsor conducted a dose normalized, cross-study analysis of the data from a pool of 80 males and 65 females with valid data sets. Reproduced below are comparative bar charts of $AUC_{inf}/Dose$ and $C_{max}/Dose$:



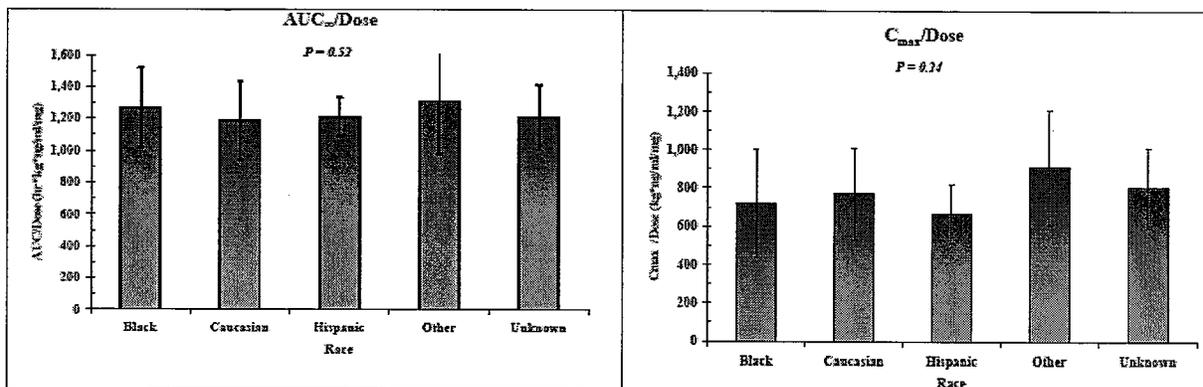
Comparison of Pharmacokinetic Metrics of SC MNTX by Gender
($p < 0.05$, significant difference)

Pooled Doses	Dependent Variable	N	df Between Groups	df Within Groups	F	P-value
0.15 to 0.50	C_{max}/D (kg*ng/mL/mg)	145 80 male; 65 female	1	143	4.49	0.04
0.15 to 0.50	AUC_{∞}/D (hr*kg*ng/mL/mg)	137 73 male; 64 female	1	135	0.17	0.68
0.15 to 0.50	V/F (L/kg)	137 73 male; 64 female	1	135	0.05	0.82
0.15 to 0.50	Cl/F (mL/min/kg)	137 73 male; 64 female	1	135	0.09	0.77
0.15 to 0.50	t_{max} (h)	145 80 male; 65 female	1	143	0.44	0.51
0.15 to 0.50	$t_{1/2}$ (h)	137 73 male; 64 female	1	135	0.01	0.92
0.15 to 0.50	MRT (h)	137 73 male; 64 female	1	135	4.94	0.03

From this analysis, minor differences were seen in parameters such as $C_{max}/Dose$ and MRT. Even so the differences noted, while statistically significant do not rise to the level where alternative dosing recommendations should be considered.

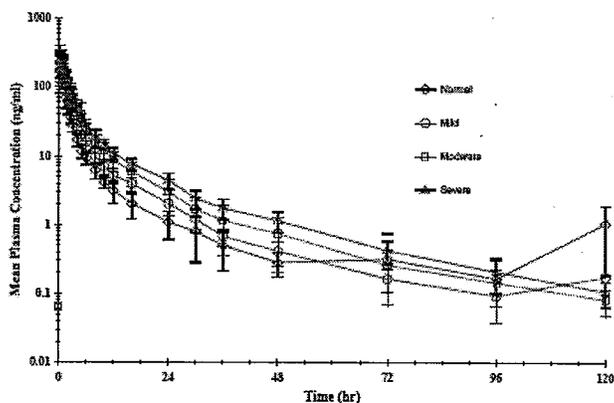
2.3.2.4 Race

A similar cross-study analysis to the one conducted for gender difference was also conducted using race as a co-variate. Again while some variability was seen in individual parameters among races again they did not rise to the level requiring dose adjustment. Reproduced below are comparative bar charts of AUC_{inf}/Dose and C_{max}/Dose for the different races reported in the clinical pharmacology/biopharmaceutics dataset:



2.3.2.5 Renal impairment

The effect of renal impairment on the pharmacokinetics of MNTX was evaluated in 32 subjects with varying degrees of renal failure in Study MNTX 1105. Eight subjects were enrolled in four panels representing normal renal function and mild, moderate, severe renal impairment. As with the rest of the subjects in this NDA this was a single dose study using a 0.30mg/kg dose SC.

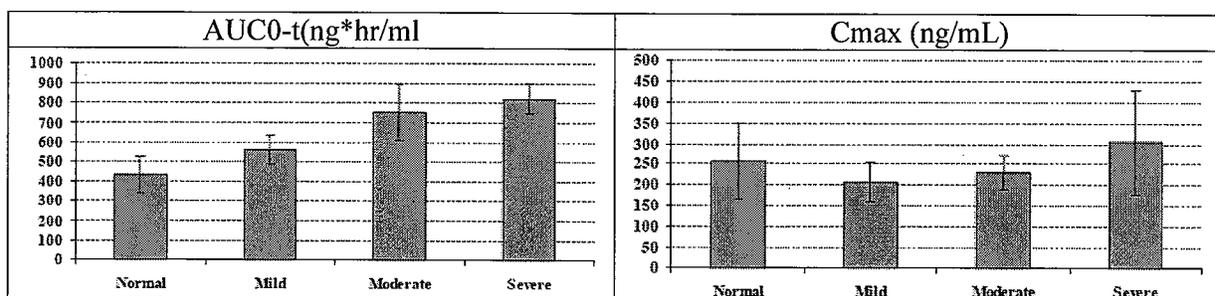


Total exposure (AUC_∞) increased as a function of the renal impairment, and was approximately doubled in the severe renal impairment group (89% increase). While, a relatively large variance made the effect on mean C_{max} difficult to interpret, C_{max} for an SC dose is a relatively fleeting phenomena and can be related to the SC technique and other variables as well, so it is a less sensitive measure of absorption than usual.

Study MNTX 1105 Mean Data %CV

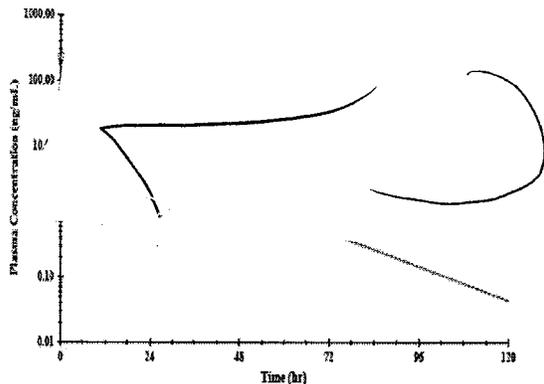
	AUCt	AUCinf	Cmax	Fr%
Normal	427(15%)	433 (21%)	257 (36%)	45.2 (30%)
Mild	560 (12%)	566 (13%)	208 (23%)	31 (47%)
Moderate	752 (19%)	754 (19%)	231 (18%)	17 (49%)
Severe	819 (9%)	822 (9%)	304 (41%)	10 (64%)

The fact that the Cmax for Normal subjects is also the second highest value strongly suggests that this is not a significant finding and may be related to other factors. Further, examination of the data in bar charts below also shows this quite clearly with the second highest variability for Cmax being the normal group. Given that renal function should have little impact on Cmax for a SC (or IV) administered drug (especially following a single dose), it is likely that this is an artifactual finding.



Again, as would be expected from a drug that is renally eliminated, the cumulative quantity excreted unchanged (fr(%)) declined from 45.2% in the normal subjects to 10.3% in the subjects with severe renal impairment.

One difference that was noted on the original review of this data by the FDA was that the terminal half-life ($t_{1/2}$) also increased as a function of severity of impairment, from a mean of 13.4 h in the normal group to 19.6 h in the severe group. While changes in terminal half-life are not surprising for a renally eliminated drug (see results of the mass balance study) the finding is a bit more unusual as the half-life previously seen with MNTX in normal subjects was in the range of 6-9hrs. While the true reason for this difference in half-life between the normal subjects in this study in other studies is unknown, one possibility, and the most likely one, was the analysis itself. One of the limitations of the original study report was the lack of data from a number of subjects in this study due to problems with the assay. As will be covered in the analytical section of this review, the sponsor apparently (in the FDA's opinion) set the LLOQ too low, such that at low concentrations there were occasional spikes in concentration seen with the last timepoint. Due to poor quality control, the sponsor's consultant, rather than truncating the AUC earlier, elected to drop these subjects from the analysis. In the normal subject group this resulted in 4 subjects out of 8 being dropped from the analysis. An example of the fitting of pharmacokinetic data from this study is shown below:



While the sponsor did not feel that this removal of subjects from the analysis affected their results, a subsequent re-analysis, truncating the AUC to eliminate these apparently spurious concentrations yielded a revised estimate of 10.8+/-4.9hrs for half-life (down from the original estimate of 13.4+/-4.8hrs). A value that while still higher than most other normal subjects data was at least in the ballpark.

In terms of the interpretation of these results the sponsor is recommending a reduction in dose only in subjects with severe renal impairment. In that situation the sponsor is recommending a halving of the dose. For mild and moderate renal insufficiency no dose reduction is being recommended by the sponsor based on both the lack of a dose response and the demonstrated safety of the compound in the clinical studies.

2.3.2.6 Hepatic impairment

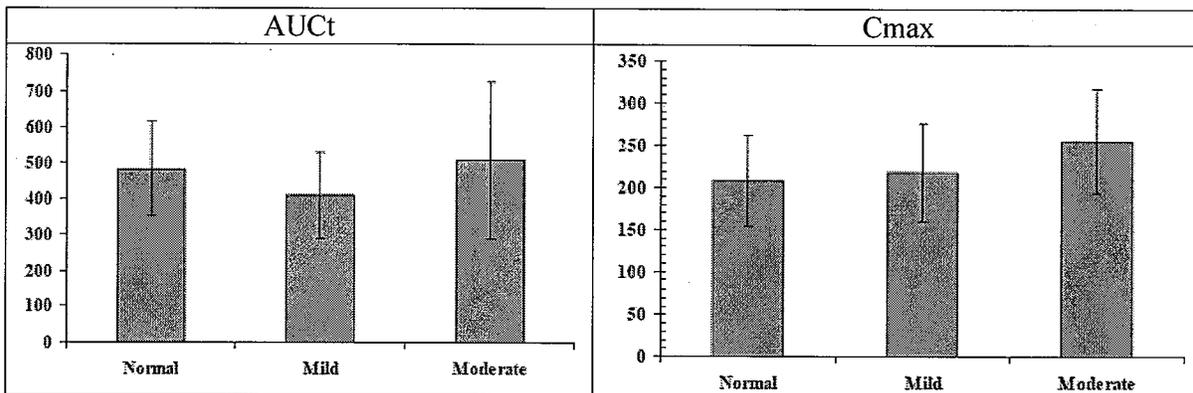
Twenty-four subjects/patients were enrolled, 8 subjects with normal hepatic function (matched reference) and 8 patients from each category of hepatic impairment (mild or moderate), using the Child-Pugh classification, as recommended by FDA guidelines. Subjects with severe renal impairment were not included in the study. Based on the results of the mass balance study it was not considered likely that hepatic impairment would have a marked effect on the disposition or elimination of MNTX. The results of this trial supported this assumption with there being only modest changes in the pharmacokinetics of MNTX in subjects with hepatic insufficiency.

Hepatic Function	Statistic	PK Metrics					
		C _{max} (ng/mL)	t _{max} ^a (hr)	AUC _t (ng•hr/mL)	AUC _∞ (ng•hr/mL)	t _{1/2} (hr)	f _R (%)
Normal	MEAN	208	0.47	482	441 ^b	11.7	53
	SD	54	(0.25, 1.00)	132	47	6	7
	N	8	8	8	6	6	8
Mild	MEAN	218	0.47	410	412	7.8	34
	SD	58	(0.25, 0.75)	120	121	1.5	15
	N	8	8	8	8	8	8
Moderate	MEAN	256	0.34	508	511	14.5	39
	SD	62	(0.25, 0.50)	218	219	10.6	14
	N	8	8	8	8	8	8

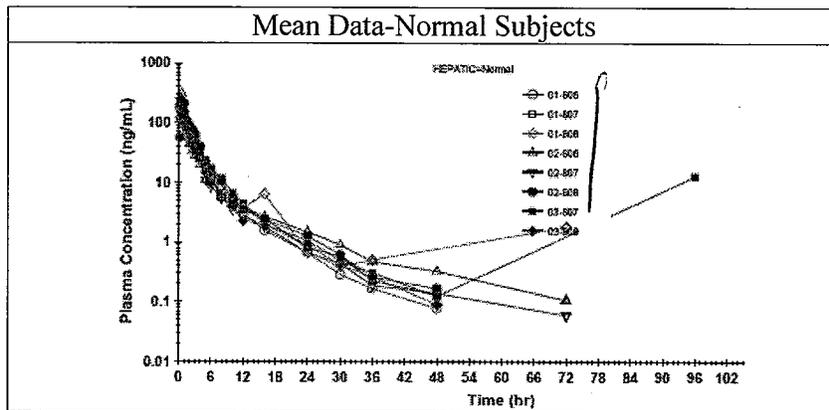
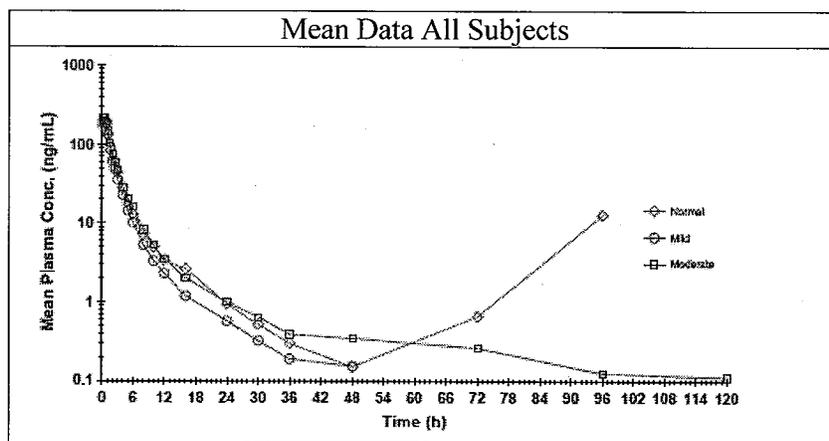
^aMedian (min, max) shown for T_{max}

^bFor the matched reference group, mean AUC_∞ is less than mean AUC₀₋₄ due to a difference in the number of subject/patients used in calculating descriptive statistics.

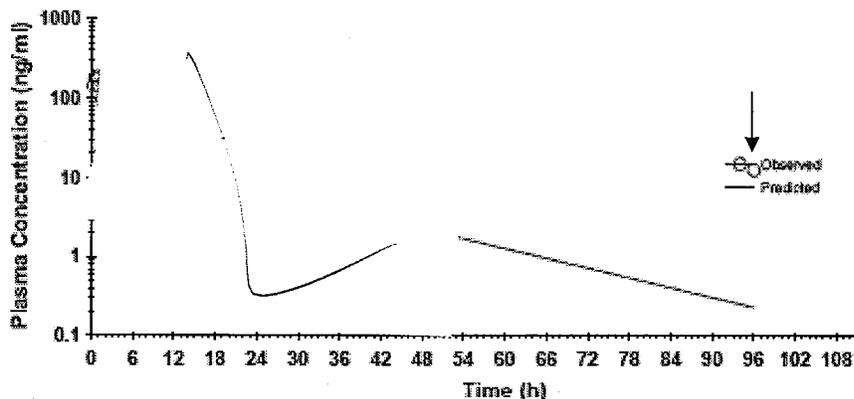
Reference: Appendix 16.2.6, 16.2.6.1 - Pharmacokinetic Report



As has been noted in previous studies in this NDA there was a continued problem with estimation of half-life due to “apparently” spurious concentration values at the end of the sampling intervals. However, in this study the impact was quite a bit more pronounced, even for the mean data collected for the normal subjects:



Again, two subjects were excluded from the half-life estimation due to a poor regression and the half-life was estimated by the regression with 18-19 points, when in fact the data should have been truncated earlier.



Per Agency's request, the terminal half-life estimation with data truncation at 48 h was provided (amendment 010). In addition, the sponsor provided reanalysis of the AUC and $T_{1/2}$ in the amendment 011 after excluding anomalous data points from two previously excluded subjects. The reanalysis resulted in 12% decrease in the half-life from 11.7 ± 5.9 h to 10.4 ± 5.6 h and 10% decrease in AUC_t from 482 to 438 ng/ml·h and 0.2% change in AUC_∞ from 441 to 440 ng/ml·h.

While the overall conclusion from the study did not change, i.e., dose reduction is not required in hepatic insufficiency, the study again points to both analytical problems that need to be addressed and problems in the sponsors reliance on the analysis without proper scientific review.

2.3.2.7 What pregnancy and lactation use information is there in the application?

None, given this intended patient population it is unlikely that pregnant or lactating women will be using this product for this indication. Reproduction studies have been performed in pregnant rats and rabbits. There were no effects on fetal development at intravenous dosages of up to 25 mg/kg/day in the rat or up to 16 mg/kg/day in the rabbit. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been given a Category B rating based on the animal data.

2.4 Extrinsic Factors

2.4.1 What are the extrinsic factors that influence exposure or response?

Extrinsic factors that would effect exposure or response in the target patient population would be primarily related to the end-of-life process itself, prior laxative use, prior radiation therapy, nutritional status, prior chemotherapy, and the degree of opiate use required for pain management. In addition, the use of drugs such as NSAIDs in pain management that would decrease renal function would also be expected to have an impact on the elimination of MNTX and thus its clinical effect.

2.4.2 Drug-drug interactions

The potential for MNTX to interfere with CYP450 mediated metabolism was evaluated in vitro using human microsomes as part of the non-clinical development of MNTX in study 107n-0304 (see pharmacology review). The probe substrates used were phenacetin (CYP1A2), coumarin (CYP2A6), tolbutamide (CYP2C9), *S*-mephenytoin (CYP2C19), dextromethorphan (CYP2D6),

midazolam (CYP3A4) and testosterone (CYP3A4). The corresponding enzyme activities were measured by LC/MS/MS as the formation of acetaminophen, 7-hydroxycoumarin, 4-hydroxytolbutamide, 4'-hydroxymephenytoin, dextrophan, 1'-hydroxymidazolam and 6-hydroxytestosterone.

Summary of Inhibition of CYP450 Activity by MNTX

MNTX Concentration (µM)	CYP450 Activity Expressed as % Vehicle Control						
	CYP1A2	CYP2A6	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	CYP3A4/5
100	75	98	96	108	18	109	110
33.3	72	101	96	108	36	109	102
11.1	75	99	93	102	58	103	98
3.70	80	99	97	105	76	102	95
1.23	96	101	107	109	95	110	105
0.41	89	99	109	112	101	110	104
0.137	87	100	109	106	97	106	105
0.046	90	96	105	111	104	107	107
0.015	87	99	101	106	97	101	95
0 (VC)	100	100	100	100	100	100	100
IC ₅₀ (µM)	> 100 µM	> 100 µM	> 100 µM	> 100 µM	15.92 µM	> 100 µM	> 100 µM
Substrate	Phenacetin	Coumarin	Tolbutamide	S-Mephenytoin	Dextromethorphan	Midazolam	Testosterone

VC = Vehicle Control.

The results demonstrate that MNTX does not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A4 activity using selected probe substrates. MNTX does appear to be a CYP2D6 inhibitor with IC₅₀ value of 15.92 µM. For comparison, quinidine inhibited CYP2D6 with an IC₅₀ of 0.098 µM. The positive controls were determined to be potent CYP450 inhibitors using selected probe substrates. The calculated IC₅₀ values for positive controls were consistent with reported literature values.

As a follow-up to these in vitro results the sponsor conducted MNTX-1108, a study in which the effect of either SC or IV doses of MNTX (according to sponsor's proposed regimen) dextromethorphan (a known 2D6 substrate) was studied. The results of this study demonstrated that while paroxetine (a known 2D6 inhibitor) caused a marked change in dextromethorphan excretion, MNTX did not have a marked effect using a doubling of the urinary ratio as a marker of 2D6 inhibition:

Categorical analysis of urinary ratios of dextromethorphan/free dextrophan in subjects co-administered either MNTX or paroxetine

Variable	Group 1 MNTX 0.30 mg/kg SC	Group 2 MNTX 0.45 mg/kg IV	Group 3 Paroxetine 20 mg PO	Group 4 Placebo SC
Doubling of Baseline Dextromethorphan / Free Dextrophan Ratio				
Yes	2 (25.0%)	2 (25.0%)	7 (100.0%)	1 (12.5%)
No	5 (62.5%)	5 (62.5%)	0 (0.0%)	7 (87.5%)
p-value vs. Placebo	0.5692	0.5692	0.0014	---
p-value vs. Paroxetine	0.0210	0.0210	---	0.0014

2.4.3 What issues related to dose, dosing regimens, or administrations are unresolved and represent significant omissions?

The remaining dosing issues, as outlined in the Executive Summary relate to mg/kg dosing, dose reduction in moderate renal failure and the resolution of the TQT issue. These issues have been previously detailed in the appropriate sections of this review.

2.5 General Biopharmaceutics

2.5.1 BCS

N/A

2.5.2 Bioavailability(Absolute)

Study MNTX 103 incorporated a single IV dose along with 3 SC doses in a randomized cross-over trial. Absolute bioavailability results (from the 5 subjects who completed all legs of the trial) for the SC treatment legs are presented below:

	Mean(sd)			
	0.30 mg/kg IV	0.10 mg/kg SC	0.30 mg/kg SC	0.45 mg/kg SC
AUC _∞ (ng/mL*h)	379.8 (52.9)	73.3 (10.6)	303.2 (43.14)	545.7 (34.6)
F		0.58	0.79	0.96

A phenomenon that has been seen previously in this data is the apparent increasing bioavailability with dose. It may be that giving a larger SC dose (i.e., a larger injection volume) causes a higher level of absorption due to tissue effects. While no direct conclusions can be drawn from this data, it does suggest that the dose of MNTX should be given as a single injection and not as a split injection if at all possible.

2.5.3 Food Effect

N/A

2.5.5 Dissolution

N/A

2.6 Analytical Section

Overview

A number of analytical methods were used in the development of MNTX, depending on the timeframe and the species of interest. These methods included a high-performance liquid chromatography (HPLC) with electrochemical (EC) detection method that was used for both plasma and urine samples in an early ascending dose IV PK study and a refined HPLC method that use used in the first single dose SC study. Both of these methods have been published:

Foss JF, O'Connor MF, Yuan CS, Murphy M, Moss J, Roizen MF, "Safety and tolerance of methylnaltrexone in healthy humans: a randomized, placebo-controlled, intravenous, ascending-dose, pharmacokinetic study." J Clin Pharmacol. 1997 Jan;37(1):25-30.

Osinski J, Wang A, Wu JA, Foss JF, Yuan CS "Determination of methylnaltrexone in clinical samples by solid-phase extraction and high-performance liquid chromatography for a pharmacokinetics study." J Chromatogr B Analyt Technol Biomed Life Sci. 2002 Nov 25;780(2):251-9.

For this NDA, the majority of the analytical work was done using an LC/MS/MS procedure that was originally developed and validated by _____ based on work done by _____. Later in the development, the methodology was transferred to _____ and "partially validated" for use in one study:

Analytical Site Used	Study Number
C >	102
	KI-103,1105, 1106, 1107,1108

Analytical-Methods

In general following sample preparation, either plasma or urine samples were spiked with IS and were extracted by with a MPC-standard density 96-well extraction plate. The extracted samples were analyzed by reversed-phase HPLC with a mass spectrometer. Positive ions were monitored in the multiple reaction monitoring mode. Quantification was by peak area ratio. The regression type was linear analysis with a $1/x^2$ weighting.

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, in this NDA the sponsor followed the parent compound. This decision was based on the results of the radiolabeled mass balance study (MNTX-102) which demonstrated that the parent compound was the predominant species present in the blood and urine:

Relative abundance of methylnaltrexone metabolites in urine and feces

MNTX/Metabolite ^a	Percent of Dose		
	Urine 0-24 Hours Post dose	Feces 0-168 Hours Post dose	Total ^c
Mean (\pm SD) Radiodose Excreted	43.9 \pm 17.2	17.3 \pm 6.2	61.2
Methylnaltrexone (MNTX)	37.1	11.4	48.5
M1 (Methyl-6-naltrexol Sulfate)	0.14	ND	0.14
M2 (Methylnaltrexone Sulfate)	1.26	ND	1.26
M3 (Dihydroxy-methyl-6-naltrexol)	0.04	ND	0.04
M4 (Methyl-6-naltrexol Isomer)	4.25	0.83	5.08
M5 (Methyl-6-naltrexol Isomer)	0.74	0.24	0.98
Total ^b	43.5	12.5	56.0 ^c

ND Not detected.

a Tentatively identified by LC/MS analysis.

b Recovered radiodose for 0-24 hour urine and selected feces samples over 0-96 hour post dose.

c Includes Subject 03 (incomplete collections)

Of the other metabolites M2 is roughly equipotent with parent, but it is present at much lower levels while the other metabolites in animal models of opiate potency have much less binding affinity to the opiate receptor.

deviation). In some cases, the back-calculated concentration was deviated more than ten times from the nominal concentrations such as 2.4 ng/ml for 0.15 ng/ml and 3.9 ng/ml for 0.05 ng/ml.

This point is relevant as throughout the NDA the sponsor's consultant (_____) rejected some subject's data as the presence of high "unexpected" plasma concentrations at the end of the plasma level time curve resulted in poor computer "fits" of the data. This has previously been discussed in detail in this review in relation to the data from the hepatic and renal impairment studies (MNTX 1107 and 1105, respectively). Given what appears to be the presence inconsistent reproducibility at low concentration, it would have been better to select a more stable LLOQ or manually evaluate the goodness of fit rather than relying on the computer for interpretation. While it is unlikely that this represents a fatal flaw to the analytical method, it does raise the issue of the wisdom of selection the LLOQ at 0.05 ng/ml and the over-reliance on computer methods and a lack of oversight of the analysis, per se. These issues have been raised with the sponsor in communications on this NDA during the review cycle, _____

Analytical-Conclusion

While there is a concern about the selection of LLOQ for MNTX, we do not believe that it represents a major stumbling block to the assay. In general the selection of controls and preparation of standard curves is appropriate and adequately documented. The assay could be improved up as indicated above, also by validating the ability of the assay to discriminate between MNTX, naltrexone, and 6- β -naltrexol (the primary metabolite of naltrexone). These issues have and will be raised with the sponsor in _____

3 Detailed Labeling Recommendations

At the present time detailed labeling recommendations are being deferred as labeling negotiations have been deferred until the submission of the pending TQT study.

4 Appendices

Appendix-General Studies		Page #
<u>MNTX-102-</u> An Open-Label, Phase 1, Single Dose Study of the Pharmacokinetics, Mass Balance and Disposition of Intravenously Administered 14C-Methylnaltrexone in Normal, Healthy Volunteers	34	
<u>MNTX-103-</u> An Open-Label Phase I Study of the Pharmacokinetics and Bioavailability of Single, Ascending Subcutaneous Doses of Methylnaltrexone vs. an Intravenous Dose in Normal, Healthy Male Volunteers	40	
<u>MNTX-206-</u> A Phase 1 Urodynamic Study of the Opioid Antagonist Naloxone and Intravenous Methylnaltrexone to Reverse Opioid Effects on Bladder Function in Healthy Volunteers	45	
<u>MNTX-3200KI-103</u> An Open-Label, Single-Dose, Randomized, 2-Period Crossover, Bioequivalence Study Between the Current Formulation and the New Formulation of MOA-728 Administered Subcutaneously in Healthy Subjects-(Aug. 3 Submission #4)	49	
Special Population Studies		
<u>MNTX 1105-</u> Phase 1, Open-Label Study to Evaluate Single Dose Pharmacokinetics, Safety, and Tolerability of Methylnaltrexone (MNTX) in Subjects with Impaired Renal Function	54	
<u>MNTX-1107-</u> Phase 1, Open-Label Study to Evaluate Single Dose Pharmacokinetics, Safety, and Tolerability of Methylnaltrexone (MNTX) in Subjects with Impaired Hepatic Function	60	
Safety Studies		
<u>MNTX-1106-</u> A Randomized, Double-Blind, Placebo/Positive Controlled Evaluation of the Effects of MNTX on ECG Parameters and Cardiac Repolarization in Normal Volunteers	65	
<u>MNTX-1108-</u> A Phase I, Randomized, Open-Label, Active- and Placebo-Controlled Parallel Group Study of the Effect of Subcutaneous and Intravenous Methylnaltrexone on CYP450 2D6 Activity in Healthy Extensive Metabolizers of Dextromethorphan	68	
Labeling		
Original Proposed Labeling (3/20/2007)		73

STUDY MNTX-102

Title: An Open-Label, Phase 1, Single Dose Study of the Pharmacokinetics, Mass Balance and Disposition of Intravenously Administered ¹⁴C-Methylnaltrexone in Normal, Healthy Volunteers

Study Site:



Clinical Lab:



Analytical Lab:



Overview

This was an open-label, non-randomized, single-dose study conducted at a single site. Six healthy adult male human subjects were assigned and treated as a single group. A single intravenous 0.3 mg/kg (99.975 µCi) dose of ¹⁴C-MNTX was administered to each subject followed by serial blood sampling and cumulative urine and feces sampling for 120 hrs post-dose. In addition, expired CO₂ sampling was done for 8 hrs post-dose according to the following schedule:

Sample	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Blood ¹	0 (predose), 2, 5, 15, 30, 45 min 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 h	24, 36 h	48 h	72 h	96	120
Total Urine Collection ²	0-24 h	24-48 h	48-72 h	72-96 h	96-120	(*)
Total Stool Collection ³	0-24 h	24-48 h	48-72 h	72-96 h	96-120	(*)
Expired CO ₂	0-8 h (see details below)	---	---	---	---	---

- (1) 10-mL aliquots were collected from forearm vein in arm *contra-lateral* to that used for dosing, into lavender top (K₂EDTA preservative). The stopper was removed, and two 0.50-mL aliquots of whole blood were transferred to labeled scintillation vials, and frozen upright at -20° C. Remaining blood was centrifuged, and approximately equal portions of the plasma carefully transferred via disposable glass pipet into two labeled, screw-cap polypropylene tubes, and frozen upright at ~ -20° C. were stored in ice water between drawing and processing.
- (2) For each volunteer, total collections during each indicated time period were pooled in a single, polypropylene or glass container and stored refrigerated during each collection period. Upon completion of the collection interval, contents were mixed well, the volume measured = 5 mL, and three 50-mL aliquots transferred to labeled, NMSC containers, and frozen at ~ -20° C. Ambulatory collections were kept cold as much as possible.
- (3) Total stool for each laxation was collected separately during the intervals specified. Time and date of each laxation were recorded (as obtained from subject's diary for ambulatory visits), and individual stools were not pooled over 24-h periods. Samples were label and stored at ca. -20° C.
- (4) Excreta were collected at the end of the 120 h post dose interval unless deemed incomplete.

Expired CO ₂ Sample Collections - Day 1 ⁴		
Period Post Dose	0-4 h	4-8 h
Collection Intervals	q15min	q30min

Subjects were confined under supervision in the clinical facility beginning ~12 hr prior to dosing (~8pm). After administration of a single i.v. dose of study drug, subjects remained confined and

under supervision until 48 hr post dose for blood sampling and collection of excreta. All subsequent sample collections and assessments were performed on an ambulatory basis at 24-h intervals until study completion.

In any event, to avoid environmental contamination, all participants who received any dose of ¹⁴C-MNTX, remained confined under supervision until the investigator considered that residual radioactivity had been cleared sufficiently to avoid risk of exposing others. The total, whole-body radiation exposure (0.156 MeV β-emission) expected for subjects participating in this study was estimated to be 0.21 REM, based on the results of a ¹⁴C-MNTX tissue distribution study conducted in Sprague-Dawley rats (contained in the pharmacology section of this NDA). This constitutes ~ 4.2% of the total annual exposure (5 REM) permitted by FDA in such clinical trials and ~7% of the total exposure (3 REM) permitted by FDA from a single dose of radiolabeled material.

The demographics of the study population are summarized below:

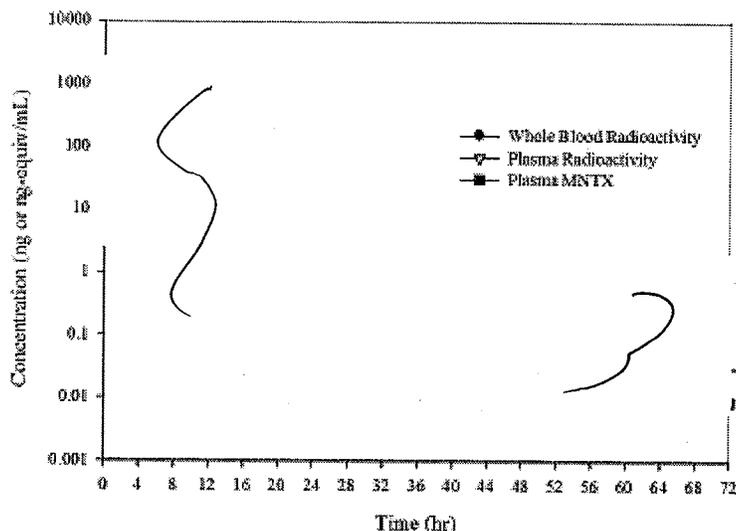
Table 6 Screening Demographics by Subject

Subject Number	Gender	Race	Age (years)	Height (cm)	Weight (kg)	Elbow Breadth (cm)	Frame Size
01	Male	Caucasian	21	174.5	67.1	7.20	Medium
02	Male	Caucasian	19	178.0	84.0	7.20	Medium
03	Male	Caucasian	27	173.5	78.5	7.00	Medium
04	Male	Caucasian	20	174.0	86.5	7.20	Medium
05	Male	Caucasian	23	172.0	78.5	6.50	Small
06	Male	Asian	22	167.5	66.6	6.30	Small
Mean ± SD			22±2.8	173.3±3.5	79.6±8.4		
Median			22	173.8	78.5		

Reference: Table 14.1-1.

Results

After intravenous administration of MNTX, concentrations of both unchanged drug and total radioactivity in plasma and blood declined in a polyexponential manner, with a relatively rapid distribution phase followed by a slower terminal phase. In all subjects total radioactivity in both matrices declined to below the limit of quantification after 24 hours post dose. Concentrations of MNTX were still detectable in most subjects at 48 hours.



Concentration versus time profiles of MNTX and total radioactivity in plasma and whole blood

Pharmacokinetic metrics (mean \pm SD) for MNTX and total radioactivity in plasma and whole blood

Metric	Units	Plasma	Total Plasma	Total Whole Blood
		MNTX	^{14}C -MNTX	^{14}C -MNTX
C_{\max}	(ng/mL) ^b	1151 (305)	1183 (260)	646 (139)
t_{\max}	(h)	0.0500 (0.0500, 0.100) ^a	0.0500 (0.0500, 0.100) ^a	0.0500 (0.0500, 0.100) ^a
AUC ₁₂	(ng·h/mL) ^b	368 (44)	622 (47)	NA
AUC ₁	(ng·h/mL) ^b	393 (52)	652 (84)	301 (31)
AUC _∞	(ng·h/mL) ^b	394 (52)	748 (103)	392 (42)
AUC _∞	(%)	0.335 (0.119)	12.7 (1.8)	23.5 (2.1)
λ	(1/h)	0.0822 (0.0179)	0.125 (0.041)	0.130 (0.027)
$t_{1/2}$	(h)	8.89 (2.59)	6.15 (2.27)	5.51 (0.97)
V_{diss}	(L/kg)	7.92 (1.54)	2.84 (0.68)	4.98 (0.83)
Cl	(mL/min/kg)	10.5 (1.5)	5.55 (0.81)	10.5 (1.2)
Cl _R	(mL/min/kg)	6.37 (3.00)	3.01 (0.54)	NA

NA=not applicable

^a Median (min, max) shown for t_{\max}

^b units for ^{14}C -MNTX are ng equivalents rather than ng

The results of the study indicate that MNTX is rapidly absorbed from the site of administration as evidenced from the extrapolated values for both T_{\max} (0.05hr or 3min) and C_{\max} . The mean volume of distribution of MNTX in plasma was 7.92 L/kg, indicating that MNTX is distributed extensively outside the central compartment.

Renal Clearance

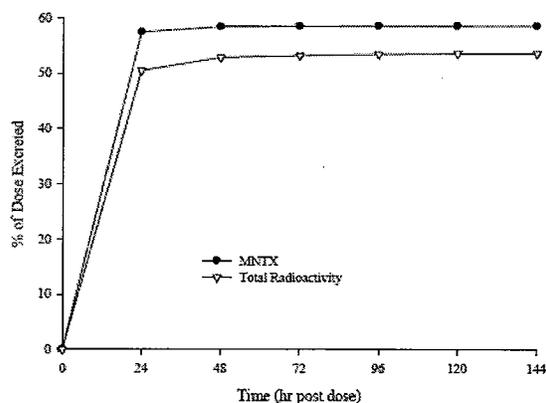


Figure 2: Cumulative Mean Percent of Dose and Radiodose Excreted in Urine

Renal clearance for MNTX accounted for approximately 60% of the total plasma clearance, suggesting appreciable non-renal elimination. The renal clearance of MNTX (6.37 mL/min/kg, 446 mL/min for a 70-kg man) is greater than the glomerular filtration rate, 125 mL/min (7.5 L/hr), indicating that active transport plays a role in the renal excretion of MNTX. Excretion of MNTX and total radioactivity in urine were generally similar, with mean total percent recovery of 58.6 and 53.6%, respectively. These results indicate that most of the radioactivity excreted in urine represents unchanged MNTX.

Total Recovery

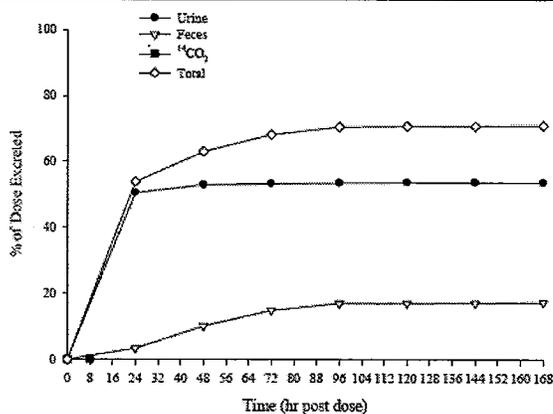


Figure 3: Mean Percent of Administered Radioactivity Excreted in Urine, Feces, and as ¹⁴CO₂

Note: Subject 3 excluded from urine and total recovery due to incomplete urine collection.

Mean total percent recovered in feces was 17.3%. Exhaled CO₂ accounted for less than 0.08% of excreted radioactivity in all subjects. Most of the radioactivity in urine was recovered in the first 24 hours post dose. Mean total percent of radioactivity recovered in urine and feces together was 70.8%, with the majority occurring in the first 48 hours post dose. The reasons for incomplete recovery of total radioactivity were not clear and no conclusions were offered by the sponsor. The two most likely cause of incomplete recovery is incomplete urine and/or fecal collection (as seen with subject #3) and deep compartment sequestration of radio-labeled MNTX.

Mean recoveries of MNTX and total radioactivity in urine, feces and expired air

Collection Interval (h) ^a	Total % MNTX Recovered	Total % Radioactivity Recovered			
	Urine	Urine	Feces	Exhaled CO ₂ ^a	Total
0-24 ^a	57.4	50.5	3.32	0.0556	53.9
24-48	0.959	2.38	6.72	NA	9.10
48-72	0.105	0.356	4.82	NA	5.18
72-96	0.0604	0.244	2.10	NA	2.34
96-120	0.0267	0.130	0.0733	NA	0.203
120-144	0.0198	0	0.0367	NA	0.0367
144-168	NA	NA	0.240	NA	0.240
Total ^b	(A _{MNTX}) 58.6 (18.2) ^c	(A _{ur} *) 53.6 (6.2) ^c	(A _{fec} *) 17.3 (6.2)	(A _{CO2} *) 0.0556 (0.0184)	70.9 (8.5) ^c

NA – No sample was taken

* CO₂ was collected 0-8 h post dose

^b Mean (SD) of individual totals

^c Excluding Subject 03 (incomplete collections).

Metabolism

The mean plasma AUC0-12 ratio of unchanged MNTX to total radioactivity was 0.59. Because the relative proportions of radioactivity and unchanged MNTX recovered in urine were comparable, the AUC0-12 ratio likely reflects minor pharmacokinetic differences (e.g., volume of distribution and clearance) between parent drug and metabolites. Overall, approximately 50% of the recovered radio-label was present as unchanged MNTX.

Relative abundance of methylaltraxone metabolites in urine and feces

MNTX/Metabolite ^a	Percent of Dose		
	Urine	Feces	Total ^c
	0-24 Hours Post dose	0-168 Hours Post dose	
Mean (± SD) Radiodose Excreted	43.9±17.2	17.3±6.2	61.2
Methylaltraxone (MNTX)	37.1	11.4	48.5
M1 (Methyl-6-naltrexol Sulfate)	0.14	ND	0.14
M2 (Methylaltraxone Sulfate)	1.26	ND	1.26
M3 (Dihydroxy-methyl-6-naltrexol)	0.04	ND	0.04
M4 (Methyl-6-naltrexol Isomer)	4.25	0.83	5.08
M5 (Methyl-6-naltrexol Isomer)	0.74	0.24	0.98
Total ^b	43.5	12.5	56.0 ^c

ND Not detected.

a Tentatively identified by LC/MS analysis.

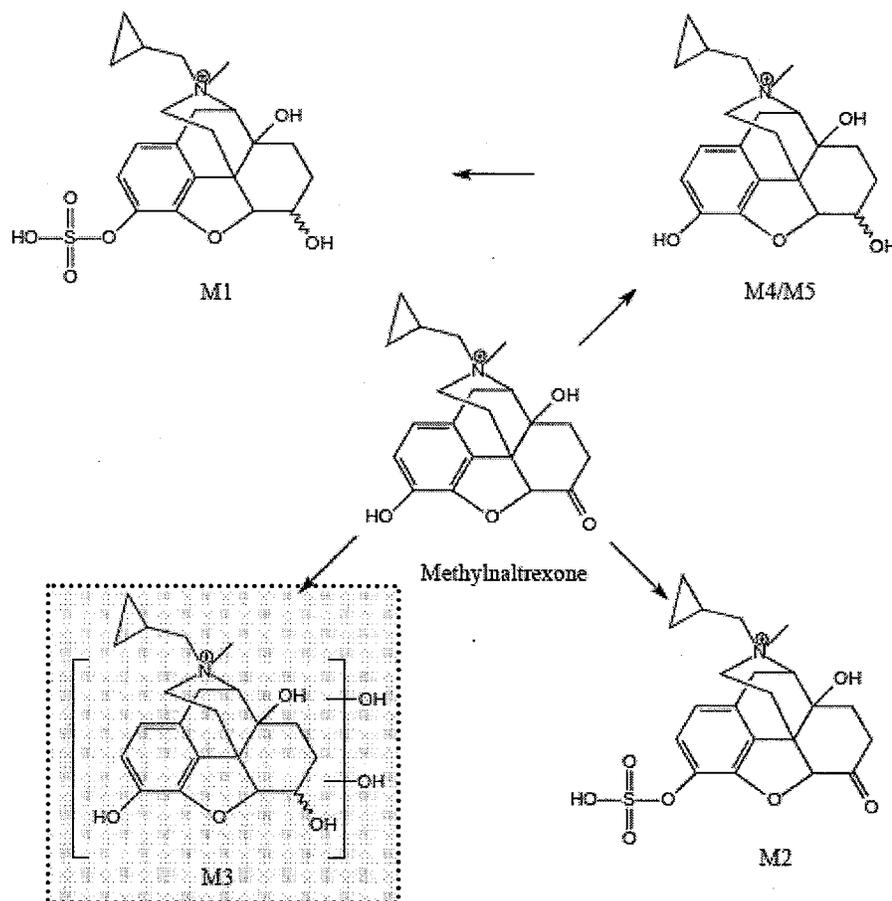
b Recovered radiodose for 0-24 hour urine and selected feces samples over 0-96 hour post dose.

c Includes Subject 03 (incomplete collections)

Conclusions

Based on the results of this study, the following metabolic scheme is proposed for MNTX.

Proposed biotransformation pathway of methylnaltrexone in human



MNTX is quickly absorbed into systemic circulation following SC administration. It is highly distributed (as evidenced by a V_d of approx. 8L/kg) and the levels of total radioactivity in plasma were roughly twice as high as levels in whole blood, indicating that MNTX is not bound to red blood cells or other whole blood components. It is primarily eliminated in the urine as unchanged drug with lesser amounts of radioactivity being excreted into the feces. Approximately 60% of the administered radioactivity was recovered with 5 distinct metabolites being resolved, none of which being detected in amounts over 6% of total. Of the metabolites 1 of them (M3) was only detected in 1 subject and then a very low amounts only. Limitations of this study include the lack of complete recovery of the radioactivity and the potential impact of depletion of sub-cutaneous fat stores in end stage cancer patients and its potential impact on SC absorption. This latter issue is not so much a limitation of the study itself but in the ethical issues of doing such a study.

Study MNTX-1103

Title: An Open-Label Phase I Study of the Pharmacokinetics and Bioavailability of Single, Ascending Subcutaneous Doses of Methylnaltrexone vs. an Intravenous Dose in Normal, Healthy Male Volunteers

Objective: The purposes of this study were to determine the plasma pharmacokinetics and urinary excretion pattern of single, ascending, subcutaneous doses and a single intravenous dose of methylnaltrexone (MNTX) in normal healthy male subjects, and to determine the relative bioavailability (dose proportionality) of single, ascending subcutaneous doses of MNTX and their absolute bioavailability vs. a single, intravenous dose.

Study site:

Bioanalysis stie:



Subject: A total of six subjects were enrolled in the study, and five subjects completed the study. All six subjects were considered for safety evaluation. Pharmacokinetic analysis was based only on the data from the five subjects who completed the study.

Study design: A four-period crossover design with a seven-day washout period and the same treatment was given to all subjects in each period in order of dose administration as follows:

- 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

PK sampling

Table 9.5.1:2 Sampling Schedule for Dose 1: 0.30 mg/kg, Intravenous (IV)

Samples	Day 1														Day 2-3	Day 3-4
	0	2 min	5 min	10 min	20 min	40 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
Total Urine Collection ²	Predose ³ and 0-6 hr												6-12 hr	12-24 hr	24-48 hr and 48-72 hr	

Table 9.5.1:3 Sampling Schedule for Dose 2-4: 0.10, 0.30, and 0.45 mg/kg, Subcutaneous

Samples	Days 15, 22, 29													Days 16-17, 23-24, 30-31	Days 16-17, 24-25, 31-32
	0	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr	48 hr ⁴
Total Urine Collection ²	Predose ³ and 0-6 hr										6-12 hr	12-24 hr ⁴	24-48 hr and 48-72 hr ⁴		

¹ 7 mL aliquots collected from forearm vein in arm contralateral to that used for dosing. Either drawn into a lavender top (K₂EDTA preservative) or drawn by syringe and transferred to a lavender top centrifuged, transferred plasma with disposable glass pipet to labeled, screw-cap, polypropylene vials, and frozen at ≤70° C. For details, see Appendix 3 of Protocol (Appendix 16.1.1).

² Total collections during each time period indicated, pooled in single, plastic or glass container for each volunteer and stored refrigerated during each collection period. Upon completion of collection interval, contents were to be well mixed, volume measured ±5 mL and at least three 50-mL aliquots removed to labeled, glass or polypropylene NMSC containers, and frozen at ≤70° C. For details, see Appendix 3 of Protocol (Appendix 16.1.1).

³ Completed collection of first morning urine sample, not total collection from approximately -12 to 0 hr.

⁴ Ambulatory collection.

Bioanalytical procedures: MNTX in human K₃EDTA plasma was analyzed using HPLC-MS/MS and the bioanalytical method covered a range of 0.050 to 100 ng/mL.

Reviewer’s comment: The *Pharmacokinetics of the metabolites were not studied.*

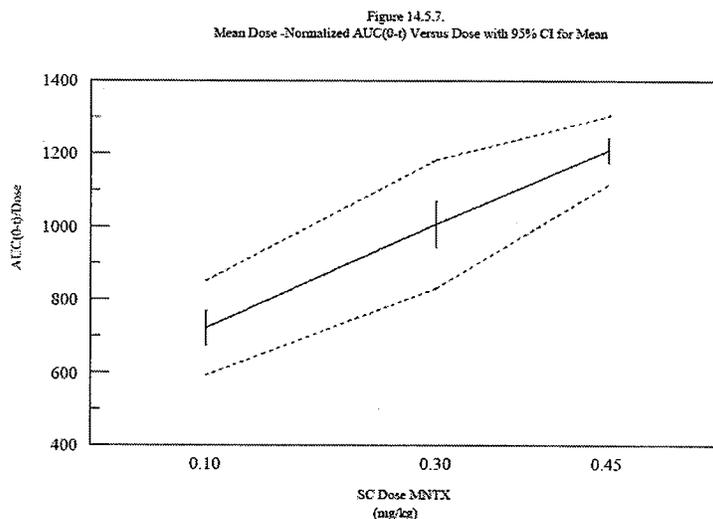
Pharmacokinetics analysis: Pharmacokinetic metrics were estimated following noncompartmental analysis of plasma concentration time course data.

Protocol deviations: According to the protocol, the subcutaneous injection site was to be documented for Periods 2-4 but no documentation completed for the dosing event. The SC dose was supposed to be given in the inner thigh.

Subject 2 had positive test for drugs of abuse at Period 3 check-in and did not complete all 4 periods and was excluded from the pharmacokinetic analysis. The nature of drugs of abuse was not reported.

Results-Pharmacokinetics:

The plasma concentration-time profile of MNTX exhibited multi-compartmental behavior following IV and SC administration. The C_{max} was achieved around 0.3-0.45 hour post-dose and the terminal half-life ranged 6.14 to 8.83 hr independent of dose and administration route. The AUC at 0.3 mg/kg of MNTX given by IV and by SC was 379.8 ng/ ml·h and 303.2 ng/ ml·h, respectively. The AUC of MNTX increased in a roughly dose-proportional manner with an increase in SC dose of MNTX.



The absolute bioavailability of MNXT SC administration compared to 0.3 mg/kg MNXT IV administration was 0.6, 0.82, and 0.99 after 0.1, 0.3 and 0.45 mg/kg of SC administration, respectively. The renal clearance of MNTX was greater than renal creatinine clearance indicating active renal secretion of MNTX. Following IV dose of MNXT, the fraction dose of unchanged urinary excretion of MNTX (f_R) was 43.5% and it accounts for less than half of the total elimination suggesting appreciable non-renal elimination. Notably, f_R increased at higher dose of MNTX such as 24.3% and 50.5% after 0.3 and 0.45 mg/kg MNTX SC administration, respectively. While the underlying mechanism is unclear, slight deviation of AUC and C_{max} from a dose-proportionality may possibly account for the variability of the increased urinary excretion of MNTX at higher dose. It is also conceivable to hypothesize that the self-induction

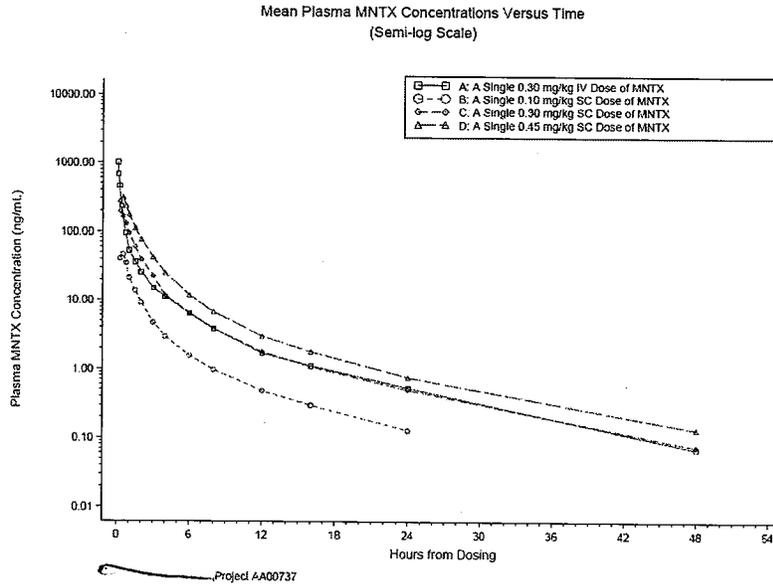
of active excretion at a high dose of MNTX. Nonetheless, the small number of subjects (n=5) in study MNXT 1103 cautions the interpretation of the results. The sponsor stated that the mechanism of atypical urinary excretion would be addressed but no further studies were conducted and urinary excretion at different dose levels was not evaluated in other PK studies.

Pharmacokinetic metrics estimated by noncompartmental analysis of plasma concentration time course data and cumulative urine data

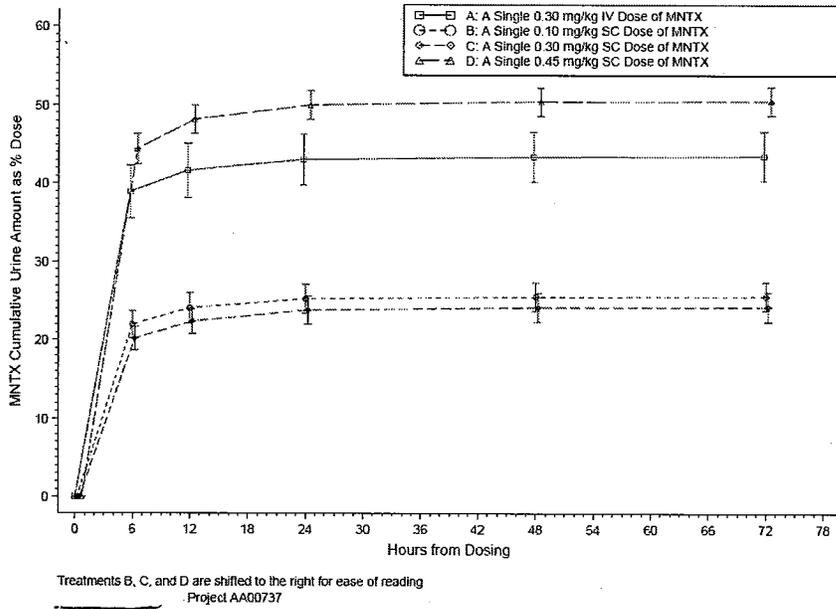
	0.30 mg/kg IV	0.10 mg/kg SC	0.30 mg/kg SC	0.45 mg/kg SC
	Mean (SD)			
C_{max} (ng/mL)	1006 (190)	47.5 (12.3)	197.0 (47.0)	317.0 (82.0)
AUC_t (ng/mL)*h	378.6 (52.3)	72.1 (10.4)	301.9 (42.5)	544.0 (33.9)
AUC_{∞} (ng/mL*h)	379.8 (52.9)	73.3 (10.6)	303.2 (43.14)	545.7 (34.6)
t_{max} (h)	0.06 (0.01)	0.45 (0.21)	0.30 (0.11)	0.45 (0.11)
$t_{1/2}$ (h)	7.81 (1.17)	6.14 (0.88)	8.04 (1.67)	8.83 (0.85)
Cl (L/h/kg)	0.80 (0.11)	-	-	-
Cl/F (L/h/kg)	-	1.39 (0.21)	1.00 (0.14)	0.83 (0.05)
V (L/kg)	9.05 (1.81)	-	-	-
V/F (L/kg)	-	12.3 (2.1)	11.7 (2.9)	10.5 (1.1)
F	-	0.60 (0.07)	0.82 (0.08)	0.99 (0.14)
f_R (%)	43.5 (7.1)	25.6 (4.0)	24.3 (4.2)	50.5 (4.1)
Cl_R (mL/min)	401.6 (88.6)	397.5 (84.0)	270.6 (44.8)	469.5 (59.3)

Data source: Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4

Mean Plasma MNTX Concentrations versus time (semi-log scale)



Mean (S.E.) MNTX Cumulative Urine Amount Versus Time



Results-Safety:

Total 10 AE episodes were reported and two subjects (subjects 3 and 5) experienced multiple AEs. There were no SAEs, no discontinuations because of AEs, and no deaths during the study. No subject required concomitant medication administration for AE resolution. Excluding one moderate episode of insomnia, all AEs were mild in severity.

1) Treatment Emergent Adverse Effects

Adverse Events Treatment

	Treatment				Total
	0.30 mg/kg IV	0.10 mg/kg SC	0.30 mg/kg SC	0.45 mg/kg SC	
Subjects Dosed	6	6	5	5	6
AE Episodes	3	6	0	1	10
Subjects with AEs	3	2	0	1	3
Headache	2	1	0	1	2
Neck pain	0	1	0	0	1
Nausea	1	0	0	0	1
Insomnia	0	1	0	0	1
Somnolence	0	1	0	0	1
Pruritus	0	1	0	0	1
Rash	0	1	0	0	1

Of the four headache episodes reported, three were considered either possibly or probably related to study drug. One subject required application of an ice bag for treatment of a headache. Following the 0.30 mg/kg IV dose, one subject experienced nausea either possibly or probably related to study drug. Subject 3 experienced the AEs of rash and pruritis on the upper arm following the 0.10 mg/kg SC dose; this episode lasted for more than seven days. It is unclear if it was at the injection site because **the actual injection site was not documented**. All other AEs were resolved in less than 48 hours.

2) Vital Signs, physical findings and other observations related to safety

Subject 4 experienced an elevation of AST and ALT and likely exercised-induced creatine kinase elevation to 8335 U/L at Period 2. Subject 5 had abnormal Alkaline phosphatase level from the screening (176 U/L) and through out the study period. It was not considered clinically significant by the investigator.

Four of the five subjects (subjects 1, 3, 4, and 5) experienced a pulse increase of 13 to 24 bpm with the position change from sitting to standing one hour following the 0.45 mg/kg dose. At the one-hour postdose time point, only two of these five subjects (Subjects 4 and 5) experienced a standing pulse increase from baseline of ≥ 10 bpm and none of the five subjects experienced corresponding orthostatic blood pressure decreases. Orthostatic pulse increases were not noted at the remaining postdose time points.

The sponsor's conclusion

MNTX administered as a single 0.30 mg/kg intravenous dose and single subcutaneous doses up to 0.45 mg/kg appeared to be safe and well tolerated by the healthy male subjects in this study.

Reviewer's comments

This study mainly contributed to determination of the absolute bioavailability. The renal clearance of MNTX is higher than normal GFR by about 3-4 folds suggesting that the renal elimination of MNTX involves active renal secretion. Also MNTX is a quaternary amine compound and quaternary amine compounds are known to be actively secreted via the same transport systems which transport other drugs including morphine. It is unknown that if concomitant administration of MNTX affect morphine clearance. Potential drug-drug interactions with concomitantly administered drugs which are eliminated by kidney should be addressed. The explanation for atypical urinary excretion was not provided by the sponsor. While it may have possibly been resulted from incomplete urine collection, notably AUC of MNXT was not compromised despite the increased urinary excretion of MNTX.

STUDY MNTX-206

Title: A Phase 1 Urodynamic Study of the Opioid Antagonist Naloxone and Intravenous Methylnaltrexone to Reverse Opioid Effects on Bladder Function in Healthy Volunteers

Primary Investigator: _____

Study Site: _____

Clinical Lab: _____

Overview

The present pilot study was designed to explore the potential benefit of MNTX _____ The study was designed to test the hypothesis that a significant proportion of opioid-induced changes in bladder function, (measurable as detrusor pressure [Pdet] or maximal force of bladder contraction), are due to activation of peripheral opioid receptors and can be reversed by MNTX.

It should be noted that his study *was not done* with the to-be-marketed subcutaneous formulation, but with the IV formulation which _____ It is included in this NDA package as part of the demonstration, on a mechanistic basis, of the _____

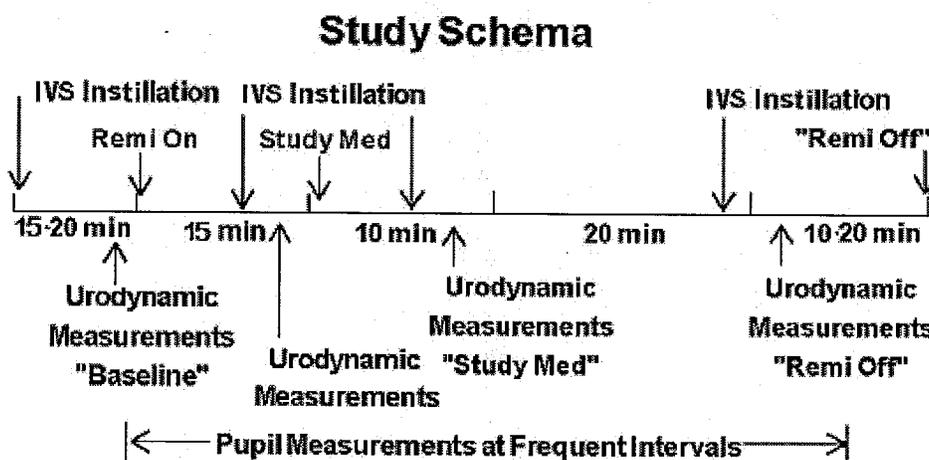
Study Design and Methods

This was to be a single-center, double-blind, randomized, placebo and active comparator-controlled phase 1 pilot study of the urodynamic effects of the opioid antagonists MNTX and naloxone in healthy male volunteers who had received a short acting opioid, remifentanyl (REMI). A hybrid, 3-drug, 2-period crossover design was to be used. During the screening visit, subjects were to undergo screening tests including a review of medical history and physical examination. Although the protocol specified recruitment and randomization of 15 subjects, it was assumed that 2 or 3 would be unable to void following opioid administration, yielding an ultimate sample size of 12 or 13. In practice enrolled and randomized subjects (#10, #14) failed to void after catheterization at baseline and were discontinued before receiving study drug. One additional subject (#2) was withdrawn due to a failure to void at session 2 after completing 1 session (naloxone). Therefore, the study was able to reach its powered study size of 12 to complete all phases of the trial.

Subject Groupings	Number of Subjects
Screened	15
Enrolled and randomized	15
Received at least one dose of study drug	13
Withdrawn before receiving at least one dose of study drug	2
Evaluated for safety	13
Evaluated for efficacy	13
Completed study	12

The study period was to consist of 2 sessions separated by at least 1 week. Assignment to a study drug sequence per session was to be made using a randomization schedule. During each session, urodynamic measurements were to be made at baseline, during administration of intra-venous (IV) REMI (remifentanyl), after administration of study drug (0.3 mg/kg IV MNTX, 0.01 mg/kg IV naloxone, or IV placebo [normal saline]), and after discontinuation of REMI. All subjects were to receive a single dose of MNTX during one session, and single doses of either naloxone or placebo during the other session.

Figure 1: Schema of timepoints for urodynamic (P_{det}) measurements



For all urodynamic measurements, a 7-French urethral catheter was inserted while the subject was in a recumbent position. A small rectal catheter was inserted for measurement of intra-abdominal pressure. The instillation of fluid (saline) and the measurement and recording of urine volume and intravesicular pressure were performed with the same device

used for routine urodynamic studies at 1-minute intervals. Fluid was instilled at 50 mL/minute, and the subject reminded at 1-minute intervals to state when he first had a sense of bladder fullness and when he first reported an urgency to void. The subject was to be asked to void, and P_{det} measured (P_{det} =maximal intravesicular pressure minus intra-abdominal pressure). If the subject was unable to void voluntarily, the study was terminated for that subject. After recording baseline P_{det} , pupil size was to be determined using an infrared pupillometer with an accuracy of ± 0.1 mm. Ambient light was to be < 50 lux, as determined by an incident light meter held at the subjects face. Baseline pupil size was determined as the average of three reading that did not differ by $> 10\%$.

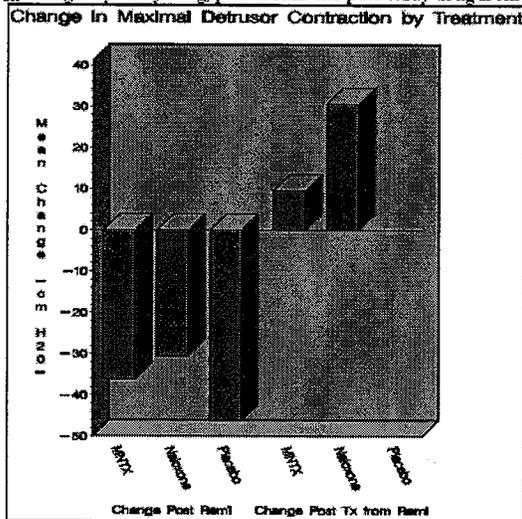
Results-Bladder Effects

Mean values (SD) of P_{det} by timepoint and study drug

Study drug	Timepoints and timepoint changes	Mean	SD	Lower 95% CL	Upper 95% CL
MNTX (n=12)					
	Baseline P_{det}	48.8	18.87	36.9	60.8
	REMI P_{det}	12.6	25.51	-3.6	28.8
	Study drug P_{det}	22.2	38.57	-2.3	46.7
	Final P_{det}	38.8	18.38	27.1	50.4
	Change post-REMI	-36.3	20.95	-49.6	-23.0
	Study-drug change from REMI	9.6	22.07	-4.4	23.6
	Reversal change from REMI	26.2	20.09	13.4	38.9
	Final change from baseline	-10.1	14.71	-19.4	-0.7
Naloxone (n=7)					
	Baseline P_{det}	61.4	34.13	29.9	93.0
	REMI P_{det}	31.1	29.28	4.1	58.2
	Study drug P_{det}	61.7	27.69	36.1	87.3
	Final P_{det}	37.0	24.55	14.3	59.7
	Change post-REMI	-30.3	38.88	-66.2	5.7
	Study-drug change from REMI	30.6	37.42	-4.0	65.2
	Reversal change from REMI	5.9	27.57	-19.6	31.4
	Final change from baseline	-24.4	31.45	-53.5	4.7
Placebo (n=6)					
	Baseline P_{det}	46.3	11.96	33.8	58.9
	REMI P_{det}	0.0	0.00	.	.
	Study drug P_{det}	0.0	0.00	.	.
	Final P_{det}	46.3	24.95	20.2	72.5
	Change post-REMI	-46.3	11.96	-58.9	-33.8
	Study-drug change from REMI	0.0	0.00	.	.
	Reversal change from REMI	46.3	24.95	20.2	72.5
	Final change from baseline	0.0	31.56	-33.1	33.1

Key: CL=confidence limit; n=number of subjects. Note: Missing P_{det} values due to inability to void are replaced for analysis purposes with a value of zero (0).

Mean P_{det} changes by study drug, post-REMI and post-study drug from REMI



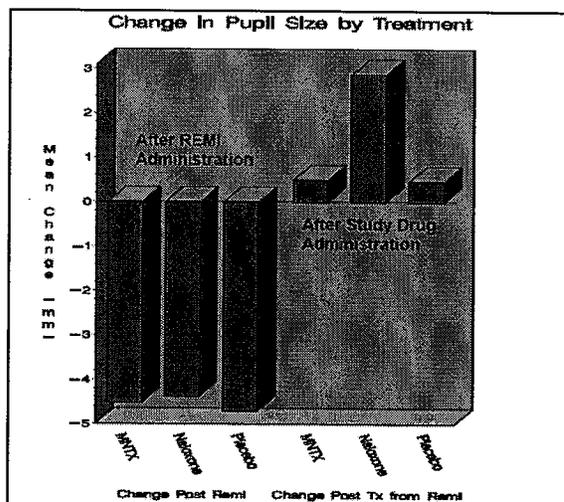
Overall, REMI decreased P_{det} from baseline in 21 of 25 sessions (84%), and in 12 of 13 subjects (92.3%), and caused complete urinary retention (defined as $P_{det}=0$) in 18 of 25 sessions (72%) and in 10 subjects (76.9%). REMI did not reduce P_{det} in 4 sessions (3 naloxone session subjects and 1 MNTX session subject). Decreases in P_{det} (of any intensity) were inhibited by study drug administration on 7 occasions in 6 of 13 subjects (46.2%). Of the 4 naloxone session subjects with pre-drug P_{det} decreases, all showed inhibition of the effect (100%) with naloxone. Of the 11 MNTX session subjects with pre-drug P_{det} decreases, 3 (27.3%) showed effect inhibition with MNTX. None (0%) of the 6 placebo subjects with P_{det} decreases showed any evidence of inhibition of P_{det} reduction after placebo (saline) administration.

Results-Pupillary

Mean values (SD) with CIs for eye pupil measurements by timepoint and study drug

Timepoint	Mean (mm)	SD	Lower 95% CL	Upper 95% CL
MNTX				
Baseline scan (n=12)	6.7	0.78	6.2	7.2
Scan post-REMI, pre-study drug (n=11)	2.2	0.49	1.9	2.5
Scan 10 min post-study drug (n=9)	2.8	0.80	2.2	3.5
● Scan change post-REMI (n=11)	-4.5	0.66	-5.0	-4.1
● Scan change 10 min post-study drug (n=9)	0.5	0.74	-0.1	1.1
Naloxone				
Baseline scan (n=7)	6.8	1.04	5.8	7.7
Scan post-REMI, pre-study drug (n=4)	1.9	0.50	1.1	2.7
Scan 10 min post-study drug (n=6)	5.2	1.49	3.6	6.8
● Scan change post-REMI (n=4)	-4.4	1.07	-6.1	-2.7
● Scan change 10 min post-study drug (n=4)	2.9	1.46	0.6	5.2
Placebo				
Baseline scan (n=6)	6.8	0.86	5.9	7.7
Scan post-REMI, pre-study drug (n=6)	2.1	0.42	1.7	2.5
Scan 10 min post-study drug (n=5)	2.6	0.58	1.9	3.2
● Scan change post-REMI (n=6)	-4.7	0.70	-5.4	-4.0
● Scan change 10 min post-study drug (n=5)	0.5	0.42	0.0	0.9

Key: n=number of subjects who had measurements at specified timepoints for each study drug group; min=minutes.



Eye pupil size reversal was defined as a change 10 minutes post-study drug. Across all subjects, REMI administration caused a mean pupillary constriction of 4 to 5 mm. Following administration of study drug 30 to 60 minutes post-baseline, all subjects receiving naloxone (100%) showed an increase in pupil size, while subjects receiving MNTX and placebo showed no significant increase, suggesting that MNTX did not cross into the CNS and thus was unable to reverse the REMI induced effects. By 160 minutes, all three groups showed pupil size returned to baseline levels

Summary

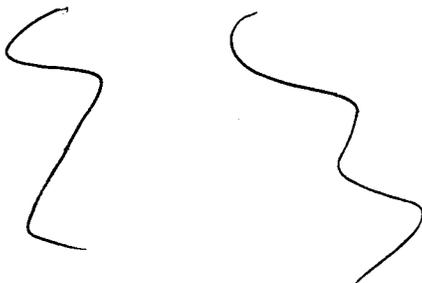
This pilot study was designed to explore the potential of MNTX

As a positive control naloxone, being a pure μ -opioid antagonist, successfully reversed opioid bladder effects, preventing REMI-induced urinary retention during all 4 sessions in which urinary retention was present. Administration of placebo had no effect on urinary retention. In contrast to placebo, MNTX reversed urinary retention in 3 of 11 subjects (27.3%). Infusion of the μ -type opioid, REMI, produced ocular miosis in 21 of 21 sessions (100%), and urinary retention in 18 of 25 sessions (72%). While the pure opioid antagonist naloxone successfully reversed all opioid-induced miosis in all sessions, neither placebo nor MNTX had any significant effect on miosis. Single doses of MNTX, naloxone, and placebo were well tolerated.

STUDY MNTX-3200KI-103

Title: An Open-Label, Single-Dose, Randomized, 2-Period Crossover, Bioequivalence Study Between the Current Formulation and the New Formulation of MOA-728 Administered Subcutaneously in Healthy Subjects

Study Site:



Analytical Site:

Objective:

The purpose of this study is to determine the bioequivalence between this new formulation and the current refrigerated formulation and, in a secondary fashion, to obtain additional PK and safety data on the subcutaneous administration of MNTX. It should be noted that the sponsor was previously advised by the FDA that this study was not necessary for approval and was actively discouraged from conducting this study as, from a clinical pharmacology standpoint, the study represented unnecessary human research [21CFR320.25(a)(1)]. The sponsor, however, maintains that this study was required for international registration of the new room temperature product.

This is an open-label, single-dose, randomized, 2-period, 2-sequence crossover, inpatient/out-patient study in 28 healthy subjects (27 completed all phases, 1 did not return and was lost to follow-up). The study events and sampling times are summarized in the following table.

Study Day	-1	1															2		3
Study Hour		-2 to 0	0	0.083	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	16	24	36	48
Inpatient admission	X																		X
Physical examination	X ^a																		X
Pregnancy test (β-HCG) for women	X ^b																		X
Urine drug screen	X ^b																		
Laboratory evaluation ^c	X	X						X									X		X
Vital signs ^d	X	X						X				X		X	X		X		X
ECG (12-lead)	X	X						X				X		X	X				X
Test article administration			X																
PK blood sample collection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	-----X																	
Nonstudy medication monitoring	X	-----X																	
CPE number	period 1	2	3													4	5	6	
	period 2	7	8													9	10	11	

- a. Brief physical assessment may be performed by nurse or physician's assistant and should include weight.
- b. These procedures may be omitted in period 2 if the subjects remain in the unit during the interperiod interval.
- c. Hematology, blood chemistry (fasting or non fasting), and urinalysis.
- d. Sitting blood pressure, pulse rate, and respiratory rate after at least 5 minutes of rest, and oral temperature.

Healthy men and women aged 18 to 50 years were eligible for enrollment if all other qualifying criteria were met. As noted above, a total of 28 subjects were enrolled, the general demographics of the study population are summarized below:

Characteristic	Treatment Sequence		Total (n = 28)
	Current/New (n = 14)	New/Current (n = 14)	
Age (years)			
N	14	14	28
Mean	31.50	31.50	31.50
Standard deviation	10.60	7.82	9.14
Minimum	18.00	20.00	18.00
Maximum	50.00	50.00	50.00
Median	28.50	29.00	29.00
Sex, n (%)			
Female	4 (28.57)	3 (21.43)	7 (25.00)
Male	10 (71.43)	11 (78.57)	21 (75.00)
Race, n (%)			
Black or African American	0	3 (21.43)	3 (10.71)
Other	1 (7.14)	1 (7.14)	2 (7.14)
White	13 (92.86)	10 (71.43)	23 (82.14)
Ethnic origin, n (%)			
Hispanic or Latino	1 (7.14)	3 (21.43)	4 (14.29)
Non-Hispanic and non-Latino	13 (92.86)	11 (78.57)	24 (85.71)

Upon entry into the study unit, an overnight fast was imposed so that no food was taken within at least 10 hours before administration. Water was not be permitted in the 2 hours before and 2 hours after administration which occurred at ~8am when a 0.15mg/kg SC dose was administered. Standard medium fat-meals, served according to the clinic's schedule, were provided 3 hours after test article administration.

Formulations Used

As indicated above, the objective of this study was to demonstrate bioequivalence between the original Phases 1-3 refrigerated formulation with a room temperature stable product. The original formulation was

.. According to the sponsor, the product is stable at room temperature storage conditions.

Component	Refrigerated (Phase 3)	Room Temperature
Vial glass	Amber	Clear
Stopper		
Methylhantrexone bromide	20 mg/mL	20 mg/mL
CaEDTA	Not used	mg/mL
Glycine HCl	Not used	mg/mL
NaCl	7 mg/mL	mg/mL
pH	3.5 - 7.0	3.0 - 5.0
Fill volume		
Maximum volume of injection	1.0 mL	0.6 mL

As noted above in the “objectives” section of this summary, the FDA was prepared to give the sponsor a waiver of in vivo biostudies, as given the route of administration (SC), none of the changes proposed by the sponsor would have resulted in an expected alteration in in vivo bioavailability. For this study the following lots of drug were used:

Study Drug	Strength	Dosage Form	Formulation Number	Batch Number	Manufacturing Location
MOA-728 for SC injection ^a	20 mg/mL	3 mL vial (amber vials)	NP9379	A04433	
MOA-728 for SC injection ^b	20 mg/mL	3 mL vial (flint vials)	003743	A21952	

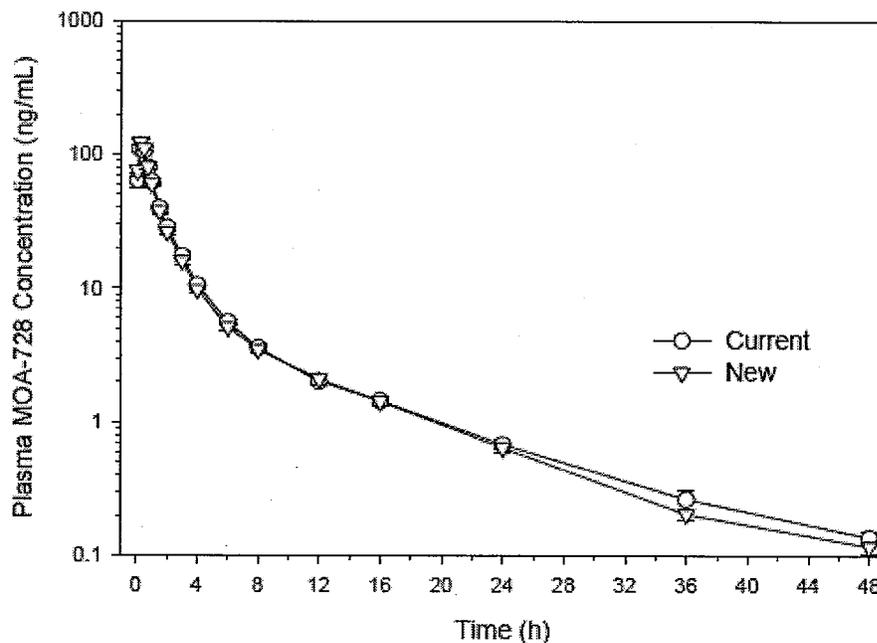
- a. Current formulation (stored under refrigeration).
b. New formulation (stored at room temperature).

Results-Pharmacokinetic

As was expected the two formulations yielded in vivo biopharmaceutic parameters that were super-imposable between the two formulations. As this was basically a comparison of two lots of the same drug substance, a different conclusion would have been almost unimaginable and again argues that this trial was unnecessary.

Formulation	C _{max} (ng/mL)	AUC _{0-t} (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	t _{1/2} (h)	t _{max} (h)
Current					
Mean ± SD	119 ± 33	221 ± 36	223 ± 36	9.2 ± 2.5	0.41
(Min, Max)	(62.6, 197)	(163, 333)	(168, 335)	(7.0, 19.4)	(0.08, 1.0)
New					
Mean ± SD	127 ± 34	218 ± 37	220 ± 37	8.4 ± 1.4	0.34
(Min, Max)	(82.9, 188)	(165, 333)	(172, 335)	(6.4, 13.8)	(0.08, 1.0)
Ratios of geometric LS means and 90% confidence intervals ^a					
Ratio of geometric LS Means	107%	98.6%	98.4%	-	-
90% Log-transformed CI	98.1 – 117%	96.2 – 101%	95.9 – 101%	-	-

Mean Plasma Level Profile New Formulation vs. Phases 1-3 Formulation (ie. Current)



Results-Safety

In this study, 14 of the 28 subjects (50%) experienced at least 1 treatment emergent adverse event (TEAE) during the study. All TEAEs were adjudged mild by the supervising clinician. There were no SAEs, no discontinuations because of AEs, and no deaths during the study.

One subject (103-001-000018) did have an elevated CPK level before, during and at the closure of this trial. This subject had a CPK of 419 U/L at screening (normal range 35-232 U/L), and 341 and 244 U/L on day 1 before receiving test article (hour -24 and hour -2, respectively). The subject's CPK continued to be near the upper limit of normal at all assessment times during period 1 (252, 207, and 210 U/L). Upon admission for period 2, the subject's CPK was increased to 1581 U/L. The subject's final CPK before discharge was 1022 U/L. The site was unable to contact this subject to return for a repeat CPK after he was discharged. The relevance of this subject is hard to evaluate, given that he probably should have been excluded from the trial anyway due to an elevated CPK at screening.

In addition to this subject an additional subject had ECG findings that were abnormal. Subject 103-001-000015 had a high QRS interval at screening, before administration of test article in period 1, and at multiple assessment times after administration of both formulations. An additional subject (103-001-000019) had a high QTc interval at 1 time of assessment (hour 48) after administration of the current formulation. As for these subjects, again the first subject probably should have been excluded from the trial and the second one, as the event is isolated and occurred 48hrs following an SC dose, it is unlikely to be related to the study drug.

Conclusion

The study demonstrated in vivo bioequivalence between the new non-refrigerated formulation of MNTX and the clinically studied refrigerated formulation. The pharmacokinetic parameters obtained in this trial are directly comparable to those from the other healthy volunteer trial and did not generate any new insights into drug absorption or disposition.

As for generating additional safety data one subject did have elevated CPK levels, however, these levels were elevated at study entry and they should probably have not been enrolled. The same can be said for the one subject that had consistent ECG issues, i.e., they were present at baseline and he should not have been enrolled. All in all, the enrollment of subjects who were clear protocol violators in terms of safety lab evaluations at entry renders the second stated objective of this trial (namely the generation of additional safety data) relatively un-fulfilled.

Appears This Way
On Original

Study MNTX-1105

Title: Phase 1, Open-Label Study to Evaluate Single Dose Pharmacokinetics, Safety, and Tolerability of Methylnaltrexone (MNTX) in Subjects with Impaired Renal Function

Objective:

- To evaluate the pharmacokinetics (PK) of MNTX, administered subcutaneously as a single dose in subjects/patients with impaired renal function, compared to the PK of MNTX administered to healthy controls.
- To evaluate the safety and tolerability of MNTX, administered subcutaneously as a single dose, in subjects/patients with impaired renal function.

Study site:



Bioanalytical site:



Subject: A total of 32 subjects/patients were dosed and analyzed: eight (8) patients with mild renal impairment, eight (8) patients with moderate renal impairment, eight (8) patients with severe renal impairment and eight (8) normal healthy subjects. Normal subjects were chosen after all renally-impaired patients had been enrolled, using demographic criteria to assure comparability with the renally-impaired patients with respect to age, weight, and gender. Subjects/patients were healthy or had mild, moderate, or severe renal impairment as determined using the FDA-recommended Cockcroft-Gault equation and confirmed by measurements of 24-hr creatinine clearance.

Reviewer's Comment: Majority of normal subjects (7/8) and patients with mild renal impairment (6/8) was Caucasian but majority of patients with moderate or severe renal impairment was black (5/8). The effect of unequal distribution of racial background is unknown.

Study design: This was an open-label, multi-center, non-randomized, single-dose study. Each subject received a single, 0.30 mg/kg, SC dose of MNTX following an overnight fast and followed by an additional 4 hours with water ad libitum two hours post-dose.

Reviewer's Comment: It was not necessary to fast subjects for an additional four hours since food intake does not affect S.C. administration of drug although the blood chemistry may be affected.

PK sampling

Table 5: Sampling for plasma pharmacokinetics and urinary excretion pattern

Samples	Days 1 through 5 (Hours Post Dose)																							
	0	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8	10	12	16	24	30	36	48	72	96	120	
Blood	0	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8	10	12	16	24	30	36	48	72	96	120	
Total Urine Collection	0-3									4-6			6-12			12-24			24-48			48	72	96
																			72	96	120			

Reference: Appendix 16.1.1

Analytical procedures: An analytical runs using HPLC-MS/MS for human K3EDTA plasma used in this study covered a range of 0.050 to 100 ng/mL with a lower limit of quantitation of 0.050 ng/mL.

Protocol deviations: Due to a miscalculation made at the study site, Patient 01-011 (moderate renal impairment) received a 0.32 mg/kg instead of 0.3 mg/kg of MNTX, resulting in a 6.5% overdose. The sponsor stated that this dose was within the range of doses employed in many other clinical trials, and had no impact on the safety assessment results. In addition, multiple screening determinations of CL_r were made for patients 02-102 and 02-103.

Results: Pharmacokinetics

Mean Plasma Methylnaltrexone Concentration versus Time profiles

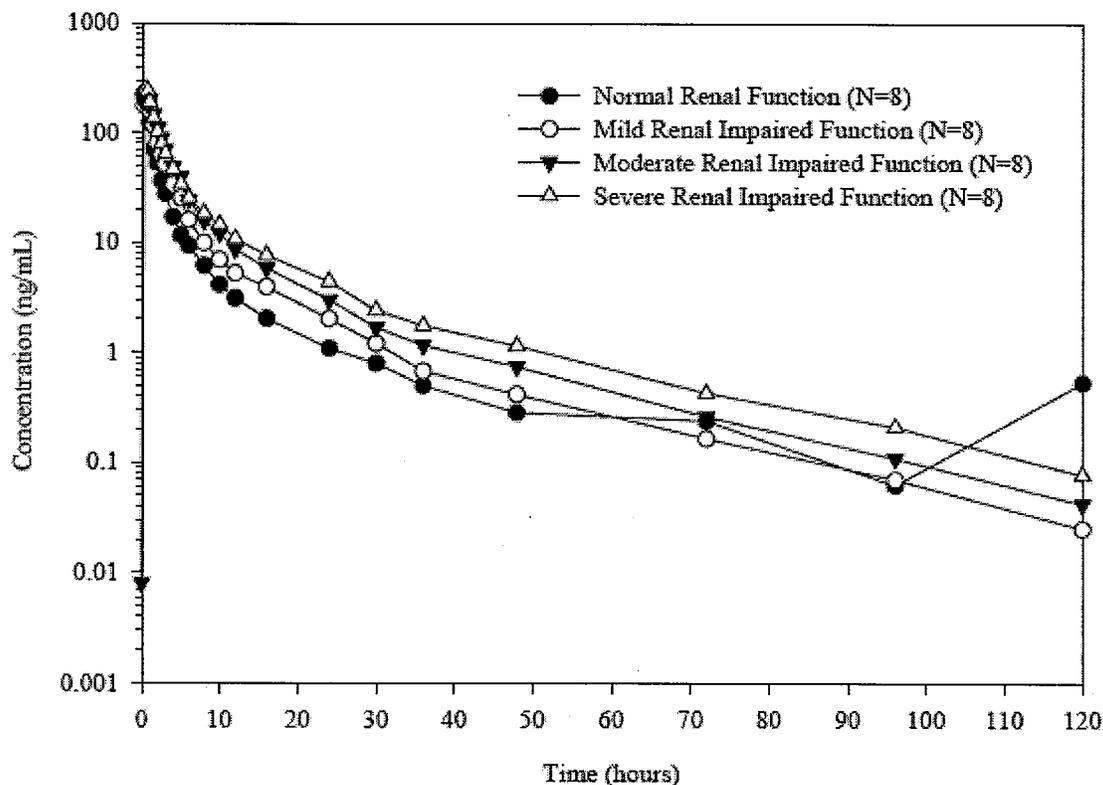


Table 18: Summary of plasma PK metrics and renal excretion of MNTX

Renal Function	Statistic	PK Metrics						
		C_{max} (ng/mL)	t_{max} (hr)	AUC_t (ng•hr/mL)	AUC_{∞} (ng•hr/mL)	$t_{1/2}$ (hr)	$f_R(\%)$	Cl_r (mL/min)
Normal	MEAN	257	0.44	427	433	13.4	45.2	441
	MEDIAN	222	0.408	425	427	13.4	44.0	455
	SD ^a	91.3	(0.22)	66	91.7	4.83	13.48	148.7
	N	8	8	8	4	4	8	8
Mild	MEAN	208	0.53	560	566	17.5	31.4	194
	MEDIAN	206	0.500	560	579	17.5	33.8	201
	SD ^a	47.7	(0.25)	69	74	2.02	14.80	89.7
	N	8	8	8	7	7	8	8
Moderate	MEAN	231	0.625	752	754	18.7	17.1	94.5
	MEDIAN	227	0.500	754	755	18.2	14.9	80.8
	SD ^a	40.6	(0.27)	141.2	140.9	3.89	8.43	43.50
	N	8	8	8	8	8	8	8
Severe	MEAN	304	0.56	819	822	19.6	10.3	51.6
	MEDIAN	260	0.63	821	824	19.9	9.86	52.0
	SD ^a	125	(0.22)	76	76	2.80	6.63	28.11
	N	8	8	8	8	8	8	8

^aRange (min, max) shown for t_{max} .

Reference: Tables 12, 13, 14 and 15.

AUC_{inf} and $T_{1/2}$ was available from only four normal subjects because the sponsor excluded 4 subjects with poor regression for terminal-half life estimation. All four excluded subjects had anomalous MNTX plasma concentration at the last time point above the LLOQ and the poor regression was done such that 16-20 points used for regression. For example, subject 03-001 with mild renal impairment was excluded from the half-life estimation because the last three time points (72, 96, 120 hr) chosen for the half-life analysis resulted in the estimation of 212 hr half-life. The half-life was probably overestimated since the concentration was practically same beyond 48 hr post-dose.

The clinical pharmacology reviewers communicated with the sponsor and requested data update via information request (8/29/2007) and a teleconference (10/12/2007). The sponsor provided reanalysis results (amendment 011). The sponsor excluded the anomalous points because they represent only a small fraction of the peak exposure ($< 3\%$ of C_{max}) to estimate $t_{1/2}$ values, and subsequently AUC_{∞} , in all subjects,.. The sponsor claimed that there was no bioanalytical issue for MNTX concentration measurement and the anomalous concentrations which were >5 times above LLOQ at 96-120h post-dose were not reanalyzed. The reanalysis of the data resulted in 25% decrease in $T_{1/2}$ such as from 13.4 ± 4.83 h to 10.8 ± 4.9 h for normal subjects while 7.1 %

decrease in $T_{1/2}$ such as from 17.5 ± 2 to 16.4 ± 3.8 h in subjects with mild renal impairment. Differences in AUCt and AUC $_{\infty}$ before and after reanalysis were less than 6%.

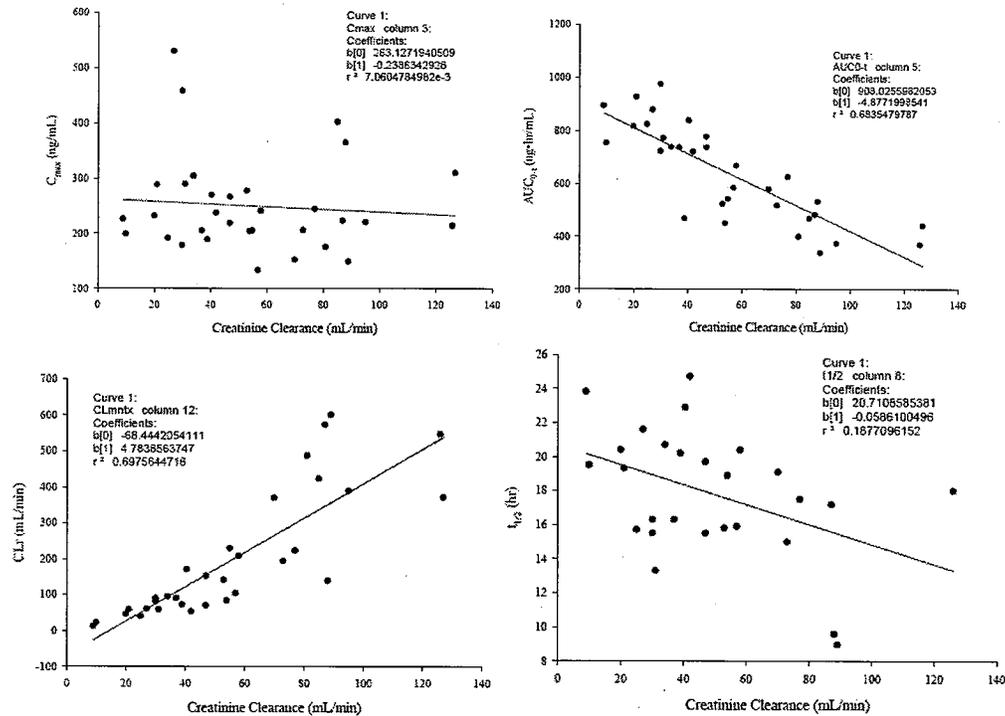
Table 21: Parametric statistical analysis of MNTX plasma PK metrics

Metric	Units	Comparison	Renal Impairment Group Mean ^a (Test)	Matched Normal Group Mean ^a (Reference)	Percent Ratio Test/Reference ^a	90% Confidence Interval ^a
C_{max}	ng/mL	Mild vs Normal	208	257	80.9	(64.5, 107)
		Moderate vs Normal	231		89.9	(72.6, 121)
		Severe vs Normal	304		118.3	(90.4, 150)
AUC _t	hr*ng/mL	Mild vs Normal	560	427	131.1	(116, 151)
		Moderate vs Normal	751		175.9	(155, 200)
		Severe vs Normal	819		191.8	(170, 220)
AUC _∞	hr*ng/mL	Mild vs Normal	565	433	130.5	(111, 157)
		Moderate vs Normal	754		174.1	(147, 207)
		Severe vs Normal	822		189.8	(163, 229)

^a Analyses of C_{max} , AUC_t, and AUC_∞ were performed on the natural log transformed data. Least squares means, ratios of least squares means, and 90% confidence intervals were obtained by taking the anti-log of the least squares means, differences of least squares means, and lower and upper confidence bounds, respectively. Reference: Table 14.2.2.1.

The renal insufficiency resulted in significant decrease in renal clearance and urinary excretion was observed. The renal clearance of MNTX in patients with severe renal impairment was decreased by 8 folds from 441 ml/min to 51.6 ml/min. Compared to in normal subjects, the AUCt of MNTX was increased by 37%, 84% and 100% in patients with mild, moderate and severe renal impairment, respectively (compared to reanalyzed AUCt). It is notable that 8 folds decrease in renal clearance resulted in only 2 folds increase in AUC in patients with severe renal impairment. The Cmax was more variable such as decreased by 20% and 10% in patients with mild and moderate renal impairment while increased by 18% in patients with severe renal impairment.

Individual Subject Creatinine Clearance vs. C_{max}, AUC_{inf}, CL_r and T_{1/2}



The degree of renal impairment expressed as renal creatinine clearance had a negative correlation with AUC and MNTX renal clearance and a positive correlation with the terminal half-life. The correlation between C_{max} and renal impairment was not observed.

Results: Safety

There were no deaths, SAEs, or significant AEs during the study. There were a total of 19 AEs reported by 7 subjects/patients. Nine (9) of the 19 AEs were experienced by three (3) subjects in the matched reference group. Thirteen (13) of the 19 AEs were reported as related to the study drug. Of the 13 related AEs, the matched reference group had four (4) possibly related (flushing, headache, nausea, and vomiting) AEs; the mild renal impairment group had one (1) definitely related (paraesthesia) and one (1) possibly related (fatigue) AEs; the moderate renal impairment group had two (2) possibly related (diarrhea and dyspepsia) AEs; and the severe renal impairment group had five (5) possibly related (dyspepsia, headache, hot flush, and vomiting) AEs. Overall, there were no meaningful differences in the number, severity, or nature of the AEs reported across the matched reference group and the three (3) renal impairment groups.

Table 23: Summary of Adverse Events by Preferred Term and Severity

Preferred Term	Renal Status/Impairment								Total		Overall Total
	Normal		Mild		Moderate		Severe		Mild	Moderate	
	Mild	Moderate	Mild	Moderate	Mild	Moderate	Mild	Moderate			
Diarrhea					1				1		1
Dyspepsia					1		1		2		2
Fatigue				1						1	1
Flushing	1								1		1
Headache	2						1	1	3	1	4
Hot Flush							1		1		1
Injection Site Stinging					1				1		1
Nausea	1								1		1
Paresthesia			1						1		1
Pharyngolaryngeal Pain	1								1		1
Pruritus	1								1		1
Rhinorrhea	1								1		1
Rigors	1								1		1
Vomiting	1						1		2		2
Total	9		1	1	3		4	1	17	2	19

*There were no AEs of severe or life threatening intensity.
Reference: Table 14.3.1-1b.

Sponsor's conclusion: The total exposure (AUC_t, AUC_∞) to MNTX was increased in patients with renal impairment, with an approximate two-fold increase in the severe renal impairment group. Further, urinary excretion of unchanged MNTX was progressively lower as the severity of renal impairment increased. Findings from this study, however, are not considered clinically significant. The proposed dose for MNTX is 0.15 mg/kg SC. Doses of as high as 0.5 mg/kg SC have been studied in healthy subjects and 0.3 mg/kg SC in the patient population with an acceptable safety profile in those studies. As total exposure in the severe impairment group was increased by no more than two fold, it appears that no dose adjustment should be necessary in patients with impaired renal function.

Reviewer's comments

Although in the study report the sponsor concluded no dose adjustment was necessary, in the dosage and administration section of the labeling a dose reduction by one-half was recommended for patients with severe renal impairment. No dose adjustment was recommended for patients with moderate renal impairment. The proposed dose-adjustment for patients with severe renal impairment by one-half appears reasonable and acceptable. Some patients will be given as low as 0.05 mg/kg after dose-adjustment from the proposed fixed dose schedule. In the clinical trial, the main studied dose was 0.15 mg/kg and a dose as low as 10 mg (equivalent to 0.08 mg/kg based on 60 kg body weight) showed efficacy in 43% of studied patients (3 out of 7). While this result has a limitation due to the small number of subjects, the efficacy of MNTX in terms of laxation response can be easily monitored and will in all likelihood be titrated to effect. As such the dose-reduction by one-half for patients with severe renal impairment is acceptable given the above considerations.

Study MNTX-1107

Title: Phase 1, Open-Label Study to Evaluate Single Dose Pharmacokinetics, Safety, and Tolerability of Methylalntrexone (MNTX) in Subjects with Impaired Hepatic Function

Objective:

- To evaluate the pharmacokinetics of MNTX administered subcutaneously as a single dose in individuals with impaired hepatic function as compared to healthy controls.
- To evaluate the safety and tolerability of MNTX administered subcutaneously as a single dose in individuals with impaired hepatic function as compared to healthy controls.

Study site: Multiple sites: _____

Bioanalytical site: _____

Subject: Twenty-four subjects/patients were enrolled, 8 subjects with normal hepatic function (matched reference) and 8 patients from each category of hepatic impairment (mild or moderate). The degree of hepatic impairment was estimated using the Child-Pugh classification, as recommended by FDA guidelines.

Study design: This was a multi-center, open-label, non-randomized, single-dose study. Each subject/patient received a single SC dose of 0.3 mg/kg MNTX into the upper medial thigh after an overnight (8h) fast and followed by 4h fast with water *ad libitum* 2h postdose.

Sample collections for PK Analysis:

Sampling for plasma pharmacokinetics and urinary excretion pattern

Samples	Day 1 Through Day 6																						
Blood	0 min	15 min	30 min	45 min	1 hr	1.5 hrs	2 hrs	2.5 hrs	3 hrs	4 hrs	5 hrs	6 hrs	8 hrs	10 hrs	12 hrs	16 hrs	24 hrs	30 hrs	36 hrs	48 hrs	72 hrs	96 hrs	120 hrs
Total Urine	0 - 12 hrs															12 - 24 hrs		24 - 48 hrs		48 hrs	72 hrs	96 hrs	

Note: This table reflects that actual samples were obtained at both the 5 and 10 hr time points, even though the source table in the protocol shows only the 5 hr sample time and the 5 hr sample time was inadvertently omitted at other points within the protocol.

Reference: Appendix 16.1.1

Pharmacokinetics analysis: model-independent PK metrics were calculated from plasma concentrations of MNTX using WinNONlin and/or SAS®

Results-Pharmacokinetics

Summary table of plasma and urine PK metrics for MNTX

Hepatic Function	Statistic	PK Metrics					
		C _{max} (ng/mL)	t _{max} ^a (hr)	AUC _t (ng•hr/mL)	AUC _∞ (ng•hr/mL)	t _{1/2} (hr)	f _R (%)
Normal	MEAN	208	0.47	482	441 ^b	11.7	53
	SD	54	(0.25, 1.00)	132	47	6	7
	N	8	8	8	6	6	8
Mild	MEAN	218	0.47	410	412	7.8	34
	SD	58	(0.25, 0.75)	120	121	1.5	15
	N	8	8	8	8	8	8
Moderate	MEAN	256	0.34	508	511	14.5	39
	SD	62	(0.25, 0.50)	218	219	10.6	14
	N	8	8	8	8	8	8

^aMedian (min, max) shown for T_{max}

^bFor the matched reference group, mean AUC_{0-∞} is less than mean AUC_{0-t} due to a difference in the number of subject/patients used in calculating descriptive statistics.

Reference: Appendix 16.2.6, 16.2.6.1 - Pharmacokinetic Report

Two subjects were excluded from the half-life estimation due to a poor regression and the half-life was estimated by the regression with 18-19 points. Per Agency's request, the terminal half-life estimation with data truncation at 48 h was provided (amendment 010). In addition, the sponsor provided reanalysis of the AUC and T_{1/2} in the amendment 011 after excluding anomalous data points from two previously excluded subjects. The reanalysis resulted in 12% decrease in the half-life from 11.7 ± 5.9 h to 10.4 ± 5.6 h and 10% decrease in AUC_t from 482 to 438 ng/ml•h and 0.2% change in AUC_∞ from 441 to 440 ng/ml•h.

There was a tendency of mean peak exposures (C_{max}) to increase slightly as a function of hepatic impairment such as 208 ng/ml in normal subjects to 218 ng/ml and 256 ng/ml in subjects with mild and moderate hepatic impairment. Relative to the normal group, mean total exposure (AUC_t and AUC_∞) was lower in the mild impairment group by 10% (90% CI: 67.8, 120) and higher in the moderate group by 8% (90% CI: 81.1, 144).

The overall results were consistent.

Recalculation of terminal half-life with truncation of the data at 48 hr (amendment #010)

Hepatic function	N	T _{1/2} (Mean ± SD h)
Normal	8	7.93 ± 1.42
mild	8	7.77 ± 1.46
moderate	8	8.46 ± 2.73

Table 14.2.2-1 Parametric Statistical Analysis of Plasma Pharmacokinetic Data: Hepatic Impaired Groups Relative to Matched Normal Group

Table 14.2.2-1
Parametric Statistical Analysis of Plasma Pharmacokinetic Data:
Hepatic Impaired Groups Relative to Matched Normal Group

Parameter	Units	Comparison	Hepatic Impaired Group	Matched Normal Group	Test/Reference	90% Confidence Interval	Group P-value ^a
			Mean (Test)	Mean (Reference)			
C _{max}	ng/mL	Mild vs Normal	211	302	105	(84.4, 130)	0.2206
		Moderate vs Normal	250		134	(99.9, 154)	
AUC ₀₋₄	hr*ng/mL	Mild vs Normal	395	470	84.0	(63.8, 110)	0.4538
		Moderate vs Normal	472		100	(76.4, 132)	
AUC _{0-∞}	hr*ng/mL	Mild vs Normal	396	439	90.4	(67.8, 120)	0.5163
		Moderate vs Normal	475		108	(81.1, 144)	
T _{1/2}	hr	Mild vs Normal	7.65	10.6	72.1	(44.9, 116)	0.2668
		Moderate vs Normal	11.5		108	(67.5, 174)	

^a Overall p-value testing the equality of Hepatic Impairment Group means from ANOVA.

NOTE: The parametric statistical analysis was performed on the ANOVA model of pharmacokinetic parameter = hepatic impairment status, where hepatic impairment status was a fixed effect.

Analyses of C_{max}, AUC₀₋₄, AUC_{0-∞}, and T_{1/2} were performed on the natural log transformed data. Least squares means, ratios of least squares means, and 90% confidence intervals were obtained by taking the anti-log of the least squares means, differences of least squares means, and lower and upper confidence bounds, respectively.

Renal excretion in the moderate (fr = 39%) and mild (fr = 34%) hepatic impairment groups was lower than in the normal group (fr = 53%). A similar trend was noted for renal clearance. The results also indicate a slightly larger inter-subject variability in renal excretion for the mild and moderate hepatic impairment groups. Notably, subject 01-802 with mild hepatic impairment had only 3% cumulative urinary excretion. The subject had positive protein (+2 at screening and +1 on Day 1) and ketones (+1 at screening and on Day1) in urine and had negative protein and ketones at discharge. Nonetheless, the AUC of the subject 01-802 was 317 ng/ml·h while the mean AUC was 412 ± 121 ng/ml·h. Note that subject 01-804 with moderate hepatic impairment had about 2-folds increased AUC and 14% cumulative urinary excretion. No adverse effect as MedDRA preferred term was reported for these subjects. It is not clear if the low urinary excretion was due to incomplete urine collection or hepatic impairment.

Urinary Recovery of MNTX

Hepatic	Normal	Mild	Moderate
Percent of Dose Recovered in Urine (%)	52%	29%	14%
	57%	51%	48%
	57%	42%	44%
	40%	36%	22%
	54%	3%	44%
	62%	31%	38%
	48%	44%	50%
	52%	34%	50%

Results Safety

There were no deaths, clinically significant AEs, or serious AEs reported during this study. A total of 16 AEs were reported by 11 of the 24 enrolled subject/patients.

Table 19: Summary of AE relationship to drug

Relationship To Drug	Subject Hepatic Status/Impairment			Overall Total
	Normal (N=8)	Mild (N=8)	Moderate (N=8)	
Definite			1	1
Probably	1	1	1	3
Possible	1	5	5	11
Not Related		1		1
Total AEs	2	7	7	16

Reference: Tables 14.3-1a and 14.3-1c.

Of the 16 AEs reported, two (2) AEs were experienced by healthy normal subjects, seven (7) AEs by the patients with mild hepatic impairment, and seven (7) AEs by patients with moderate hepatic impairment. Of the 16 AEs reported for this study, 1 AE was considered severe in intensity and 15 AEs were considered mild. The severe AE, intermittent bilateral leg cramps, was experienced by a matched reference subject and was considered possibly related to study drug. The most common AEs reported were headaches (50% mild hepatic impairment and 37.5% moderate hepatic impairment) and injection site burning (12.5% matched reference, 12.5% mild hepatic impairment, and 12.5% moderate hepatic impairment).

The sponsor's conclusion

The statistical results indicate that C_{max} was 5% and 24% higher for mild and moderate hepatic impaired groups relative to the matched reference group. Mean AUC_{∞} was about 10% lower for the mild, and 8% higher for the moderate hepatic impaired groups, respectively. Based on the ratio of means results, hepatic status does not appear to have a clinically significant impact on the plasma pharmacokinetics of MNTX.

No dose adjustment was recommended in the proposed labeling.

Reviewer's comment: The sponsor's conclusion is reasonable and acceptable. Nonetheless, it should be noted that two normal subjects had increased MNTX plasma concentrations at 72-96 h post-dose which was also observed in four normal subjects in study MNTX1105.

Appears This Way
On Original

[The following material was excerpted from the IRT/QT Review, see full document for details.]

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

NDA	21-964 / N000
Generic Name	Methylnaltrexone Injection
Sponsor	Progenics Pharmaceuticals, Inc.
Proposed Indication	Treatment of Opioid Induced Constipation in Patients Receiving Palliative Care
Dosage Forms	<ul style="list-style-type: none"> • Solution for subcutaneous injection • 
Proposed Therapeutic Dose	<ul style="list-style-type: none"> • 8 mg/day SC for patients from 38 kg to < 62 kg • 12 mg/day SC for patients from 62 kg to 114 kg • 0.15 mg/kg/day SC for other weights
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	0.64 mg/kg IV bolus
Application Submission Date	3/30/2007
Review Classification	TQT Study report in Standard NDA
Date Consult Received	6/28/2007
Date Consult Due	8/15/2007
Clinical Division	Division of Gastrointestinal Products
PDUFA Date	1/30/2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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

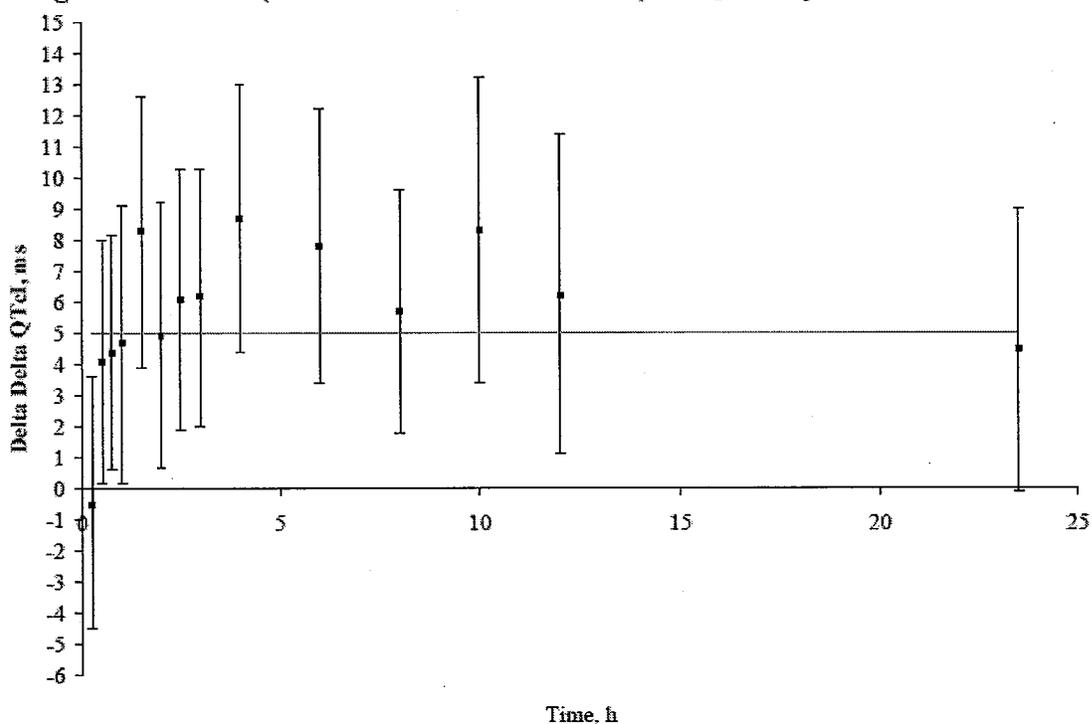
In this study the positive control, a single oral dose of 400 mg moxifloxacin, failed to have the expected effect on the QTc; at no time was the mean effect on the QTc greater than 5 ms as evidenced by a lower 90% confidence interval ≥ 5 ms. Therefore, the study lacked assay sensitivity, i.e. the ability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

methylnaltrexone on the QT interval.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

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

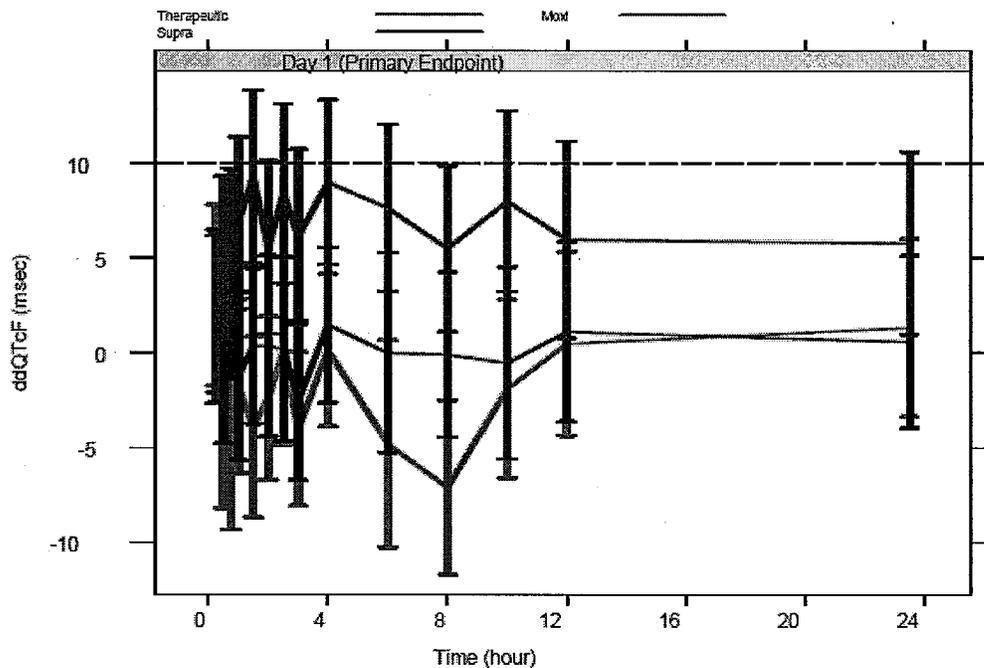
Figure 1: Mean (90% Confidence Intervals) $\Delta\Delta$ QTcI by Time for Moxifloxacin



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

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

Figure 2: Mean (90% Confidence Intervals) $\Delta\Delta$ QTcI by Time for MNTX 0.15 mg/kg, MNTX 0.5 mg/kg and Moxifloxacin



4. An unusually large number of subjects had an increase from baseline in QTc between 30 and 60 ms (over 50% among all the treatment groups) and several subjects had an increase more than 60 ms in all treatment groups (see Table 14 and Table). This anomaly suggests the study conduct was not optimal.

5. Several subjects had uninterpretable ECGs due to “technical problems,” which also suggests problems in the conduct of the study.

6. We have recently reviewed a TQT study protocol from the same sponsor under IND 64583, in which methylnaltrexone is being developed as a treatment for postoperative ileus. The results of this study, if designed and conducted appropriately, could be used to assess methylnaltrexone’s effect on the QT interval.

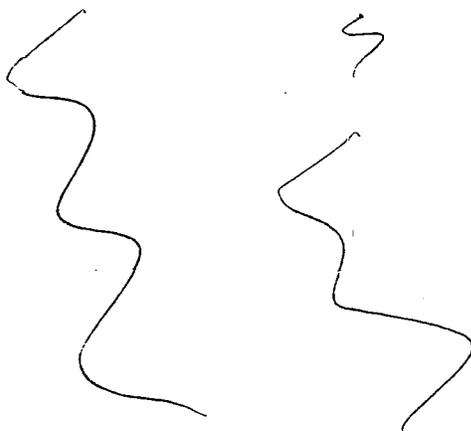
MNTX-1108

Title: A Phase I, Randomized, Open-Label, Active- and Placebo-Controlled Parallel Group Study of the Effect of Subcutaneous and Intravenous Methylnaltrexone on CYP450 2D6 Activity in Healthy Extensive Metabolizers of Dextromethorphan

Study Site:

Clinical Lab:

Analytical Lab:



Overview

Studies performed using pooled human liver microsomes in vitro have shown that MNTX is a weak inhibitor of CYP450 2D6, with a K_i of $7.93 \mu\text{M}$ vs. dextromethorphan and similar K_i values against other commonly administered CYP450 2D6 substrates [codeine ($11.3 \mu\text{M}$), hydrocodone ($11.5 \mu\text{M}$), oxycodone ($18.1 \mu\text{M}$), and imipramine ($15.7 \mu\text{M}$)]. Following therapeutic doses, observed maximum plasma concentrations of unbound MNTX were $<2.2 \mu\text{M}$ (slow push IV administration) and $<0.44 \mu\text{M}$ (SC administration), approximately 0.12- 0.28 and 0.024-0.056 times, respectively, the inhibition constants measured for these typical substrates. This suggests that therapeutic doses of MNTX are unlikely to cause clinically significant CYP450 2D6 inhibition.

Study Design and Methods

The present study was designed as an open-label, parallel group study was designed to determine the effect of a single SC dose or five IV doses of MNTX on CYP₄₅₀ 2D6 activity, measured by a change in the urine dextromethorphan/free dextromethorphan ratio following administration of a potential inhibitor of CYP₄₅₀ 2D6 (paroxetine), compared to the ratio with no inhibitor present. Subjects were randomly assigned to one of four groups:

Group 1 - MNTX 0.3 mg/kg SC single-dose

Group 2 - MNTX 0.45 mg/kg IV (20-min infusion) q 6 h for 5 doses (steady-state)

Group 3 - Paroxetine 20 mg PO single-dose (active control)

Group 4 - Placebo SC (for both active control and MNTX groups)

Each subject was randomized to one of the four treatment groups upon confirmation of qualifying "extensive dextromethorphan metabolizer" status by three separate dextromethorphan challenges during a pre-dose run-in period. Overall, 54 subjects were enrolled, 45 subjects received at least one dose of a study-prescribed drug and were evaluated for safety, and 31

subjects were randomized to one of the four treatment groups for the determination of any effect of MNTX administration on CYP₄₅₀ 2D6 activity. All 31 subjects completed the study

Disposition of Enrolled Subjects

Status	Number of Subjects
Enrolled	54
Discontinued	23
Subject did not meet entry criteria	9
Withdrawal requested by subject	1
Lost to follow-up	6
Other	7
Safety evaluable subjects	45
Randomized subjects	31
Completed	31

A priori, a doubling of the pre-dose urinary dextromethorphan/free dextrophan ratio following administration of study was used as an indicator of inhibition of CYP₄₅₀-2D₆, and was incorporated into the study design as an analytical endpoint. This end-point was selected based on published reports in the literature and is acceptable. As noted above the study incorporated both a single dose SC leg and a multiple dose IV treatment leg for MNTX.

Sample Collection-Blood

Group 1 MNTX 0.3 mg/kg SC single-dose:

- predose, 10, 20, 30 min, and 1.0, 2.0, 4.0, 6.0, and 8.0 h post-dose.

Group 2 MNTX 0.45 mg/kg IV q 6 h:

- Immediately prior to start of each infusion.
- Immediately prior to the start of the 5th infusion and at 0, 2.0, 5.0, 15.0, & 30.0 min, and 1.0, 2.0, 4.0, 6.0, and 8.0 h after the 5th infusion.

Group 3 Paroxetine 20 mg PO dose:

- 0, 0.5, 1, 2, 4, 6, 8, and 10 h post dose.

Group 4 Placebo SC dose:

- No blood samples were drawn from subjects receiving MNTX-matched placebo.

Sample Collection-Urine

All subjects were required to remain in the clinical facility throughout the urine collection period, during both the run-in and randomized treatment phases of this study. All urine collected from each subject was collected as a single 0-8 hour sample after the dextromethorphan dose (both during the run-in and randomization periods).

Results-2D6 Assessment

All 31 subjects randomized to one of four treatment groups completed the study after receiving 3 dextromethorphan challenges and their respective assigned regimens. As expected, the positive control, paroxetine (20 mg PO) exerted an inhibitory effect on CYP₄₅₀-2D₆ activity in 7/7

subjects vs. placebo which, by comparison, showed an effect in only 1/8 or 12.5% (p =0.0014) using the categorical definition of a 2 fold change in urinary excretion ratios.

Categorical analysis of urinary ratios of dextromethorphan/free dextrorphan in subjects co-administered either MNTX or paroxetine

Variable	Group 1 MNTX 0.30 mg/kg SC	Group 2 MNTX 0.45 mg/kg IV	Group 3 Paroxetine 20 mg PO	Group 4 Placebo SC
Doubling of Baseline Dextromethorphan / Free Dextrorphan Ratio				
Yes	2 (25.0%)	2 (25.0%)	7 (100.0%)	1 (12.5%)
No	5 (62.5%)	5 (62.5%)	0 (0.0%)	7 (87.5%)
p-value vs. Placebo	0.5692	0.5692	0.0014	---
p-value vs. Paroxetine	0.0210	0.0210	---	0.0014

As shown above, for MNTX, the proportion of subjects showing a doubling of the dextromethorphan/free dextrorphan urinary ratio relative to baseline following either a single SC dose or multiple doses of IV MNTX was unchanged between the two modes of administration and not statistically different from placebo.

Versus baseline, the mean change in dextromethorphan/free dextrorphan urinary ratio was not statistically significant when the MNTX-treated groups were compared to placebo (p>0.8402), but were highly significant when the paroxetine group was compared to placebo (p =0.0107).

Change in urine dextromethorphan/free dextrorphan ratios in subjects co-administered either MNTX or paroxetine: mean + (SD)

	PAROXETINE 20MG	0.30MG/KG SC	0.45MG/KG IV*	PLACEBO
BASELINE (MEAN OF 3)	0.158	0.15	0.13	0.189
POST-TREATMENT	0.736	0.152	0.195	0.285
DIFFERENCE	0.578	0.002	0.065	0.096

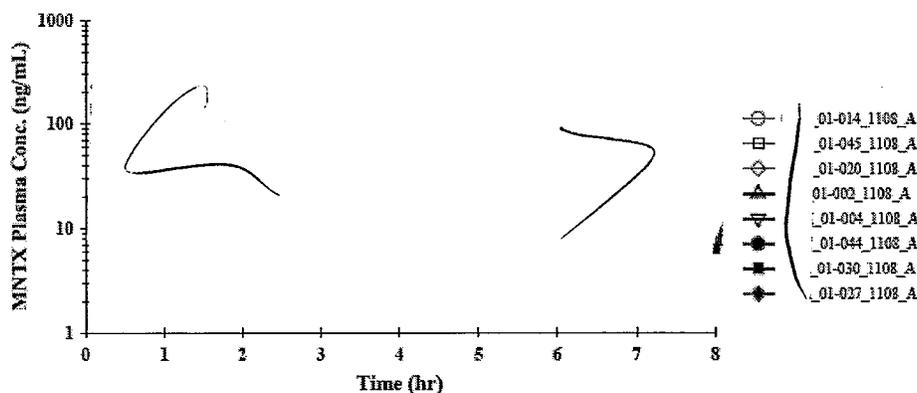
On this basis, the sponsor concluded that MNTX does not inhibit CYP450-2D6 activity in healthy male human subjects receiving MNTX SC 0.30 mg/kg as a single dose, or IV at 0.45 mg/kg q6h to steady-state.

Results-Pharmacokinetics

Although not primarily designed to be a definitive PK study the protocol did incorporate PK sampling for all treatment legs receiving active drug (MNTX or paroxetine). Graphical

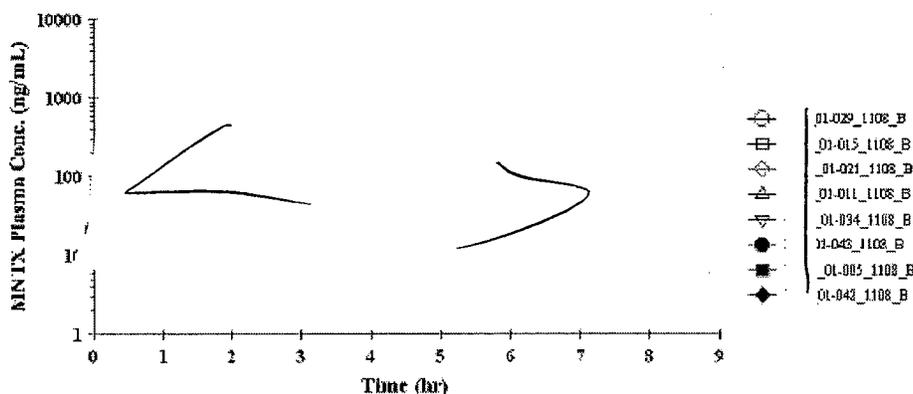
representation of the individual subjects' data for MNTX SC and IV and paroxetine oral did not reveal any subjects who can be considered outliers given the small number of subjects in the study. In general, the pk parameters for MNTX seen in this study for the SC treatment leg are similar to those seen in other studies contained in this NDA.

Spaghetti Plot of Individual Subject Profiles after MNTX 0.30 mg/kg SC (Log)



The IV data, while lacking definitive comparative data in this NDA does not show any subjects that show any unusual pharmacokinetic characteristics, given the understanding of MNTX pharmacokinetics from the SC data.

Spaghetti Plot of Individual Subject Profiles after MNTX 0.45 mg/kg IV (Log)



	AUC ¹	Cmax ²
MNTX Group 1 (0.3 mg/Kg)	457 (11.6%)	191 (19.9%)
MNTX Group 2 (0.45mg/Kg q6hr)	690 (15%)	1061 (18.7%)

1-AUC for Group 1 is AUC to last time point, the AUC for Group 2 is AUCinf

2-Cmax for Group 1 is observed Cmax, the Cmax for Goupr 2 is Cmax_{ss}

While pharmacokinetic data was collected for the paroxetine treatment leg as well, as it does not have any comparative value in this trial, it will not be summarized in this report.

Overall Conclusions

While the use of 2 fold changes in metabolic ratio has been used as a screening tool for 2D6 inhibition, it is an inexact methodology. While genetic testing predicts the PM phenotype with over 99% certainty it is not, as the sponsor seems to imply in the text of their report an "all or none" process. In fact the literature is full of references to Ultrarapid, Intermediate, Extensive and Poor metabolizers of 2D6. The "Poor Metabolizer" (PM) phenotype is characterized by the inability to use CYP2D6-dependent metabolic pathways for drug elimination. At the other extreme, the "Ultrarapid Metabolizer" (UM) phenotype can be caused by alleles carrying multiple gene copies. "Intermediate Metabolizers" (IM) are severely deficient in their metabolism capacity compared to normal "Extensive Metabolizers" (EM), but in contrast to PMs they express a low amount of residual activity due to the presence of at least one partially deficient allele. The point of this being that the steps taken by the sponsor to ensure only extensive metabolizers being present in this study are probably inadequate, as evidenced by at least 2 subjects showing some alteration in urinary metabolic ratio for both the IV and SC routes of MNTX administration. That being said, the changes in urinary metabolic ratio are not suggestive of a robust effect on 2D6, compared to those of the positive control paroxetine, and are unlikely to be clinically significant.

21 Page(s) Withheld

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

 X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Insook Kim
12/12/2007 04:55:29 PM
BIOPHARMACEUTICS

Dennis Bashaw
12/14/2007 11:34:36 AM
BIOPHARMACEUTICS

This review was presented at a required OCP internal
briefing on Dec. 7th, 2007. The input from
this briefing was incorporated into this document.