

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-964**

**MEDICAL REVIEW(S)**



Primarily Palliative". The waiver/deferral requests and above pediatric study plan were presented to Pediatric Review Committee (PeRC) on March 19, 2008 and the PeRC generally concurred with the sponsor' requests and the study plan.

Standard post-marketing surveillance (AERS) is recommended to further monitor the efficacy and safety of Relistor. The Applicant plans to \_\_\_\_\_

There are no other Phase 4 commitment, request or risk management steps recommended.

## **BACKGROUND:**

Methylnaltrexone bromide (MNTX) is a selective  $\mu$ -opioid receptor antagonist that blocks or partially blocks the intestinal smooth muscle relaxation response caused by morphine, thus decreasing or limiting the opiate's constipating side-effect. MNTX is a quaternary derivative of the  $\mu$ -opioid antagonist, naltrexone. The addition of the methyl group to naltrexone forms a compound which is more polar and less lipid soluble. Thus unlike naltrexone, MNTX does not cross the blood-brain barrier and accordingly, has the potential to block undesired peripherally-mediated side effects of opioid pain medications without affecting their centrally-mediated analgesic effects. As such, it provides a specific treatment for opioid induced constipation without affecting the pain relief provided by the opioid.

Multiple factors contribute to the development of constipation in patients receiving opioids. Opioids bind to specific receptors in the gastrointestinal tract and central nervous system to reduce motility and produce constipation by both direct and anticholinergic mechanisms. In addition, increased gastrointestinal transit time causes excessive water and electrolyte reabsorption from feces, and decreased biliary and pancreatic secretion further dehydrates stool.

The laxatives currently used to treat constipation can be classified into three general groups (bulk-forming laxatives, osmotically-acting laxatives, and stimulant laxatives), which work through different mechanisms of action. Bulk-forming laxatives cause retention of fluid in colonic contents, thereby increasing bulk and softness and facilitating transit. Osmotically-acting laxatives decrease net absorption of water and NaCl. Stimulant laxatives promote accumulation of water and electrolytes in the colonic lumen and increase intestinal motility.

The prevalence of opioid-induced constipation (OIC) in patients with advanced medical illness is reported to be nearly 50%. At the present time, there are no FDA approved therapies that are directly targeted to treat the specific cause of OIC. Laxatives currently available to treat OIC work via mechanisms that are unrelated to opioids, which act on opioid receptors in the gastrointestinal tract to alter motility and secretion.

Naltrexone hydrochloride was approved for the indication of alcohol dependence. The drug Suboxone contains naloxone HCl and buprenorphine HCl. Naloxone is also an antagonist at the  $\mu$ -opioid receptor site. Buprenorphine is a partial agonist which binds at the  $\mu$ -opioid receptor site and an antagonist at the  $\kappa$ -opioid receptor site. Suboxone is indicated for the treatment of opioid dependence.

Entereg (alvimopan), another investigational opioid antagonist for the treatment of postoperative ileus under NDA

For this NDA, Progenics evaluated the efficacy of SC MNTX in two phase 3 studies (MNTX 301 and MNTX 302) that included randomized, double-blind, placebo-controlled periods, and one phase 2, ascending-dose study (MNTX 251) that included a randomized, double-blind, controlled period. In each study, double-blind treatment was followed by a period of open-label MNTX treatment (ranging from three weeks to four months).

#### **DISCIPLINE REVIEW SUMMARY AND COMMENTARY:**

##### **OPDRA/DDMAC/DMETS:**

DMETS does not recommend the use of the proposed trade name, Relistor ✓ and finds the proposed trade name unacceptable. Specifically, DMETS objects to the use of the

DDMAC finds the proprietary name, Relistor ✓ acceptable from a promotional perspective.

Four clinical sites were inspected by the Division of Scientific Investigations. Although some of protocol violations were identified, DSI concluded that the violations, some of them due to the nature of the study being studied in terminally ill patients, would not affect the validity and acceptability of the data in support of this NDA. No follow up other than routine surveillance is recommended. See Dr. Khairy Malek's review dated December 3, 2007 for details.

**Chemistry and Manufacturing:**

From the CMC perspective, this NDA is recommended for approval pending agreement on product labeling. There is no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Based on Dr. Blair Fraser's evaluation, the chemistry, manufacturing, and controls information for the drug substance is appropriately referenced, has been reviewed, and is concluded to be adequate. The stability data for three commercial batches support a month retest period for the bulk drug substance.

Sufficient stability data for three commercial-scale batches of drug product support the requested expiry of 24 months when stored at room temperature, 68°-77°F (20°-25°C); excursions permitted to 15-30°C (59-86°F), and protected from light. Do not freeze.

The sponsor committed to placing at least one commercial production lot of the drug product per year following the approved stability protocol. All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

For more detail information, please see Dr. Blair Fraser's review dated February 5, 2008.

**Pre-Clinical Pharmacology/Toxicology:**

Pharmacology Reviewer, Dr. Tamal Chakraborti, recommended that the application be approved for the proposed indication and no recommendation for nonclinical studies.

According to Dr. Chakraborti's evaluation, the systemic toxicity of MNTX was adequately evaluated in complete range of acute, subacute/subchronic and chronic toxicity studies in mice, rats and dogs. The potential genotoxicity of MNTX was examined in an adequate battery of genotoxicity tests. In addition, MNTX has been evaluated for fertility and reproductive performance (Segment I) in rats, teratology (Segment II) in rats and rabbits and peri- and post-natal development (Segment III) in rats. Adequate safety pharmacology studies were also conducted with MNTX.

Generally, bridging studies comparing the pharmacokinetics (PK) and toxicity of MNTX following single intravenous (IV) and subcutaneous (SC) dose in dogs and single IV, SC and oral (PO) dose in rats demonstrated comparable PK and toxicity profile between SC and IV route. Based on this, pivotal IV toxicity studies in rats and dogs were considered adequate to support recommended clinical dosing using SC route.

In safety pharmacology studies, MNTX at IV doses ranging from 1 to 20 mg/kg had no apparent toxicologically significant effects on the neuropharmacological profile in mice, gastrointestinal function in rats, pulmonary function in guinea pigs, or renal function in

rats. Cardiovascular safety pharmacology studies were conducted using adequate battery of *in vitro* and *in vivo* tests. Methylnaltrexone showed significant cardiovascular effects in these studies.

Methylnaltrexone caused prolongations of QTc interval (116-122% of the pretest values and 115% of the control) on Day 8 of the treatment at 750 mg/kg/day in one male and two females in the one-month oral toxicity study in dogs. In a three-month intravenous toxicity study in dogs at 1, 5 and 20 mg/kg/day, there was a dose-related prolongation of QTc in both sexes (male at Day 6: 9 and 15% increase at 5 and 20 mg/kg/day, respectively; females at Day 6: 3%, 5% and 12% increase at 1, 5 and 20 mg/kg/day, respectively) at Day 6 and Day 83 (similar increases as at Day 6 in both sexes) post-treatment compared to vehicle control.

These QT prolongations were seen at approximately 300 and 150 times human C<sub>max</sub> at 0.15 and 0.3 mg/kg, respectively and 38 and 18 times human AUC at 0.15 and 0.3 mg/kg, respectively. Maximum QT prolongations of 12-15% were seen at 20 mg/kg, which is about 630 and 315 times human C<sub>max</sub> at 0.15 and 0.3 mg/kg, respectively and 197 and 90 times human AUC at 0.15 and 0.3 mg/kg/day, respectively. Exposure at the NOAEL of 1 mg/kg/day in rats (AUC = 286 ng·h/mL) and 1 mg/kg in dogs (AUC = 922 ng·h/mL) were approximately 2 and 5 times, respectively, the human exposure at recommended dose of 0.15 mg/kg, and approximately 0.75 and 2 times, respectively, the human exposure at maximum recommended dose of 0.30 mg/kg.

Test-article-related CNS effects in rats and dogs generally included tremors, convulsions, and decreased activity. Adverse CNS-related clinical signs were seen at IV dosages  $\geq$  15 mg/kg/day in rats and at IV dosages  $\geq$  20 mg/kg/day in dogs. These CNS adverse effects of MNTX suggested that possibly a limited amount of MNTX crosses the blood-brain barrier. The NOAELs in 90-day IV toxicity studies in rats and dogs were 1 mg/kg.

Methylnaltrexone was not shown to be mutagenic in a battery of genotoxicity studies.

Overall, the results of pharmacology studies appeared to support the intended use. For more detail information, please see Dr. Tamal Chakraborti's review dated November 29, 2007.

#### **Biopharmaceutics:**

From the viewpoint of the Office of Clinical Pharmacology, the Clinical Pharmacology and Biopharmaceutics information in the NDA is acceptable provided that a mutual agreement on label language can be reached between the sponsor and the Agency. There is no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

### **Thorough QT Study Review Summary**

According to Dr. Joanne Zhang's evaluation (reviewer for 'thorough QT' study), 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. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcN}$  for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

According to Dr. Joanne Zhang's evaluation, the methylnaltrexone doses evaluated in this study are acceptable. The mean peak plasma concentration from the suprathreshold dose (0.64 mg/kg IV) is 9-fold and 2.3-fold greater than those observed from the SC therapeutic dose (0.15 mg/kg SC) and IV therapeutic dose (24 mg). There are no known intrinsic or extrinsic factors that can increase exposure to methylnaltrexone greater than what was observed following the suprathreshold IV dose.

MNTX is primarily eliminated in the urine as unchanged drug (~50%) 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.

The effects of renal impairment on the pharmacokinetics of MNTX were evaluated in subjects with mild, moderate and severe renal impairment. Total exposure ( $\text{AUC}_{\infty}$ ) increased as a function of the renal impairment, and was approximately doubled in the severe renal impairment group (89% increase) while mean  $\text{C}_{\text{max}}$  was varied among groups. 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. Please see Dr. Insook Kim's review dated December 12, 2007 for details.

### **Clinical/Statistical:**

The efficacy of SC MNTX was evaluated in two double-blind, randomized, placebo-controlled phase 3 studies (MNTX 301 and MNTX 302). The phase 3 studies each had a three-month, open-label extension study (MNTX 301EXT and MNTX 302EXT). The

primary intent of the open-label treatment with SC MNTX was to obtain long-term safety data.

MNTX 301 included a one-day, double-blind, placebo-controlled period followed by a four-week open-label period. During the double-blind portion of the study, 154 eligible patients were randomly assigned to receive a single SC dose of MNTX 0.15 mg/kg (n=47), MNTX 0.30 mg/kg (n=55), or placebo (n=52). Twenty-four hours after the dose administration, 136 patients participated in the subsequent four-week open-label period. Patients were administered an initial dose of 0.15 mg/kg, with subsequent doses of 0.075 mg/kg, 0.15 mg/kg, or 0.30 mg/kg given daily, as needed, for up to four weeks.

MNTX 301EXT was a three-month, open-label extension of MNTX 301, in which 21 patients received SC MNTX. Patients initially received MNTX at the same dose as last received in MNTX 301. Subsequent dose adjustments to one of three dose levels (0.075, 0.15, or 0.30 mg/kg) were permitted. Doses were administered daily, as needed, for up to three months.

MNTX 302 was a phase 3, double-blind, placebo-controlled study in which 134 patients were randomly assigned to receive either SC MNTX 0.15 mg/kg (n=63) or SC placebo (n=71) QOD for two weeks. Any patient who had <3 bowel movements, not associated with rescue medications or interventions, during the first week was eligible for dose escalation (i.e., 0.30 mg/kg SC MNTX or the equivalent volume of placebo) during the second week. Doses were administered every other day, as needed, for up to two weeks.

MNTX 302EXT was a three-month, open-label extension of MNTX 302, in which 82 patients were treated with MNTX. Patients received an initial MNTX dose of 0.15 mg/kg; subsequent dose adjustments to 0.30 or 0.075 mg/kg were allowed. Doses were administered daily, as needed, for up to three months.

### **Efficacy:**

The primary efficacy endpoint of the MNTX 301 study was rescue-free laxation (i.e., no rescue laxatives were administered prior to laxation) response within 4 hours of treatment with the double-blind dose of MNTX. The proportion of patients with a positive laxation response was the basis for the point estimates of efficacy for each of the three treatment groups.

Patients with advanced medical illness with a life expectancy of 1 to 6 months and no clinically significant laxation within 48 hours were enrolled into the studies. Patients were excluded from the studies if previous treatment with MNTX or any non-opioid cause of constipation

The mean age of the 154 patients was 65.3 years (range, 21 to 100 years). More than half of the patients were male (54.5%) and the majority were Caucasian (82.5%).

Efficacy analyses were performed on the ITT analysis set, which included all randomized patients who received the single dose of double-blind medication.

Rescue-free laxation occurred for 62% of MNTX 0.15 mg/kg patients and 58% of MNTX 0.30 mg/kg patients compared with 13.5% of placebo patients 4 hours after double-blind dosing as shown in Table 1 below.

**Table 1: Laxation Response after 4 Hours: MNTX 301 Double Blind Set**

Time	Placebo (n=52)	MNTX 0.15 mg/kg (n=47)	MNTX 0.30 mg/kg (n=55)
4 Hours	7 (13.5%)	29 (61.7%)	32 (58.2%)
P-Value <sup>1</sup>		<0.0001	<0.0001

<sup>1</sup> 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.

The analyses of Laxation responses within 24 hours of treatment (one of secondary Endpoint) indicated that significantly more patients treated with MNTX had rescue-free laxation within 24 hours of receiving the double-blind dose of study drug compared with placebo-treated patients as shown in Table 2.

**Table 2: Laxation Response after 24 Hours: MNTX 301 Double Blind Set**

Time	Placebo (n=52)	MNTX 0.15 mg/kg (n=47)	MNTX 0.30 mg/kg (n=55)
24 Hours	14 (26.9%)	32 (68.1%)	35 (63.6%)
P-Value <sup>1</sup>		<0.0001	0.0001

<sup>1</sup> 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.

Results of Study MNTX 301/301EXT show that a single SC injection of MNTX at doses of either 0.15 mg/kg or 0.30 mg/kg was significantly more effective than placebo in inducing laxation in the patients studied.

The percentage of patients with laxation response to the 1<sup>st</sup> open-label dose of MNTX 0.15 mg/kg was similar to the response rate for patients who received MNTX as their double-blind dose. Four hours after the 1<sup>st</sup> open-label dose of MNTX 15 mg/kg, the rescue-free laxation response rates were 54% for patients who had been randomized to the placebo group, 62% for patients who had been in the MNTX 0.15 mg/kg group, and 52% for patients who had been randomized to the MNTX 0.30 mg/kg group during the double-blind period. By 24 hours after the 1<sup>st</sup> open-label dose of MNTX 0.15mg/kg,

rescue-free laxation rates were 71% for patients who had been randomized to received placebo during the double-blind period, 76% for patients randomized to MNTX 0.15 mg/kg, and 59% for patients randomized to MNTX 0.30 mg/kg during the double-blind period.

When used on a PRN basis, MNTX continued to be effective with 56% and 68% of patients having rescue-free laxation 4 and 24 hours after their first PRN dose. These results were consistent over time such that the average laxation response ranged from 55% to 64% over the 3-month EXT study.

As one might expect, with a decrease in constipation (four times as many MNTX-treated patients had bowel movements compared with placebo-treated patients), there were improvements in the constipation associated symptoms of distress and pain. Both patients and clinicians rated MNTX at both the 0.15 mg/kg and 0.30 mg/kg dose more favorably on the Global Clinical Impression of Change Scale, and the patient and clinician ratings were consistent.

For Study 302, there were 2 co-primary efficacy endpoints: 1) Proportion of patients with laxation within 4 hours after the first dose of study drug and 2) Proportion of patients who had a laxation response within 4 hours after at least 2 of the first 4 doses (the first week of treatment).

Of the 133 patients in the ITT analysis set, the percentage of patients who had a rescue-free laxation within 4 hours of receiving the first dose of study medication was higher in the MNTX 0.15 mg/kg group (48.4%) than in the placebo group (15.5%). The percentage of patients who had a rescue-free laxation within 4 hours after dose administration following at least 2 of the first 4 doses was also higher in the MNTX 0.15 mg/kg (51.6%) than in the placebo group (8.5%). Results of primary endpoints for Study MNTX 302 are summarized in Table 3 below.

**Table 3: Summary of Results of Primary Efficacy Endpoints: MNTX 302**

	Placebo (n=71)		MNTX 0.15mg/kg (n=62)	
	Number of Responder	% (95% CI)	Number of Responder	% (95% CI)
Laxation within 4 hours on Day 1	11	15.5 (7.1 - 23.9)	30	48.4 (35.9 – 60.8)
At least 2 laxations within 4 hours over the first 4 doses	6	8.5 (2.0 – 14.9)	32	51.6 (39.2 – 64.1)

The median time to rescue-free laxation after the first dose was 1.0 hour in the MNTX group and 11.2 hours in the placebo group, based on the patients who had laxation before receiving the second dose. Following subsequent doses, the median time to laxation ranged from 1.1 to 2.6 hours in the MNTX group and 7.2 to 22.0 hours in the placebo group based on patients who had laxation before receiving the next dose.

Global rating scales showed that higher percentages of patients in the MNTX group than in the placebo group rated their bowel status improved on Day 7 (73.5% versus 35.1%) and Day 14 (67.9% versus 44.6%). Likewise, the Investigators rated bowel status improved for higher percentages of patients in the MNTX group than in the placebo group on Day 7 (69.4% versus 35.1%) and Day 14 (67.9% versus 50.0%).

Pain scores were similar in the 2 treatment groups at baseline, and both groups showed only small mean changes in pain scores over the course of the study.

In Study MNTX 302EXT, for the subset of patients who had received placebo in the double-blind study, the response rate increased from 10.8% at the end of double-blind treatment to 46.2% during the first month of open-label MNTX treatment. This rate is comparable to the rate achieved with MNTX at the end of double-blind treatment. The rate was similar during the second month of the extension (47.7%) and lower during the third month (38.2%) when the number of patients still receiving MNTX was small (13).

The pooled results of the double-blind placebo-controlled (DBPC) data derived from the double-blind phases of studies MNTX 301 and 302 are summarized in Table 4.

**Table 4: Pooled Data of DBPC Studies Using Weight- Based Dosing in Patients with Laxation Response within Four Hours: MNTX 301 and MNTX 302**

Study	Treatment	Responder (n/N)	% (95% CI)	P-Value
MNTX 301	Placebo	7/52	13.5 (4.2-22.7)	
	0.15 mg/kg	29/47	61.7 (47.8-75.6)	p<0.0001
	0.30 mg/kg	32/55	58.2 (45.1-71.2)	p<0.0001
MNTX 302	Placebo	11/71	15.5 (7.1-23.9)	p<0.0001
	0.15 mg/kg	30/62	48.4 (35.9-60.8)	p<0.0001
Pooled	Placebo	18/123	14.6	
	0.15 mg/kg	59/109	54.1	
	0.30 mg/kg	32/55	58.2	

Source: Modified Table 35 from Dr. Ronald Orleans's review.

In summary, results demonstrate that the 0.15 mg/kg and 0.30 mg/kg SC dosages were both effective in the treatment of opioid induced constipation as measured by the four hour laxation rate versus placebo. Laxation within 24 hours after the first dose and laxation after two of the first four double-blind doses also showed a consistent advantage for MNTX over placebo. Please see Dr. Ronald Orleans's review for more detail efficacy evaluation.

### **Safety:**

The total safety data base from the studies conducted by the Applicant is 286 patients and 144 volunteers who received SC MNTX. Of the 286 patients who took MNTX, 225 had a primary diagnosis of cancer, 174 had renal dysfunction, 120 had CNS disease, 54 had heart failure, and 60 had COPD.

The longest study submitted to this NDA was MNTX 301/301EXT in which SC MNTX was given for up to four months.

### **Deaths**

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

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

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

Patient 301-19-0007 was a 73 year old Caucasian female hospice patient with Stage IV metastatic breast cancer which was originally diagnosed in 2000 and reoccurred in October of 2003. The patient was randomized and completed the double-blind, single dose period (0.30 mg/kg SC) in study MNTX 301 on 5/27/2004. She entered the open-label phase and initially received a single dose of MNTX 0.15 mg/kg SC on 5/28/2004. After this dose was given she experienced gastrointestinal cramping and an episode of two small hard stool "pebbles" about one hour post injection. She subsequently received three doses of MNTX 0.30 mg/kg SC from 5/29/2004 until \_\_\_\_\_. One hour after the dose was given on \_\_\_\_\_ the patient complained of mild abdominal pain and had massive diarrhea, nausea and vomiting which caused her to pass out. Vital signs taken during this time revealed a pulse of 60, respirations 18, and a BP of 110/60. The following day she was found dead. An autopsy was not performed. In the Investigator's

opinion, causality of the events of severe diarrhea, dehydration, and cardiovascular collapse was probably due to the study drug.

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

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

#### **Other Serious Adverse Events**

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

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

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

#### **Common adverse events**

In the DBPC Pool, Gastrointestinal Disorders and Nervous System Disorders were the organ system with rates at least 5% greater in the MNTX group (52.7%) than in the placebo group (35%). The incidence of Cardiac Disorders was higher in the placebo group (8.1%) than in the MNTX group (4.2%).

In the DBPC Pool, the most common adverse events occurring in the MNTX group at least twice that in the placebo group were abdominal pain, flatulence, nausea, diarrhea and dizziness. These gastrointestinal adverse events are not surprising for a drug that acts on the bowel by increasing motility and drug transit time. The increased dizziness may be due to vasovagal reactions from straining at stool. The adverse reactions are summarized in Table 5.

**Table 5: Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies\***

Adverse Reaction	MNTX N=165	Placebo N=123
Abdominal Pain	47 (28.5%)	12 (9.8%)
Flatulence	22 (13.3%)	7 (5.7%)
Nausea	19 (11.5%)	6 (4.9%)
Dizziness	12 (7.3%)	3 (2.4%)
Diarrhea	9 (5.5%)	3 (2.4%)

\*Doses 0.075, 0.15, and 0.30 mg/kg/dose

Abdominal pain tended to decrease in frequency after the first few doses of MNTX as the passage of stool became easier. The gastrointestinal adverse reactions identified for MNTX are not generally severe or life threatening.

The severity of the common adverse incidence did not differ significantly from those in subjects taking placebo. Adverse event profiles were similar irrespective of age or sex. There were too few non-Caucasian patients to determine if ethnic or racial differences affected adverse event profiles.

#### **Safety Summary**

The one death that was probably related to MNTX therapy was due to dehydration and diarrhea. The patient's underlying terminal breast cancer however may have played a confounding role. The incidence of non-fatal, serious adverse events was lower in the MNTX group than in the placebo group. Most of these adverse events were related to the gastrointestinal system and, more specifically, most were probably related to MNTX effects on the obstipated colon.

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

Among the MNTX treated patients there were no clinically significant changes over time with respect to liver function, renal function or hematologic test results. The only laboratory parameter associated with MNTX use was a mild lymphopenia and the clinical significance of this is uncertain.

MNTX did not appreciably interfere with the central opioid analgesic effect nor did it the symptoms of opioid withdrawal symptoms in the patients studied.

The overall conclusion is that MNTX, in doses of 8 mg and 12 mg (which roughly correspond to the 0.15 mg/kg and 0.30 mg/kg dosages) are safe and well tolerated in the treatment of constipation in patients receiving terminal, palliative care. Please see Dr. Ronald Orleans's review for more detail safety evaluation.

#### **Pediatric Use:**

The sponsor is requesting waiver pediatric studies for age of birth to 5 years and deferral pediatric studies for age of 6 and above. I recommend that the requests be granted. The sponsor submitted a pediatric study plan to conduct "A Multicenter, Open-label, Multistage Single and Multiple Dose Study of the Pharmacokinetics and Safety of Subcutaneous Methylnaltrexone Bromide in Children and Adolescents Aged 5 through 17 Years with Opioid Induced Constipation and Advanced Illness Receiving Care that is Primarily Palliative". The waiver/deferral requests and above pediatric study plan were presented to Pediatric Review Committee (PeRC) on March 19, 2008 and the PeRC generally concurred with the sponsor's requests and the study plan.

#### **Labeling Recommendations:**

I concur with Dr. Ronald Orleans and review team's labeling recommendations listed in his review.

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## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-964  
Submission Code 000

Letter Date March 30, 2007  
Stamp Date March 30, 2007  
PDUFA Goal Date April 30, 2008

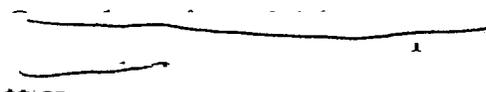
Reviewer Name Ronald J. Orleans, M.D.  
Review Completion Date February 27, 2008

Established Name Methylnaltrexone bromide  
(Proposed) Trade Name Relistor  
Therapeutic Class  $\mu$ -opioid receptor antagonist  
Applicant Progenics Pharmaceuticals, Inc.

Priority Designation S

Formulation One 8 mg or 12 mg subcutaneous injection

Dosing Regimen



Indication Treatment of opioid-induced constipation in patients receiving

palliative care

Intended Population    Terminal patients with opioid-  
induced constipation

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

Approval of Relistor™ for the treatment of opioid-induced constipation in patients receiving terminal care is recommended based on the Applicant's demonstration of an acceptable safety and efficacy profile.

The results of the studies submitted in support of this NDA are interpreted with caution because of the relatively small sample sizes and the relatively short durations of the primary trials. However, the differences between MNTX 0.15 mg/kg, and placebo, as measured by a positive laxation response within 4-hours of treatment, were highly significant despite the small numbers in each group. Therefore, the Applicant has demonstrated that MNTX 0.15 mg/kg is highly effective when given subcutaneously in treating opioid-induced constipation in patients receiving terminal care. Because the duration of the longest study submitted to this NDA was 16 weeks, it should be clearly stated in the label that the drug is intended for use in the terminally ill population only. The clinical trials providing evidence of the safety of this drug do not extend beyond 16 weeks, therefore the safety of this drug has not been established beyond this time period.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

Standard post-marketing surveillance (AERS) is recommended to further monitor the efficacy and safety of Relistor. The Applicant plans to \_\_\_\_\_

In general, the demographic and baseline characteristics of the study subjects are consistent with those of the patients who are expected to receive MNTX after it is marketed. The only exception is the racial distribution which in the clinical studies was predominantly Caucasian. Although no specific risk management steps are recommended, more data should be obtained regarding the use of MNTX in non-Caucasian populations.

#### 1.2.2 Required Phase 4 Commitments

No specific phase 4 commitments are required.

### 1.2.3 Other Phase 4 Requests

No specific phase 4 requests are required.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

The safety and efficacy of methylnaltrexone bromide (MNTX) given subcutaneously (SC) was evaluated in two double-blind, randomized, placebo-controlled phase 3 studies (MNTX 301 and MNTX 302) and one double-blind, randomized, phase 2 study dose-ranging (MNTX 251) which had no placebo arm. Each study was designed to enroll <75 patients per treatment group. The phase 3 studies each had a three-month, open-label extension study (MNTX 301EXT and MNTX 302EXT). The primary intent of the open-label treatment with MNTX was to obtain long-term safety data. The study designs are described below:

MNTX 301 was a phase 3 study that included a one-day, double-blind, placebo-controlled period followed by a four-week open-label period. During the double-blind portion of the study, 154 eligible patients were randomly assigned to receive a single SC dose of MNTX 0.15 mg/kg (n=47), MNTX 0.30 mg/kg (n=55), or placebo (n=52). The primary efficacy endpoint of the double-blind phase of this study was laxation response within 4-hours of double-blind dosing with study drug. Twenty-four hours after the dose administration, 136 patients participated in the subsequent four-week open-label period. Patients were administered an initial dose of 0.15 mg/kg, with subsequent doses of 0.075 mg/kg, 0.15 mg/kg, or 0.30 mg/kg given daily, as needed, for up to four weeks. Open-label endpoints were changes in bowel movement frequency and to test first response to active drug if the patient was originally randomized to placebo and second-dose response for patients originally treated with MNTX. Of the 147 patients who entered the open-label phase of MNTX 301, 72 (49%) completed the study.

MNTX 301EXT was a three-month, open-label extension of MNTX 301, in which 27 patients were entered. Patients initially received MNTX at the same dose as last received in MNTX 301. Subsequent dose adjustments to one of three dose levels (0.075, 0.15, or 0.30 mg/kg) were permitted. Doses were administered daily, as needed, for up to three months. Of the 27 patients who entered 301EXT, only 9 (33.3%) patients completed this study.

MNTX 302 was a phase 3, double-blind, placebo-controlled study in which 134 patients were randomly assigned to receive either SC MNTX 0.15 mg/kg (n=63) or SC placebo (n=71) QOD for two weeks. Any patient who had <3 bowel movements, not associated with rescue medications or interventions, during the first week was eligible for dose escalation (i.e., MNTX 0.30 mg/kg SC or the equivalent volume of placebo) during the second week). Doses were administered every other day, as needed, for up to two weeks. Co-primary efficacy endpoints were the proportion of patients with laxation within 4-hours after the first dose of study drug and the proportion of patients who had a laxation response within 4-hours after at least 2 of the first 4

doses of study drug were given. Of the 63 patients in the MNTX arm, 53 (84.1%) completed the study.

MNTX 302EXT was a three-month, open-label extension of MNTX 302, in which 82 patients were treated with MNTX. Patients received an initial MNTX dose of 0.15 mg/kg; but subsequent dose adjustments to 0.30 or 0.075 mg/kg were allowed. Doses were administered daily, as needed, for up to three months. The primary efficacy endpoints were the occurrence of rescue-free laxation within 4-hours of MNTX administration, expressed as a patient response rate and also as a dose response rate. Of the 89 patients who entered the 302EXT, 32 (36.0%) completed the study,

MNTX 251 was a phase 2, double-blind, dose-ranging study with a duration of up to four weeks. Thirty-three patients were randomly assigned to receive fixed SC doses of MNTX (1, 5, 12.5, or 20 mg every other day during Week 1 of the study (3 doses). The patients were then eligible for treatment with open-label MNTX starting at a dose of 5 mg as needed, with escalation to a maximum dose of 20 mg PRN, for up to three weeks. The maximum frequency of dose administration during the open-label period was every other day for up to four weeks. The primary endpoint for this study was the 4-hour laxation response for the fixed dose groups during the double-blind phase. Of the 33 patients enrolled in the double-blind phase MNTX 251, 22 (66.7%) completed the study. Eighteen patients entered the open-label phase of MNTX 251 and 14 (77.8%) completed the study.

Additional safety data was obtained from four phase 1 studies (MNTX 103, MNTX 1105, MNTX 1106, and MNTX 1107),

### 1.3.2 Efficacy

The primary efficacy objective of this study was to assess the proportion of patients with rescue-free laxation within four hours after administration of the first double-blind SC dose of study medication. In MNTX 301, rescue-free laxations occurred within four hours after dose administration in 61.7% of the patients who received a dose of MNTX 0.15 mg/kg and 13.5% of the patients who received placebo ( $p < 0.0001$ ). In MNTX 302, 48.4% of the patients had a rescue-free laxation within four hours after receiving a dose of MNTX 0.15 mg/kg, compared with only 15.5% of the patients who received placebo ( $p < 0.0001$ ). MNTX 302 also had a co-primary efficacy endpoint: the proportion of patients with laxation within four hours after two of the first four doses (the first week of double-blind treatment). The percentage of patients with positive responses after two of the first four doses was higher in the MNTX group (51.6%) than in the placebo group (8.5%) ( $p < 0.0001$ ).

Given the differences in design features among the three studies, the only data that can be pooled across studies are the laxation responses to the first double-blind dose in MNTX 301 and MNTX 302 (the two studies with weight-based dosing). The pooled results show that 18 of 123 (14.6%) placebo-treated patients had a rescue-free laxation within four hours after the first dose of double-blind study drug, compared with 59 of 109 (54.1%) patients who received MNTX 0.15

mg/kg. Based on the pooled results, response rates were similar for older and younger patients and for males and females.

Study MNTX 251 was a phase 2, open-label study of fixed doses of MNTX. No placebo was utilized in this study.

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

### 1.3.3 Safety

All deaths, serious adverse events, adverse events leading to discontinuation from the primary clinical trials, and most common adverse events were analyzed. Vital signs, chemistry labs, hematology labs, the effects of MNTX on pain control and possible opioid withdrawal symptoms were also reviewed.

A total of 321 patients received MNTX or placebo during the clinical trials. Two hundred eighty-six of these patients received MNTX. The one reported study death that was probably related to MNTX therapy was due to dehydration and diarrhea. The patient's underlying terminal breast cancer however may have played a confounding role.

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

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

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

Pain scores from both the double-blind placebo-controlled studies showed no meaningful change with MNTX treatment demonstrating that MNTX did not appreciably interfere with the central opioid analgesic effect of administered pain medications.

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

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

#### 1.3.4 Dosing Regimen and Administration

The clinical dosing of MNTX proposed by the Applicant is weight related. Eight mg SC is recommended for patients weighing between 84 and 136 pounds (38 to 61 kg) and 12 mg SC for patients weighing between 136 to 251 pounds (62 to 114 kg). For patients whose weight falls outside these ranges (< 38 kg or > 114 kg), dosing at 0.15 mg/kg is recommended. The proposed label states that MNTX should be administered no more frequently than one dose in a 24-hour period.

#### 1.3.5 Drug-Drug Interactions

Preclinical studies suggest no induction or inhibition of CYP450 isozymes by MNTX in humans. Therefore, MNTX has a low probability for drug-drug interactions that complicate concomitant use of other medications.

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

#### 1.3.6 Special Populations

There were no factors identified that altered exposure to MNTX which would require a dose adjustment except for the factors of severe renal impairment and body weight. No dose adjustment is required in patients with mild or moderate renal impairment. Severe renal impairment (creatinine clearance less than 30mL/min) would require a 50% reduction in dosage. No studies were performed in patients with end-stage renal impairment requiring dialysis.

The data collected from study MNTX 1107 showed no meaningful effect of mild to moderate hepatic impairment on the AUC or  $C_{max}$  of MNTX. Therefore, patients with mild to moderate hepatic impairment do not require a reduction in dosage. No studies were performed in patients with severe hepatic impairment.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Methylnaltrexone bromide (MNTX) is a peripheral selective  $\mu$ -opioid receptor antagonist that blocks or partially blocks the intestinal smooth muscle relaxation response caused by morphine, thus limiting the opiate's constipating side-effect. MNTX is a quaternary derivative of the  $\mu$ -opioid antagonist, naltrexone. The addition of the methyl group to naltrexone forms a compound which is more polar and less lipid soluble. Thus, unlike naltrexone, MNTX does not cross the blood-brain barrier and accordingly, has the potential to block undesired peripherally-mediated side effects of opioid pain medications without affecting their centrally-mediated analgesic effects. As such, it provides a specific treatment for opioid induced constipation without affecting the pain relief provided by the opioid.

The chemical name for this compound is (R)-N-(cyclopropylmethyl) noroxymorphine methobromide. The proprietary name may be Relistor but this is not finalized.

MNTX is administered subcutaneously (SC) and can be given either in the shoulder area, buttocks, abdomen, thighs, or extremities. Peak plasma concentrations are reached within 0.5 hours of SC administration. Approximately 60% of MNTX is excreted in the urine and approximately 20% is excreted in the feces predominantly within the first 48 hours post-dose.

#### Medical Reviewer's Comments

- *MNTX is derived from naltrexone, a  $\mu$ -opioid antagonist approved for the treatment of alcohol and opioid dependence. The addition of a methyl group at the amine ring nitrogen of naltrexone converts the compound to MNTX. MNTX has not been previously approved for any indication thus it will be reviewed as a new molecular entity.*
- *MNTX is being developed by Progenics Pharmaceuticals, Inc. of Tarrytown, NY. The company is also developing an intravenous dosage form for the treatment of — postoperative ileus and an oral formulation of MNTX for the treatment of OIC in patients receiving opioid therapy for chronic malignant and nonmalignant pain.*

### 2.2 Currently Available Treatment for Indications

Multiple factors contribute to the development of constipation in patients receiving opioids for cancer pain. Opioids bind to specific receptors in the gastrointestinal tract and central nervous system to reduce motility and produce constipation by both direct and anticholinergic mechanisms. In addition, increased gastrointestinal transit time causes excessive water and electrolyte reabsorption from feces, and decreased biliary and pancreatic secretion further dehydrates stool. Tricyclic antidepressants, clonidine, dehydration, surgical procedures, and

bowel obstruction by tumor also may contribute. Elderly patients are particularly susceptible to constipation and stool impaction.

The laxatives currently used to treat constipation can be classified into three general groups (bulk-forming laxatives, osmotically-acting laxatives, and stimulant laxatives), which work through different mechanisms of action. Bulk-forming laxatives cause retention of fluid in colonic contents, thereby increasing bulk and softness and facilitating transit. Osmotically-acting laxatives decrease net absorption of water and NaCl. Stimulant laxatives promote accumulation of water and electrolytes in the colonic lumen and increase intestinal motility.

The prevalence of opioid-induced constipation (OIC) in patients with advanced medical illness is reported to be nearly 50%. At the present time, there are no FDA approved therapies that are directly targeted to treat the specific cause of OIC. Laxatives currently available to treat OIC work via mechanisms that are unrelated to opioids which act on opioid receptors in the gastrointestinal tract to alter motility and secretion. The laxatives 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. Effectiveness may decrease over time. Orally administered laxatives may not be tolerated because these patients often have diminished oral intake, chronic nausea, anorexia, or dysphagia. The number of tablets or volume of liquid required may become problematic. Finally, each class of laxatives is associated with side effects that are particularly troublesome for these patients. Bulk-forming products can cause intestinal obstruction and impaction, and some reduce the intestinal absorption of drugs such as cardiac glycosides and salicylates. Osmotically-acting laxatives can cause electrolyte imbalances. Stimulant laxatives can produce abdominal pain or fluid and electrolyte deficits. If laxatives become ineffective or intolerable due to side effects, patients who require palliative opioid therapy may be forced to limit analgesic opioid use, trading effective pain management for the ability to have a bowel movement.

The long-term administration of opioids may be complicated by a number of adverse effects and the most prevalent of these is constipation. There is no single definition of constipation but for the purpose of this NDA, OIC is defined as the occurrence of either <3 bowel movements during the week preceding the first dose or no significant laxation within the 48 hours preceding the first dose.

#### **Medical Reviewer's Comments**

- *According to the Applicant, OIC can be a serious aspect of terminal disease because it can cause such things as inadequate absorption of oral medications, vomiting with possible dehydration, fecal impaction, bowel obstruction, and possible intestinal perforation.*
- *The Applicant's proposed indication "Treatment of opioid-induced constipation in patients receiving palliative care" does not define the population in which this drug was studied. MNTX was studied in a population of patients with a life expectancy of 6 months or less due to a terminal illness. The term "palliative care" may imply long term care.*

*Therefore, a more appropriate indication would be "Treatment of opioid-induced constipation in patients with terminal illness receiving palliative care."*

- *Constipation is generally defined in terms of laxation frequency and stool consistency. The Rome Criteria definition is  $\leq 2$  bowel movements per week with the presence of straining, passage of hard stools or pellets. Relief from constipation is defined as  $\geq 3$  bowel movements per week.*

### 2.3 Availability of Proposed Active Ingredient in the United States

Several subcutaneous formulations of MNTX have been developed for use in clinical development. The proposed formulation was developed by Wyeth Research and Progenics Pharmaceuticals. The active ingredient of the study drug is methylnaltrexone bromide. Commercial manufacture of MNTX is conducted at Mallinckrodt Inc., St. Louis, Missouri. MNTX is \_\_\_\_\_ Commercial manufacture of the product will be at \_\_\_\_\_

### 2.4 Important Issues With Pharmacologically Related Products

There are three well defined types of opioid receptors ( $\mu$ ,  $\kappa$ , and  $\delta$ ).

Naltrexone hydrochloride was first approved under the tradename Trexan® (NDA 18-932) in November of 1984. After the New Drug Application was filed, DuPont evaluated naltrexone for \_\_\_\_\_ indications \_\_\_\_\_ In 1994, it was approved for the indication of alcohol dependence and was marketed under the tradename ReVia®. The recommended dose was one tablet (naltrexone 50 mg) once daily. At high doses, elevations of serum transaminases have been reported with this drug.

Vivitrol™ (NDA 21-897) was approved on 4/13/2006. It is an injectable extended release form of naltrexone. Its highest affinity is for the  $\mu$ -opioid receptor and it is indicated for the treatment of alcohol dependence. The Vivitrol™ label contains a warning that the drug has the capacity to cause hepatocellular injury when given in excessive doses. This label also states that the naltrexone is contraindicated in acute hepatitis or liver failure and should be used with caution in patients with active liver disease.

The drug Suboxone contains naloxone HCl and buprenorphine HCl. Naloxone is also an antagonist at the  $\mu$ -opioid receptor site. Buprenorphine is a partial agonist which binds at the  $\mu$ -opioid receptor site and an antagonist at the  $\kappa$ -opioid receptor site. Suboxone is indicated for the treatment of opioid dependence. Significant respiratory depression has been associated with the buprenorphine component particularly when administered by the intravenous route.

Currently, Entereg (alvimopan), another investigational opioid antagonist, has a fast track designation for the treatment of postoperative ileus under NDA \_\_\_\_\_

## 2.5 Presubmission Regulatory Activity

A Type C meeting to discuss the MNTX development plan was held with Progenics Pharmaceuticals Inc., (the Applicant) on 11/3/2002. The following issues were discussed:

- The definition of constipation used as an entry criterion ( $\leq 2$  bowel movements/week with the presence of straining, passage of hard stools or pellets).
- The primary endpoint should be relief of constipation.
- \_\_\_\_\_ should not be used as a primary endpoint.
- Interim analysis for efficacy and possible early termination of the study was not recommended.
- It was recommended by the Division that the Sponsor study "long-term" administration.
- Chronic subcutaneous studies toxicity studies of 6-month duration in rats and 9-month duration in dogs were recommended.

An End-of-Phase 2 meeting with the Applicant was held on 7/10/2003 to update the Agency on the phase 2 results and obtain the Agency's input on the final content of the preclinical and clinical packages for the proposed submission. The Agency agreed that the designs of MNTX 301 and MNTX 302 were adequate for phase 3 evaluations and that the approach to the safety database was acceptable. Studies in patients with renal or hepatic impairment were requested, and these studies were subsequently conducted (MNTX 1105 and 1107).

A teleconference was held on 4/1/2004 to discuss MNTX 1106, the proposed phase 1 study to assess possible effects of SC MNTX on the QTc intervals of healthy subjects. The Agency agreed that the proposed design was adequate. Recommendations from the Agency were incorporated into the final study design, including adding a group that would receive 0.30 mg/kg SC MNTX, changing the proposed supra-therapeutic SC dose \_\_\_\_\_ to 0.50 mg/kg, comparing the rates of clinically significant adverse events across the proposed treatment groups, addition of electrocardiograms (ECGs), change in blood sampling to characterize pharmacokinetics up to 10-12 hours post-dose, and the use of skilled blinded readers.

A pre-NDA meeting was held on 8/15/2005 to reach agreement on the proposed content of the clinical, nonclinical, and package insert sections of the submission. Suggestions regarding the clinical section were incorporated into the analysis and summarization of the efficacy and safety results. These suggestions included excluding patients who used rescue laxatives within four hours after dose administration from the efficacy analyses in MNTX 301 and MNTX 302; assessing rescue laxatives administered within four hours prior to dose as a possible confounding factor; inclusion of baseline opioid use as a covariate in analyses of efficacy endpoints in those studies; and inclusion of an Integrated Summary of Safety in the submission.

A teleconference with the Clinical Pharmacology reviewers was held on 8/16/2005 and the Agency's suggestions were incorporated into the analyses of PK profiles in specific populations, e.g., the elderly, and also into the design of MNTX 1108, a drug-interaction study. A request for information regarding the requirement to conduct a specific bioequivalence study was submitted to the Agency on 6/2/2006, in which Progenics described the new room-temperature formulation of SC MNTX. Progenics indicated that the bioequivalence of the new formulation and the refrigerated formulation used in the phase 3 clinical studies would be evaluated, and proposed that the results of the study (3200K1-103-US) would be included in the 120-day safety update rather than in the original submission. The Agency confirmed on 7/12/2006 that this approach was acceptable.

## 2.6 Other Relevant Background Information

Clinical trials with MNTX were initially performed by a group of investigators from the University of Chicago under their own IND. The results of these studies showed that intravenous (IV) MNTX reversed the decreases in gastrointestinal motility and the prolongation of gut transit time induced by morphine, without affecting analgesia, in healthy volunteers. Subcutaneous (SC) doses of MNTX 0.1 and 0.3 mg/kg reversed morphine-induced prolongation of oral/cecal transit time in 12 healthy volunteers. In 22 patients who experienced constipation while in a methadone maintenance program, laxation occurred in 10 of 11 patients who received the first MNTX IV dose (mean dose of approximately 0.10 mg/kg) compared with none of 11 patients who received IV placebo. No opioid withdrawal effects were observed, and the only clinically-relevant adverse effect reported was transient abdominal pain associated with defecation.

Based on the pharmacology of MNTX and the results of the University of Chicago clinical studies, the Applicant initiated a clinical program to evaluate the efficacy and safety of MNTX as a treatment for OIC in patients with advanced illness receiving palliative care. IND 64,583 was originally submitted on 4/19/2002. This population was selected for investigation because these patients typically do not obtain satisfactory relief of constipation from laxatives and thus require other therapeutic alternatives. The SC route of administration was selected for development because SC doses can be administered when needed to provide a rapid and predictable onset of action that is lacking with currently available laxatives. In addition, SC doses can be given by caregivers or patients who are at home or in a nursing home or hospice.

For this NDA, Progenics evaluated the efficacy of SC MNTX in two phase 3 studies (MNTX 301 and MNTX 302) that included randomized, double-blind, placebo-controlled periods, and one phase 2, ascending-dose study (MNTX 251) that included a randomized, double-blind, controlled period. In each study, double-blind treatment was followed by a period of open-label MNTX treatment (ranging from three weeks to four months). Although the primary intent of open-label treatment with MNTX was to obtain long-term safety data, efficacy was also evaluated. These studies were conducted in patients with advanced illness in the US and one site in Canada.

Data relevant to the safety of SC MNTX come from four phase 1 studies (MNTX 103,

MNTX 1105, MNTX 1106, MNTX 1107), one phase 2 study (MNTX 251), and two phase 3 studies with open-label extensions (MNTX 301/301EXT, MNTX 302/302EXT). All of these studies were complete at the time of data cut-off (6/30/2006) for this submission. Additional safety data come from the clinical studies performed by investigators at the University of Chicago under their own IND. Case report forms and other source documents for the University of Chicago studies reside with these investigators. The safety results from these clinical studies were derived from available publications and University of Chicago IND Annual Reports.

Progenics also conducted one phase 2 study (MNTX 203) and three phase 1 studies (MNTX 102, MNTX 103, and MNTX 206) of IV MNTX, which are not relevant to efficacy but contribute to the pharmacology evaluation of MNTX. An additional phase 1 drug interaction study (MNTX 1108) was conducted to study subjects who also received dextromethorphan.

As of the data cut-off date of 6/30/2006, there were two ongoing studies of SC MNTX: MNTX 901, an open-label, compassionate use study, and 3200K1-103-US (Wyeth Pharmaceuticals), a study to establish the bioequivalence of the proposed registration formulation and the primary stability formulation.

#### **Medical Reviewer's Comment**

- *In December 2005, Progenics and Wyeth Pharmaceutical entered into an exclusive, worldwide agreement for the joint development and commercialization of MNTX. Under the terms of the licensing agreement, Wyeth has worldwide rights to the compound and Progenics retains the option to co-promote MNTX in the US. Wyeth plans to develop oral MNTX worldwide while Progenics will lead the US development of subcutaneous and intravenous MNTX.*

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 CMC (and Product Microbiology, if Applicable)**

The active pharmaceutical ingredient, MNTX, is a quaternary derivative of the opioid receptor antagonist, naltrexone. Commercial manufacture of MNTX is conducted at Mallinckrodt Inc., St. Louis, Missouri. MNTX is \_\_\_\_\_

#### **Medical Reviewer's Comment**

- *Product Quality Microbiology Review of 11/23/2007 recommended approval of this drug from the microbiology product quality standpoint.*

### 3.2 Animal Pharmacology/Toxicology

MNTX at IV doses ranging from 1 to 20 mg/kg had no clinically significant effects on the neuropharmacological profile in mice, gastrointestinal function in rats, pulmonary function in guinea pigs, or renal function in rats. However, in certain toxicology studies in dogs, MNTX was associated with QTc prolongation at doses that exceeded the highest proposed SC clinical dose (0.15 mg/kg).

#### Medical Reviewer's Comment

- *A definitive QT/QTc clinical study of SC MNTX (MNTX 1106) was provided to the Agency as part of the NDA submission; however the study had several deficiencies. The Applicant was asked to submit a thorough QT/QTc study to assess the effects of a single dose of MNTX infused intravenously on cardiac repolarization. The results of this study (3200L2-104-US) were submitted on 11/29/2007 as a final QT/QTc summary report and Statistical Analysis Plan. The Applicant believes that this study report demonstrates that single IV doses of MNTX at 0.3 and 0.64 mg/kg did not produce any evidence of an effect on QT/QTc prolongation and that this study also showed that the positive control (orally administered 400 mg moxifloxacin) caused QT/QTc interval prolongation, with the 90% CIs containing 10 msec, thus validating the sensitivity of the study to detect small effects on QT/QTc intervals. This recently submitted study report is currently under Agency review (See Section 7.1.9).*

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The following documents were reviewed:

- NDA 21-964 electronic submission including the phase 2 and 3 clinical trials
- Clinical review of IND 64,583 (S-037)
- NDA 18-932 ReVia® postmarketing data

### 4.2 Tables of Clinical Studies

The major clinical trials supporting NDA 21-964 are listed in Table 1.

**Table 1 Overview of Major Clinical Phase 2 and Phase 3 Trials**

Study/Sites/Dates	Design/Duration	Treatment	Treated Subjects
<b>MNTX 301</b>			
-Phase 3 -17 Sites all in the US -16 Investigators -2/11/03 to 2/28/05	-Double-Blind Placebo-Controlled -Single Dose Phase	- <u>Single double-blind dose</u> of either: 1. MNTX 0.15 mg/kg SC (n=47) or 2. MNTX 0.30 mg/kg SC (n=55) or 3. Placebo SC (n=52)	-155 randomized <sup>1</sup> -154 treated -102 received MNTX
	-Open-Label Phase -4 Weeks	-Began 24 hours after dosing in the double-blind single dose phase (n=136) -Initial dose of 0.15 mg/kg SC followed by daily (QD) doses as needed (PRN) of : 1. MNTX 0.075 SC or 2. MNTX 0.15 SC or 3. MNTX 0.30 mg/kg SC for up to 4 weeks -QD prn dosing for up to 4 weeks	-147 entered -136 received MNTX
<b>MNTX 301/EXT</b>			
-Phase 3 -6 Sites all in the US -6 Investigators -2/11/03 to 2/28/05	-Open-Label Treatment Extension of Protocol MNTX 301 -12 Weeks	-Same dose as last received in MNTX 301 (n=21) -Dose adjustments made -Minimum dose of 0.075 mg/kg and maximum dose of 0.30 mg/kg -QD PRN dosing for up to 12 weeks	-27 entered -21 received MNTX
<b>MNTX 302</b>			
-Phase 3 -26 Sites in the US -1 Site in Canada -27 Investigators -2/28/04 to 10/16/05	-Double-Blind, Randomized, Placebo-Controlled, Parallel-Group -2 Weeks	- <u>One double blind dose given every other day (QOD) for seven days</u> of either: 1. MNTX 0.15 mg/kg SC (n=63 ) on Days 1, 3, 5, and 7 or 2. Placebo SC (n=71) followed by: 3. MNTX 0.15 mg/kg SC on Days 9, 11, 13 for patients with at least 3 laxations by Day 8 or 4. MNTX 0.30 mg/kg SC on Days 9, 11, 13 for patients with less than 3 laxations by Day 8 or 5. Placebo SC	-134 randomized -134 treated -63 received MNTX

MNTX 302/EXT			
- Phase 3  -25 Sites all in the US  -3/12/04 to 1/16/06	-Open-Label Treatment Extension of Protocol MNTX 302  -12 Weeks	-Initial dose of 0.15 mg/kg for all patients (n=82)  -Subsequent dose adjustments increased to 0.30 mg/kg or decreased to 0.075 mg/kg permitted.  -QD dosing PRN	-89 enrolled  -82 received MNTX
MNTX 251			
-Phase 2  -3 Sites all in the US -3 Investigators  -4/4/02 to 1/26/03	-3 Double-Blind Doses  -1 Week	-One double-blind dose QOD for 7 days of either: 1. MNTX 1 mg (n=10) on Days 1, 3, and 5 or 2. MNTX 5 mg (n=7) on Days 1, 3, and 5 or 3. MNTX 12.5 mg (n=10) on Days 1, 3, and 5 or 4. MNTX 20 mg (n=6) on Days 1, 3, and 5  -No placebo arm	-33 patients enrolled  -33 received MNTX
	-Open-Label Dose Ranging  -3 Weeks	-Starting dose of 5 mg QOD PRN with escalation to a maximum dose of 20 mg for up to 3 weeks	

<sup>1</sup> Patient 401 did not receive study medication due to a bowel obstruction.

**Medical Reviewer's Comment**

- *A total of 321 patients received either MNTX or placebo in the above protocols.*

**4.3 Review Strategy**

The review was conducted utilizing the following:

- Review of the electronic submission
- Independent review of the literature
- Consultative meetings regarding the data findings and clinical issues
- Interactions with the Sponsor for clarification and additional data

**Medical Reviewer's Comments**

- *The Division of Scientific Investigations (DSI) submitted a Clinical Inspection Summary dated 12/3/2007. Two study sites (Sites 13 and 7) from study MNTX 301 and two study sites (Sites 17 and 24) from study MNTX 302 were inspected. The final classification for each site was VAI which means there were some deviation(s) from regulations but the submitted data from all inspected sites were acceptable.*
- *The Division of Medication Errors and Technical Support (DMETS) was consulted regarding the use of the proposed proprietary name of Relistor —DMETS objected to*



### **Medical Reviewer's Comments**

- *The Sponsor submitted the appropriate Form FDA 3454 and listed the investigators for all the clinical studies.*
- *All of the studies had multiple investigators and objective endpoints. Dr. \_\_\_\_\_ treated / subjects in MNTX 301 and 5 in 301/EXT. He treated / subjects in MNTX 302 and 12 subjects in MNTX 302/EXT. There was no evidence that the data from his site was biased in either of the studies.*

## **5 CLINICAL PHARMACOLOGY**

### **5.1 Pharmacokinetics**

The clinical pharmacokinetic studies submitted with this NDA include:

- MNTX 102: Phase 1 single dose pharmacokinetic study of IV MNTX administered to healthy volunteers (General pK-Radiolabel Mass Balance Study)
- MNTX 103: Phase 1 pharmacokinetic and bioavailability study of single ascending SC doses
- MNTX 1105: Phase 1 single dose pharmacokinetic, safety and tolerability study in subjects with impaired renal function
- MNTX 1107: Phase 1 single dose pharmacokinetic safety and tolerability study in subjects with impaired hepatic function
- MNTX 1201: Replicate design pharmacokinetics study of MNTX tablets in healthy volunteers
- MNTX 1202: Phase 1 pharmacokinetics and bioavailability comparison of immediate-release and enteric-coated MNTX tablets in normal volunteers.

MNTX is absorbed rapidly with peak concentrations ( $C_{max}$ ) achieved approximately 0.5 hours following subcutaneous administration. The  $C_{max}$  and AUC increased as dose increased from 0.15 mg/kg to 0.50 mg/kg in a dose proportional manner. The half-life ( $t_{1/2}$ ) following SC administration in healthy subjects is approximately six to nine hours. Overall, the  $t_{1/2}$  appears to be independent of dose and route of administration.

**Table 2 PK Parameters of MNTX Following SC Administration**

Parameters	MNTX 0.15 mg/kg	MNTX 0.30 mg/kg	MNTX 0.50 mg/kg
$C_{max}$ (ng/mL)	117	239	392
AUC <sub>0-24h</sub> (ng.h/mL)	175	362	582

Source: Reports of Analysis of Data, Fixed Dose Justification, NDA 21-964, Page 7

Urinary and fecal metabolic profiles suggest that MNTX undergoes minimal metabolic breakdown in humans. Metabolism appears to account for less than 10% of MNTX clearance. The N-demethylation of MNTX to produce naltrexone is also not significant (0.06% of the administered dose) so that MNTX is eliminated primarily as the unchanged drug. Renal

excretion and hepatobiliary secretion and/or gastrointestinal reflux of unchanged drug appear to be the major mechanisms of MNTX clearance.

The most abundant metabolites are the methyl-6-naltrexol isomers and methylnaltrexone sulfate. Approximately half of the dose is excreted in the urine and somewhat less in the feces.

Renal clearance exceeds creatinine clearance indicating a significant extent of active tubular excretion of MNTX.

Preclinical studies suggest no induction or inhibition of CYP450 isozymes by MNTX in humans. Therefore, MNTX has a low probability for drug-drug interactions that complicate concomitant use of other medications.

### **Medical Reviewer's Comments**

- *The pharmacokinetics of a multiple-dose regimen of MNTX administered as 12 consecutive intravenous doses (0.3 mg/kg every six hours) in 12 healthy subjects has been previously studied (Yuan et al.). There was essentially no accumulation of MNTX, based on the ratio of AUC values. This study also showed that repeated administration of intravenous MNTX was well tolerated in humans, with no significant adverse events and no noteworthy alterations in pharmacokinetics.*
- *Based on the pharmacokinetic data obtained from healthy subjects, the Applicant has concluded that there was an effect of body weight on MNTX mg/kg dose-adjusted exposure (AUC). The clearance of MNTX per kg body weight decreases as body weight increases. Therefore, a slightly higher or lower mg/kg dose can be given to patients with body weights at the lower and higher extremes and still result in a relatively consistent exposure to MNTX. The Applicant uses this pharmacokinetic property to justify the weight-band based dose adjustments that are being proposed for clinical use. (See Section 8.1.)*
- *See the clinical pharmacology review of these studies for further information.*

## **5.2 Pharmacodynamics**

The clinical pharmacodynamic studies submitted with this NDA include:

- MNTX 203: Phase 2 study of intravenous MNTX in the prevention of postoperative ileus
- MNTX 206: Phase 1 urodynamic study of naloxone and intravenous MNTX to reverse opioid effects on bladder function in healthy volunteers
- MNTX 251: Phase 2 dose ranging study of SC MNTX in patients with opioid induced bowel dysfunction
- MNTX 1106: Effects of MNTX on ECG parameters and cardiac repolarization (This QTc study also represents the largest single database of pK data collected in this NDA.)
- MNTX 1108: Phase 1 study of the effect of subcutaneous and intravenous MNTX on CYP<sub>450</sub>2D6 activity in healthy extensive metabolizers of dextromethorphan

- MNTX 301/301EXT: Phase 3 study of SC MNTX for the relief of symptomatic constipation due to chronic opioid therapy inpatients with advanced medical illness
- MNTX 302: Phase 3 study of SC MNTX for the relief of symptomatic constipation due to chronic opioid therapy inpatients with advanced medical illness
- MNTX 302EXT: A three-month open-label treatment extension of Protocol MNTX 302
- MNTX 901: A compassionate use study of MNTX in patients with opioid-induced side effects

### 5.3 Exposure-Response Relationships

There are no significant review issues with Exposure-Response relationships.

#### Medical Reviewer's Comment

- *In study MNTX 301, laxation response within 4 hours of the administered dose of MNTX was similar at both the 0.15 mg/kg (61.7%) and 0.30 mg/kg (58.2%) dosage levels.*

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The claimed indication for this product is the treatment of opioid-induced constipation in patients receiving palliative care.

#### Medical Reviewer's Comment

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A large, handwritten signature in black ink, consisting of a stylized, cursive 'S' followed by a '3'.

#### 6.1.1 Methods

The efficacy of SC MNTX was evaluated in two double-blind, randomized, placebo-controlled phase 3 studies (MNTX 301 and MNTX 302) and one double-blind, randomized, dose-ranging phase 2 study (MNTX 251) which had no placebo arm. Each study was designed to enroll <75 patients per treatment group. The phase 3 studies each had a three-month, open-label extension study (MNTX 301EXT and MNTX 302EXT). The primary intent of the open-label treatment with SC MNTX was to obtain long-term safety data. The study designs are described below:

MNTX 301 was a phase 3 study that included a one-day, double-blind, placebo-controlled period followed by a four-week open-label period. During the double-blind portion of the study, 154 eligible patients were randomly assigned to receive a single SC dose of MNTX 0.15 mg/kg (n=47), MNTX 0.30 mg/kg (n=55), or placebo (n=52). Twenty-four hours after the dose administration, 136 patients participated in the subsequent four-week open-label period. Patients were administered an initial dose of 0.15 mg/kg, with subsequent doses of 0.075 mg/kg, 0.15 mg/kg, or 0.30 mg/kg given daily, as needed, for up to four weeks.

MNTX 301EXT was a three-month, open-label extension of MNTX 301, in which 21 patients received SC MNTX. Patients initially received MNTX at the same dose as last received in MNTX 301. Subsequent dose adjustments to one of three dose levels (0.075, 0.15, or 0.30 mg/kg) were permitted. Doses were administered daily, as needed, for up to three months.

MNTX 302 was a phase 3, double-blind, placebo-controlled study in which 134 patients were randomly assigned to receive either SC MNTX 0.15 mg/kg (n=63) or SC placebo (n=71) QOD for two weeks. Any patient who had <3 bowel movements, not associated with rescue medications or interventions, during the first week was eligible for dose escalation (i.e., 0.30 mg/kg SC MNTX or the equivalent volume of placebo) during the second week. Doses were administered every other day, as needed, for up to two weeks.

MNTX 302EXT was a three-month, open-label extension of MNTX 302, in which 82 patients were treated with MNTX. Patients received an initial MNTX dose of 0.15 mg/kg; subsequent dose adjustments to 0.30 or 0.075 mg/kg were allowed. Doses were administered daily, as needed, for up to three months.

MNTX 251 was a phase 2, double-blind, dose-ranging study with a duration of up to four weeks. Thirty-three patients were randomly assigned to receive fixed SC doses of MNTX (1, 5, 12.5, or 20 mg every other day during Week 1 of the study (3 doses). The patients were then eligible for treatment with open-label MNTX starting at a dose of 5 mg as needed, with escalation to a maximum dose of 20 mg PRN, for up to three weeks. The maximum frequency of dose administration during the open-label period was every other day for up to four weeks.

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 four months in MNTX 301/301EXT, three months in MNTX 302/302EXT, and three weeks in MNTX 251.
- MNTX 251 was a dose-ranging study that included a subtherapeutic MNTX dose (1 mg). There was no placebo group studied in MNTX 251.
- MNTX was administered as fixed doses in MNTX 251 but as doses per kilogram of body weight in MNTX 301/301EXT and MNTX 302/302EXT.

## 6.1.2 General Discussion of Endpoints

### MNTX 301

The primary efficacy endpoint was 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.

Secondary efficacy endpoints were:

- 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).

Open-label efficacy endpoints included the above secondary endpoints with the addition of:

- 8) Changes in bowel movement frequency.
- 9) Repeat of the double-blind period to test 1<sup>st</sup> response to active drug if patient was randomized to placebo and second-dose response for patients originally treated with MNTX.
- 10) Similar tabulations as described for the double-blind efficacy assessments were repeated to evaluate the change from baseline for up to 4 weeks.

### MNTX 301EXT

The efficacy endpoints were:

- 11) Same endpoints used in the double-blind and open-label periods were repeated to evaluate the change from baseline for up to 4 months of exposure.
- 12) Summary of changes from baseline for constipation distress, pain evaluation, opioid withdrawal, laxative and/or opioid therapy, bowel movement assessment log, and GCIC.

### MNTX 302

Co-primary efficacy endpoints were:

- 1) Proportion of patients with laxation within 4 hours after the first dose of study drug
- 2) Proportion of patients who had a laxation response within 4 hours after at least 2 of the first 4 doses (the first week of treatment)

Secondary and tertiary endpoints were:

- 1) Proportion of patients with laxation within 4 hours after at least 4 of the maximum 7 doses
- 2) Proportion of patients with laxation within 4 or 24 hours of each dose
- 3) Time to laxation
- 4) Laxation responses by week
- 5) Evaluations of bowel movement consistency and difficulty
- 6) Evaluations of constipation distress, pain, opioid withdrawal symptoms, and use of rescue laxatives
- 7) Patient and Investigator Global Clinical Impression of Change in bowel status

### MNTX 302EXT

The efficacy endpoints were:

- 1) The occurrence of rescue-free laxation within 4 hours after the administration of a dose of MNTX, expressed as a patient response rate (number of doses per patient with laxation response divided by total number of doses taken per patient) and as a dose response rate (number of doses with laxation response for all patients divided by total number of doses taken by all patients); A laxation was rescue-free if no rescue laxative was taken between administration of study drug and occurrence of laxation.
- 2) Time to laxation response
- 3) Bowel movement consistency and difficulty
- 4) Constipation distress
- 5) Pain
- 6) Opioid withdrawal symptoms
- 7) Use of rescue laxatives
- 8) Patient and Investigator Global Clinical Impression of Change in bowel status

### MNTX 251:

The primary endpoint was 4-hr laxation response for the fixed dose groups during the double-blind phase.

Secondary efficacy endpoints were 24-hr laxation response, patient-assessed evaluation of bowel movement (frequency, consistency, and difficulty), constipation (severity and distress), and pain. In addition, opioid withdrawal, opioid side effects, and patient satisfaction were studied during Week 1 (double-blind study period) and during the 3-week open-label period.

### Efficacy Assessments

1. Each patient was asked to complete an assessment of each bowel movement using the following ratings:
  - Date and time of bowel movement.
  - Consistency: 1-watery, 2-soft-formed, 3-firm, 4-slightly hard, 5-hard, 6-very hard.
  - Difficulty (straining): 1-none, 2-slight, 3-moderate, 4-considerable, 5-great.
2. The patient was also asked to grade the current level of constipation distress on a 5-point scale. (1-none, 2-little bit, 3-somewhat, 4-quite a bit, 5-very much).
3. The patient was asked to evaluate pain at screening, prior to dosing and 4 hours after dosing (double-blind and first open-label dose), and at study termination as follows:
  - The patient was asked to grade his or her current level of pain relating to the primary diagnosis on a scale of 0 (no pain) to 10 (worst possible pain).
  - The patient was asked to grade his or her worst level of pain in the past 24 hours on a scale of 0 to 10.
4. The patient was asked to grade the following symptoms associated with opioid withdrawal, described in nonmedical terms on the CRF, on a scale of 1 (none), 2 (mild), 3 (moderate), or 4 (severe):
  - Rhinorrhea (runny nose.)
  - Tremor (shaking.)
  - Piloerection (goosebumps.)

- Yawning
  - Perspiration (sweating.)
  - Restlessness
  - Lacrimation (teary-eyed.)
5. Both the patient and the Investigator (or a designated study staff member) rated the overall change in bowel status since prior to dosing on the following 7-point scale Global Clinical Impression of Change (GCIC):
- Much worse
  - Somewhat worse
  - Slightly worse
  - No change
  - Somewhat better
  - Slightly better
  - Much better
6. Each patient was evaluated for their level of performance using the 5-point WHO Performance Status:
- 0 = Able to carry out all normal activity without restriction.
  - 1=Restricted in physically strenuous activity but ambulatory and able to carry out work.
  - 2=Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
  - 3=Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
  - 4=Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

#### **Medical Reviewer's Comments**

- *The multiple endpoints and efficacy assessments used in this NDA measure constipation relief but do not measure MNTX effects on decreasing the incidence of constipation related complications such as vomiting, fecal impaction, bowel obstruction, bowel perforation or prolonged hospitalization.*
- *In patient's who are suffering from a terminal illness requiring chronic narcotic use, it seems to this reviewer that isolating the distress that is solely due to constipation is problematic.*

#### 6.1.3 Study Design

NDA 21-964 consists of three primary clinical trials.

**MNTX 301: A Double-Blind, Placebo-Controlled Study (with an Extension Study) of Methylnaltrexone (MNTX) for the Relief of Constipation Due to Chronic Opioid Therapy in Patients with Advanced Medical Illness**

**Treated Patients in Double-Blind Phase: 154**  
**Treated Patients in the Open-Label Phase: 136**

Study Design

MNTX 301 was a double-blind, randomized, placebo-controlled, single-dose, phase 3 study of MNTX administered SC in patients with advanced illness who were receiving opioid therapy and had OID poorly controlled with laxatives. The trial utilized 17 investigators at 17 sites. Sixteen investigators treated patients in the 301 study. The first subject was enrolled 2/11/2003 and the last subject was completed on 2/28/2005.

178 patients were enrolled; 155 randomized; and 154 treated (52 in the placebo group, 47 in the 0.15 mg/kg group and 55 in the 0.30 mg/kg group) in the double-blind phase of the study. 147 subjects were entered and 136 patients were treated in the open-label phase of the study.

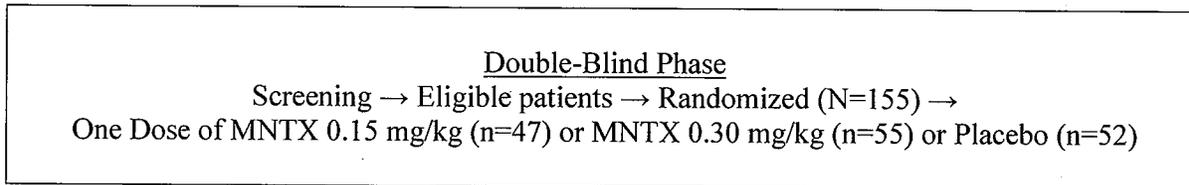
This study was divided into two phases. During the double-blind phase, eligible patients were screened and then, within 5 days, were randomly assigned to receive either MNTX 0.15 mg/kg SC, MNTX 0.30 mg/kg SC or placebo as a single SC dose. All of these injections were in the shoulder area, buttocks, abdomen, thighs, or extremities. Twenty-four hours after dosing, eligible patients participated in a 4-week, open-label phase of the study during which they were treated with MNTX starting at 0.15 mg/kg for the first dose and then PRN at doses of 0.075, 0.15 or 0.30 mg/kg based upon efficacy or side effects. No placebo arm was utilized in the open-label study. Study drug was administered daily if needed. Patients who completed the MNTX 301 study were eligible to enter a 3-month open-label extension study (MNTX 301EXT).

The primary objective of the study was to determine the efficacy of SC MNTX administered as a single dose of 0.15 mg/kg or 0.30 mg/kg compared with placebo in inducing laxation within 4 hours in the study patients.

Secondary objectives of the double-blind and open-label periods of the 301 study were to determine the safety of SC MNTX at both of the study doses (0.15 mg/kg and 0.30 mg/kg) compared with placebo as measured by AEs, changes in pain scores, and opioid withdrawal symptoms in the study population; to determine the efficacy of SC MNTX at a single dose of either 0.15 mg/kg or 0.30 mg/kg compared with placebo to induce laxation within 24 hours in terminally ill patients receiving chronic opioids who are poorly responsive to laxatives; and to gain experience regarding short-term use of MNTX. Assessments following the first open-label dose tested the efficacy response to active drug for patients who were randomized to placebo, and second-dose response for those originally treated with MNTX and to obtain safety and tolerability data.

### Study Design Double-Blind Phase

**Figure 1 Study Design Double-Blind Phase: MNTX 301**



Source: Adapted from the Clinical Study Report (CSR), MNTX 301/301EXT, Page 26

### Protocol Amendments

There were 4 amendments to the original study protocol MNTX 301, which was dated 11/27/2002.

Amendment 1 (12/16/2002): Significant changes made to the protocol included the allowance for a dose increase from 0.15 mg/kg to a maximum of 0.30 mg/kg as well as a dose decrease to a minimum of 0.075 mg/kg as appropriate in the open-label treatment phase of the study

Amendment 2 (9/8/2003): Significant changes made to the protocol which included clarification that no clinically significant laxation was permitted within 48 hours prior to the first dose of study drug. It also revised stable opioid regimen to be  $\geq 3$  days prior to randomization and specified that all dosed patients would be contacted 30 days after the last dose of study drug not only for follow up AEs but also regarding concomitant medications associated with those AEs.

Amendment 3 (4/5/2004): This amendment clarified the inclusion criteria regarding clinically significant laxation prior to dosing and the stable opioid regimen for pain control. It also clarified that subsequent doses of study drug could be adjusted to one of the three levels (0.075, 0.15, or 0.30 mg/kg) and updated the planned interim analysis.

Amendment 4 (10/29/2004): This amendment specified that rescue laxatives were not permitted within 4 hours of taking the study drug.

No patients were enrolled in the study under the original protocol. However, 63 patients were enrolled under Amendment 1, 50 patients were under Amendment 2, 43 were enrolled under Amendment 3, and 22 patients were enrolled under Amendment 4.

### Medical Reviewer's Comment

- *The amendments were relatively minor in nature and this reviewer does not believe they affected the outcome of the study.*

### Inclusion Criteria

1. Advanced medical illness with a life expectancy of 1 to 6 months.

2. No clinically significant laxation within 48 hours prior to the first dose of study drug.
3. On a stable (no reduction of greater than 50% of the opioid dose within 3 days of randomization) opioid regimen for the control of pain for  $\geq 3$  days prior to randomization.
4. On a stable laxative regimen for  $\geq 3$  days prior to treatment.
5. Stable vital signs and systolic blood pressure ( $\geq 80$  mmHg/ $\geq 45$  mmHg)
6. Age greater than or equal to 18 years of age.
7. Signed Informed Consent
8. Females of childbearing potential must have a negative pregnancy test and use appropriate birth control.

Exclusion Criteria

1. Previous treatment with MNTX
2. Any investigational drug in the previous 30 days
3. Any disease suggestive of gastrointestinal obstruction
4. Any nonopioid cause of constipation
5. History of/or current peritoneal catheter for chemotherapy or dialysis
6. Clinically significant acute diverticular disease
7. Evidence of fecal impaction
8. Surgical abdomen
9. fecal ostomy
10. Females who are pregnant or nursing

Study Procedures Double-Blind Phase

Table 3 summarizes the study assessments in the double-blind phase of MNTX 301.

**Table 3 Double-Blind (DB) Phase Assessments: MNTX 301**

	Screening	Dose #1 Predose	Dose #1 4-hours Postdose	Day 2 24-hours Postdose
Randomization		X		
Clinical Lab Tests (Serum chemistry and hematology)	X			X
Pregnancy Test	X			
Physical Exam.	X			X
WHO Performance Status	X			X
Vital Signs	X	X	X	X
Administration of Study Drug		X		
Global Clinical Impression of Change (GCIC)				X

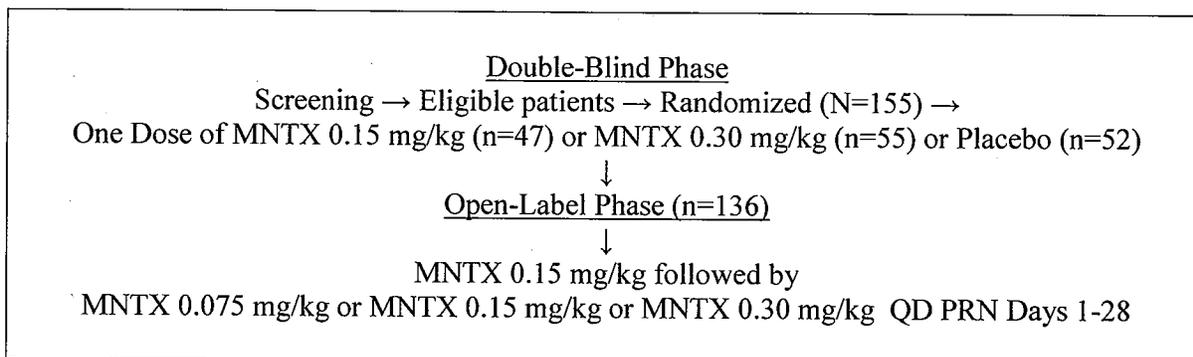
Assess Bowel Movement (Frequency, Consistency, Difficulty)	X	X	X	X
Constipation Distress	X	X	X	X
Pain Evaluation	X	X	X	X
Opioid Withdrawal Scale	X	X	X	X
Prior and Concomitant Medications	X	X	X	X
Adverse Events		X	X	X

Source: Adapted from the Clinical Study Report (CSR), MNTX 301/301EXT, Page 34

All patients completing the double-blind treatment phase were eligible for open-label, daily PRN treatment as needed.

Study Design Open-Label Phase

**Figure 2 Study Design Open-Label Phase: MNTX 301**



Source: Adapted from the CSR, MNTX 301/301EXT, Page 26

Table 4 summarizes the study assessments.

**Table 4 Open-Label (OL) Assessments: MNTX 301**

	Dose #1 Predose	Dose #1 4-hours Postdose	Dosing Days 2- 27 (ongoing)	Day 28 End of Study or Early Termination
Vital Signs	X	X		X
Physical Examination				X
Administration of Study Drug	X		PRN	
Clinical Laboratory Tests				X

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WHO Performance Status				X
Global Clinical Impression of Change (GCIC)				X
Assess Bowel Movement (Frequency, Consistency, Difficulty)	X	X	X	X
Constipation Distress	X	X		X
Pain Evaluation	X	X		X
Opioid Withdrawal Scale	X	X		X
Prior and Concomitant Medications	X	X	X	X
Adverse Events	X	X	X	X

Source: CSR, MNTX 301/301EXT, Page 34

Patients who did not enter the EXT study were contacted 30 days after the last dose of study drug was administered. At that time, the Investigator or a staff member asked each patient about AEs and the use of concomitant medication associated with those AEs.

### Demographics

The mean age of the 154 patients was 65.3 years (range, 21 to 100 years). More than half of the patients were male (54.5%) and the majority were Caucasian (82.5%). Table 5 summarizes the baseline demographics of the patient population.

**Table 5 Demographics and Baseline Characteristics: MNTX 301 DB**

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

WHO Performance Status (%)	3	40.4	40.4	54.5
	4	23.1	25.5	16.4

Source: CSR, MNTX 301/301EXT, Page 59-60

### Medical Reviewer's Comments

- Overall, the three treatment groups were balanced with regard to baseline demographic characteristics, baseline opioid use, and pain scores. The majority of patients had a primary diagnosis of cancer, a WHO performance status of 3 or 4, and most patients were using 2 laxatives at baseline.
- The mean oral morphine equivalent intake was much higher in the MNTX 0.15 mg/kg group (3289.8 mg/day) than in the 0.30 mg/kg group (207 mg/day). In spite of this disparity, the dosages were found to be equally effective. Median values between the groups were much closer (207.0 mg/kg and 188.0 mg/kg, respectively).
- The baseline use of laxatives was comparable across the 3 treatment groups.

### Subject Disposition

A total of 178 patients provided informed consent. Of these, 24 patients did not receive study drug because they (a) failed to meet the inclusion and exclusion criteria (n=20), (b) administrator/investigator decision (n=1), and (c) patient request for withdrawal (n=3). Twenty-three of these patients were never randomized. Patient 301-401 was randomized but subsequently was diagnosed with a bowel obstruction and was no longer eligible for study participation.

A total of 154 patients completed the screening procedures and received a single injection of double-blind placebo (n=52), MNTX 0.15 mg/kg (n=47), or MNTX 0.30 mg/kg (n=55). Two patients in the 0.30 mg/kg group failed to complete the double-blind period of the study: Patient 301-1204 received MNTX 0.30 mg/kg one day prior to her death of complications of advanced pancreatic cancer. The death was assessed by the Investigator not to be related to the study drug. Patient 301-1321 was discontinued for non-compliance with the visit schedule. Both of these patients were in the MNTX 0.30 mg/kg group.

Two patients died during the double-blind follow up. Patient 301-1508 was an 84 year old Caucasian female who received MNTX 0.15 mg/kg SC 21 days prior to her death due to metastatic lung cancer. Patient 301-2010 was a 58 year old Caucasian female who received placebo SC 16 days prior to her death due to a rectal melanoma. Table 6 summarizes the patient disposition.

**Table 6 Patient Disposition by Treatment Group: MNTX 301 DB**

Category	Placebo	0.15 mg/kg	0.30 mg/kg	Entered (N=178) and Randomized (N=155)
Number of Patients Received DB Dose	52 (100%)	47 (100%)	55 (100%)	154 (100%)

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Number of Patients Completed the DB Period	52 (100%)	47 (100%)	53 (96.4%)	152 (98.7%)
Number of Patients Discontinued the DB Period	0	0	2 (3.6%) <sup>1</sup>	2 (1.3%) <sup>1</sup>

<sup>1</sup> One patient died and one patient was non-compliant with the visit schedule.  
 Source: CSR, MNTX 301/301EXT, Page 51

Of the 154 patients who entered the double-blind phase of the study, one patient died and six patients did not continue on to the open-label phase. All six patients were followed for 30 days. Of these six patients, four survived and two died of their underlying disease within the 30 day follow-up period.

Of the 147 patients who entered the open-label period of the 301 study, 39 died, 27 continued into the EXT study, and one patient had no 30 day follow-up (Patient 301-501 was lost to follow-up.) 136 patients were treated with MNTX.

Seventy-two (49.0%) patients completed the open-label period and 75 (51.0%) patients discontinued prematurely. The primary reason for premature discontinuation was death while on the study which occurred in 39 (26.5%) patients. Other reasons for premature discontinuation included disease progression (8 patients, 5.4%), patient request (7 patients, 4.8%), other (6 patients, 4.1%), unresponsive to treatment (5 patients, 3.4%) and intolerable AEs (4 patients, 2.7%). All other reasons were reported by 2 or fewer (<1.5%) patients each.

Table 7 summarizes the patient disposition.

**Table 7 Patient Disposition: MNTX 301 OL**

Category	Total
Number of Patients Entering 301 OL Period	147 (100.0%)
Number of Patients Dosed in 301 OL Period	136 (92.5%)
Number of Patients Completed 301 OL Period	72 (49.0%)
Number of Patients Discontinued 301 OL Period	75 (51.0%)
Reason for Premature Discontinuation in 301 OL Period	
Ineligibility Determined	1 (0.7%)
Non-compliance	2 (1.4%)
Intolerable Adverse Event	4 (2.7%)
Withdrawal Request by Patient	7 (4.8%)
Disease Progression	8 (5.4%)
Adm. or Investigator Decision	2 (1.4%)
Lost to Follow-Up	1 (0.7%)

Number of Patients who Died During OL Phase	39 (26.5%)
Unresponsive to Treatment	5 (3.4%)

Source: CSR, MNTX 301/301EXT, Table 6B, Page 52

**Medical Reviewer's Comments**

- *A majority of the patients who completed the double-blind phase of the study entered the open-label phase.*
- *As noted in Table 7, seven patients voluntarily withdrew from the open-label phase of the study. The reasons for withdrawal are outlined in Table 8.*
- *High mortality and morbidity rates from underlying disease make interpretation of patient tolerance to study drug difficult to evaluate.*

**Table 8 Discontinuations Due to "Patient Request": MNTX 301 OL**

Patient Number	Original Double-Blind Treatment Group	Reasons for Withdrawal
904	MNTX 0.30 mg/kg	No response after 4 doses
1501	Placebo	Received 4 doses - Patient's health declined
1603	Placebo	Received 2 doses - Patient moved away
1614	MNTX 0.30 mg/kg	Received 2 doses - Patient felt "too much stress"
1630	Placebo	Received 6 doses - Patient refused end-of-study visit
1901	MNTX 0.30 mg/kg	Received 0 doses - Oral meds. began working
2209	MNTX 0.30 mg/kg	Received 1 dose - Patient felt "overwhelmed"

Source: CSR, MNTX 301/301EXT, Table 7, Page 53

Of the 80 patients who did not enroll in the 301EXT study, 48 patients survived, 29 died, and 3 were lost to follow-up.

**Table 9 30-Day Follow-up Status: MNTX 301 OL**

Category	Total
Number of Patients Who Died During OL Phase	39
Number of Patients Who Completed OL Phase	72
Number of Patients with 30-Day Follow-Up	80 (Patients who did not go into EXT Study)
Number of Patients Who Survived	48
Number of Patients Who Died	29
Number of Patients Lost to Follow-Up	3
Number of Patients with No 30-Day Follow-Up	1
Number of Patients Who Entered 301EXT	27

Source: CSR, MNTX 301/301EXT, Table 8B, Page 55

Primary Efficacy Endpoint

The primary efficacy endpoint of the MNTX 301 study was rescue-free laxation (i.e., no rescue laxatives were administered prior to laxation) response within 4 hours of treatment with the double-blind dose of MNTX. The proportion of patients with a positive laxation response was the basis for the point estimates of efficacy for each of the three treatment groups.

Efficacy analyses were performed on the ITT analysis set, which included all randomized patients who received the single dose of double-blind medication. The ITT patient analysis set is also the double-blind or safety analysis set. For purposes of distinguishing between the other populations in this study, the ITT analysis set will be referred to as the double-blind analysis set. The double-blind analysis set is comprised of the 154 patients who received double-blind treatment in MNTX 301.

Primary Endpoint Analysis

The primary efficacy endpoint of the MNTX 301 study was rescue-free laxation (i.e., no rescue laxatives were administered prior to laxation) response within 4 hours of treatment with the double-blind dose as tabulated in Table 10. When all bowel movements were considered, regardless of the use of rescue intervention given within 4 hours of the double-blind dose, the results are also tabulated in Table 11.

Rescue-free laxation occurred for 62% of MNTX 0.15 mg/kg patients and 58% of MNTX 0.30 mg/kg patients compared with 13.5% of placebo patients 4 hours after double-blind dosing.

**Table 10 Laxation Response by Treatment Group after 4 Hours: MNTX 301 DB**

Time	Placebo (n=52)	MNTX 0.15 mg/kg (n=47)	MNTX 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 <sup>1</sup>		<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 <sup>1</sup>		<0.0001	<0.0001

<sup>1</sup> 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. Source: CSR, MNTX 301/301EXT, Table 11, Page 65

### Medical Reviewer's Comments

- *In MNTX 301, the laxation response rate in both MNTX arms showed a highly significant advantage for MNTX over placebo.*
- *Increasing the dose to 0.30 mg/kg does not necessarily increase the efficacy.*
- *The average weight in the 0.15 mg/kg arm of the study was 70.4 kg so the mean dose given in this arm of the study was 10.56 mg.*
- *The average weight in the 0.30 mg/kg arm of the study was 65.5 kg so the mean dose given in this arm was 19.65 mg.*
- *Study MNTX 301 studied 154 subjects each taking one double-blind dose of MNTX.*
  - *-The 0.15 mg/kg dose given to patients weighing between 38 and 62 kg ranged from 5.7 to 9.3 mg.*
  - *-The 0.30 mg/kg dose given to patients weighing between 38 and 62 kg ranged from 11.4 to 18.6 mg.*
- *The Applicant is recommending fixed dosages of 8 mg for patients weighing less than 62 kg and 12 mg in patients weighing over 62 kg. In a patient weighing 62 kg, this is roughly corresponds to a 0.15 mg/kg dosage used in Study MNTX 301.*
- *Similar results were observed when rescue laxatives were given within the four hour window.*
- *MNTX 0.15 mg/kg was successful in achieving the primary endpoint of the study.*

### Secondary Efficacy Endpoints

Secondary efficacy endpoints were evaluated during both the double-blind and open-label periods. The secondary efficacy endpoints included:

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

The first open-label dose tested the first response to active drug for patients randomized in the double-blind period to placebo, and the second-dose response for patients originally treated with MNTX. This open-label period provided information regarding multiple-dose response in those who did not experience laxation following the first dose of MNTX.

### Secondary Endpoint Analyses

1. Laxation responses within 24 hours of treatment:  
Significantly more patients treated with MNTX had rescue-free laxation within 24 hours of receiving the double-blind dose of study drug compared with placebo-treated patients as shown in Table 11.

**Table 11 Laxation Response by Treatment Group after 24 Hours: MNTX 301 DB**

Time	Placebo (n=52)	MNTX 0.15 mg/kg (n=47)	MNTX 0.30 mg/kg (n=55)
Number of Patients with Rescue-Free Laxation Response within the Time Interval			
24 Hours	14 (26.9%)	32 (68.1%)	35 (63.6%)
P-Value <sup>1</sup>		<0.0001	0.0001
Number of Patients with Laxation Response within the Time Interval and with or without Rescue			
24 Hours	17 (32.7%)	35 (74.5%)	35 (63.6%)
P-Value <sup>1</sup>		<0.0001	0.0014

<sup>1</sup>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. Source: CSR, MNTX 301/301EXT, Table 12, Page 66

**Medical Reviewer's Comments**

- *At 24 hours after double-blind dosing, 68% of MNTX 0.15 mg/kg patients had a laxation response compared with 27% of placebo patients (p<0.0001).*
  - *The MNTX 0.15 mg/kg dose seems to work well within the first 24 hours.*
2. Changes in constipation distress, bowel movement consistency, bowel movement difficulty and patient and clinician global impression of change:

**Table 12 Qualitative Change in Bowel Movements from Baseline: MNTX 301 DB**

Baseline	Placebo (n=52)	MNTX 0.15 mg/kg (n=47)	MNTX 0.30 mg/kg (n=55)
Changes in the 5-point constipation distress scale-Better than Baseline after 4 hours/24 hours	34%/29.4%	64.4%/64.4%	63.5%/56.9%
Consistency (within 24 hours)- Better than Baseline	29.41%	50.0%	54.3%
Difficulty (within 24 hours)- Better than Baseline	53.8%	50%	65.7%
Global Clinical Impression of Change Improvement (Patient and Clinician) at the End of Double-Blind Phase	Patient: 21.6% Clinician: 19.6%	Patient: 58.7% Clinician: 60.9%	Patient: 58.8% Clinician: 57.7%

This includes laxations within 24 hours of the double-blind dose, excluding laxations after rescue laxatives or the first open-label dose. Baseline: Double-blind Day 1 pre-dose value or screening value if pre-dose value is missing.

Source: CSR, MNTX 301/301EXT, Pages 72- 78

3. Changes in pain scores

At 4 hours post dosing, little change was observed in either current or worst pain scores for all 3 treatment groups.

4. Changes in opioid withdrawal symptoms (using a Modified Himmelsbach scale)

By the end of the double-blind period, the MNTX groups had essentially no change from baseline in withdrawal symptoms compared with the placebo group.

5. Use of rescue laxative medication

During the 1-day double-blind period, routine use of laxatives was comparable across the 3 treatment groups, ranging from 41 (75%) patients in the MNTX 0.30 mg/kg group to 47 (90%) patients in the placebo group. Rescue laxatives were used by 8 (15%) of placebo patients compared with 3 (6%) and 2 (4%) patients in the MNTX 0.15 mg/kg and 0.30 mg/kg groups, respectively.

**Table 13 Summary of Rescue Laxative Use by Treatment Group: MNTX 301 DB**

	Placebo N=52 n (%)	MNTX 0.15 mg/kg N=47 n (%)	MNTX 0.30 mg/kg N=55 n (%)
Patients taking any laxative medication on Day 1	8 (15%)	3 (6%)	2 (4%)

Source: CSR, MNTX 301/301EXT, Adapted from Table 22B, Page 81

**Medical Reviewer's Comment**

- *These are small numbers but more patients in the placebo group required the use of rescue laxatives than in the MNTX groups.*

6. Laxation response for 1<sup>st</sup> dose of open-label period

All patients were to receive MNTX 0.15 mg/kg as their 1<sup>st</sup> open-label dose of study medication. This meant that patients from the placebo group were to initiate MNTX treatment, and patients treated at the 0.30 mg/kg dose in the double-blind period of the study were to have a dose decrease. Subsequently, in both the open-label period of the study and in the EXT study, patients were allowed to decrease their dose of study drug to a minimum of 0.075 mg/kg or increase it to a maximum of 0.30 mg/kg after the 1<sup>st</sup> open-label dose.

Four hours after receiving the 1<sup>st</sup> open-label dose of MNTX, patients who had received placebo during the double-blind period had a rescue-free laxation response of 54%, which was similar to the response rate of 62% seen for the MNTX 0.15 mg/kg group during the double-blind period. Patients who had received MNTX 0.15 mg/kg or 0.30 mg/kg during the double-blind period had rescue-free laxation response rates of 62% and 52%, respectively, 4 hours after taking the 1<sup>st</sup> open-label dose, which were similar to the response rates seen during the double-blind period. Results were similar when all bowel movements were considered, which included the use of rescue intervention given within 4 hours of the 1<sup>st</sup> dose of open-label dose of study drug.

**Table 14 Laxation Response After 1<sup>st</sup> OL Dose of 0.15 mg/kg: MNTX 301**

Time	Treatment during Double-Blind Period			Total (n=136)
	Placebo (n=48)	0.15 mg/kg (n=42)	0.30 mg/kg (n=46)	
Number of Patients with Rescue-Free Laxation Response within the Time Interval				
4 Hours	26 (54.2%)	26 (61.9%)	24 (52.2%)	76 (55.9%)
95% CI	40.1% – 68.3%	47.2% – 76.6%	37.3% – 66.6%	47.5% – 64.2%
24 Hours	34 (70.8%)	32 (76.2%)	27 (58.7%)	93 (68.4%)
95% CI	58.0% – 83.7%	63.3% – 89.1%	44.5% – 72.9%	60.6% – 76.2%
Number of Patients with Laxation Response within the Time Intervals (with or without Rescue)				
4 Hours	26 (54.2%)	26 (61.9%)	25 (54.3%)	77 (56.6%)
95% CI	40.1% – 68.3%	47.2% – 76.6%	40.0% – 68.7%	48.3% – 65.0%
24 Hours	36 (75.0%)	33 (78.6%)	30 (65.2%)	99 (72.8%)
95% CI	62.8% – 87.3%	66.2% – 91.0%	51.5% – 79.0%	65.3% – 80.3%

Source: CSR, MNTX 301/301EXT, Page 67

**Medical Reviewer’s Comments**

- *The percentage of patients with laxation response to the 1<sup>st</sup> open-label dose of MNTX 0.15 mg/kg was similar to the response rate for patients who received MNTX as their double-blind dose.*
- *This data suggests that the efficacy of MNTX is maintained in patients who have previously taken the drug.*

**MNTX 301EXT: A Double-Blind, Placebo-Controlled Study (with an Extension Study) of Methylnaltrexone (MNTX) for the Relief of Constipation Due to Chronic Opioid Therapy in Patients with Advanced Medical Illness**

**Treated Patients: 21**

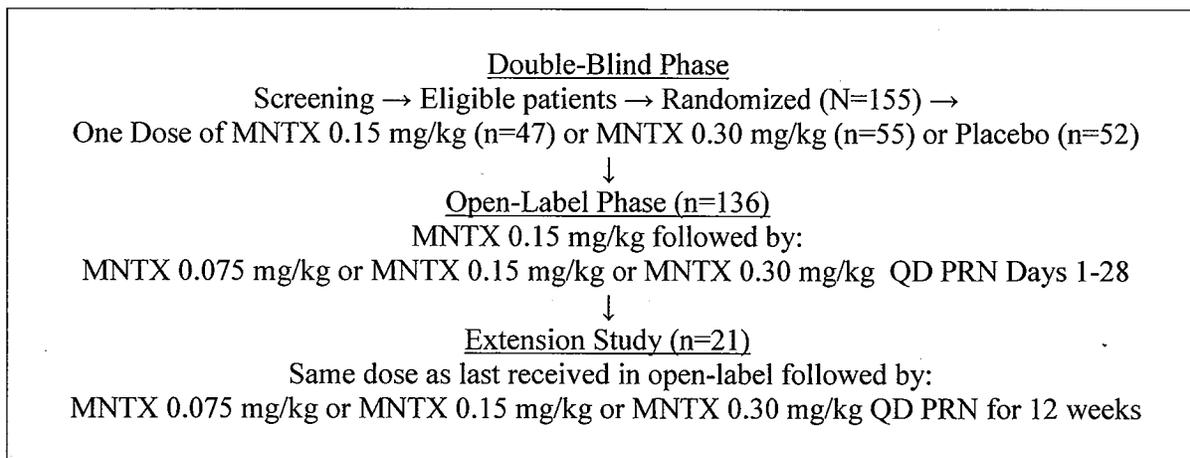
**Study Design**

A total of 27 patients from the MNTX 301 study were eligible to enter this 3-month open-label study. Subjects in the 301EXT study received MNTX once daily on a PRN basis and were started at the dose level last administered in Protocol MNTX 301. Subsequently, doses were adjusted to one of three levels (0.075 mg/kg, 0.15 mg/kg, or 0.30 mg/kg) at the discretion of the investigator to accommodate the intended, desired clinical efficacy and/or to ameliorate any AEs. The maximum dose level was 0.30 mg/kg and the maximum dosing frequency was one dose per 24-hour period. No placebo arm was included in this extension study.

Patients were not eligible for the 301 EXT study if any of the following criteria were met:

1. Used any concurrent investigational drug (experimental) therapy.
2. Any disease process suggestive of gastrointestinal obstruction.
3. Emergence of clinically significant active diverticular disease.
4. Evidence of fecal impaction by physical exam or x-ray.
5. Surgically acute abdomen.
6. Was pregnant (as determined by a screening pregnancy test).

**Figure 3 Study Design: MNTX 301EXT**



Source: Adapted from the CSR, MNTX 301/301EXT, Page 26

### Protocol Amendments

There were two amendments to the original study protocol MNTX 301EXT dated 3/10/2003.

Amendment 1 (4/5/2004): This amendment specified that dosing should begin with the dose level last received in Protocol MNTX 301, and allowed subsequent doses of study drug to be adjusted in intervals to either 0.075, 0.15, or 0.30 mg/kg. It also clarified that the Drug Enforcement Agency (DEA) determined that MNTX is not a controlled substance.

Amendment 2 (10/29/2004): This amendment added instructions for estimating weight for patients who cannot be weighed and specified that MNTX 301 end of study assessments would serve as baseline for the 301EXT study on the condition that the informed consent for the 301 EXT study was signed within 7 days of the last day on the MNTX 301 study.

In the 301EXT study, 18 patients were enrolled under the original protocol, 4 patients were enrolled under Amendment 1, and 5 patients were enrolled under Amendment 2. All patients were to sign a new informed consent form to participate in the 301 EXT study.

### Study Procedures

**Table 15 Study Assessments: MNTX 301EXT**

Study Assessment	First Day of 301 EXT	Daily	Monthly and at Study Termination
Clinical Lab (Serum Chemistry and Hematology)			X
Pregnancy Test	X		
Physical Exam			X
WHO Performance Status			X
Vital Signs			X
Administration of Study Drug		PRN	
Global Clinical Impression of Change (GCIC)			X
Assess Bowel Movement (Frequency, Consistency, Difficulty)		X	
Constipation Distress		X	
Pain Evaluation			X
Opioid Withdrawal Scale			X
Concomitant Medications		X	X
Adverse Events		X	X

Source: CSR, MNTX 301/301EXT, Page 35

### Demographics

The mean age of the 27 patients who entered Study 301 EXT was 64.1 years (range, 26 to 91 years). Patients were equally divided by gender (51.9% male), and 23 (85.2%) were Caucasian. The majority of patients had a primary diagnosis of cancer, and a WHO performance status of 2 or 3.

### Subject Disposition

A total of 27 patients entered the EXT study and 21 (77.8%) received at least one dose of MNTX. Nine (33.3%) patients completed the 301 EXT study, and 18 (66.7%) discontinued prematurely. The primary reasons for premature discontinuation from the 301 EXT study were death on study (12 patients, 44.4%) and patient request (4 patients, 14.8%). All other reasons were reported by only 1 patient (3.7%) each.

**Table 16 Patient Disposition by Treatment Group: MNTX 301EXT**

Category	Total
Number of Patients Entering 301 EXT Study	27 (100.0%)
Number of Patients Dosed in 301 EXT Study	21 (77.8%)
Number of Patients Completed 301 EXT Study	9 (33.3%)
Number of Patients Discontinued 301 EXT Study	18 (66.7%)
Reason for Premature Discontinuation in 301EXT Study	
Noncompliance	1 (3.7%)
Withdrawal Request by Patient	4 (14.8%)

Disease Progression	1 (3.7%)
Death on Study	12 (44.4%)

Source: CSR, MNTX 301/301EXT, Table 6C, Page 52

**Medical Reviewer’s Comment**

- *A total of 72 patients completed the open-label phase of MNTX 301. Of these, 27 patients entered the MNTX 301EXT study.*

**Subject Discontinuations**

**Table 17 Discontinuations Due to “Patient Request”: MNTX 301EXT**

Patient Number	Original Double-Blind Treatment Group	Reasons for Withdrawal
721	MNTX 0.30 mg/kg	Received 0 doses - Patient left hospice and withdrew from the study
1001	MNTX 0.30 mg/kg	Received 9 doses - Patient withdrew because of planned surgery
1643	MNTX 0.15 mg/kg	Received 0 doses - Patient requested discontinuation
2006	MNTX 0.30 mg/kg	Received 0 doses - Patient doing well with oral meds.

Source: CSR, MNTX 301/301EXT, Table 7, Page 53

**Primary Efficacy Assessments and Endpoints**

The 301EXT study provided safety data regarding repeated dose MNTX administration. The efficacy data collected included the time of each bowel movement and a rating of its consistency and difficulty of passage (straining). This was used to describe the effect of continued use of MNTX on bowel movements. Fewer efficacy measures were recorded during this study because clinical evaluations were only collected monthly.

Monthly efficacy assessments included:

1. Pain scores
2. Constipation distress scale
3. Opioid withdrawal symptoms (Modified Himmelsbach scale)
4. Global clinical impression of change ratings (patient and clinician)
5. Use of concomitant medication

**Summary of Primary Efficacy Analysis Across MNTX 301 Double-Blind, Open-Label and Extension Studies**

Data on laxation were collected throughout the open-label period and during the 301EXT study. Laxation responses that were not reported were treated as no laxation. Since specific

information was not collected for use of rescue laxatives after the 1<sup>st</sup> open-label dose, only laxation response rates without regard to use of rescue laxative intervention were calculated.

Table 18 summarizes 4-hour laxation response over time for all patients treated with at least one dose of MNTX in the 301 and 301EXT studies. The average laxation response for any period was between 56% and 64%. The number of patients dosed with MNTX remaining in the study decreased over the course of the open-label period and in the 301EXT which was expected given their underlying terminal diseases. Consequently, in this review emphasis is placed on results from the double-blind period and Day 1 of the open-label period for which the most data are available.

**Table 18 4-Hour Laxation Response Across DB, OL, and EXT Studies: MNTX 301**

Study Interval	Number of Patients Dosed	Total Number of Doses <sup>1</sup>	Total Number of Laxation Responses Reported <sup>2</sup>	Average Patient Laxation Response Rate (%) Mean (SD)
0 – 2 Weeks	150	574	329	55.8 (37.35)
>2 – 4 Weeks	66	192	119	61.7 (40.25)
>4 – 8 Weeks	34	152	97	58.8 (40.64)
>8 Weeks	17	242	146	63.7 (36.11)
Overall	150	1160	691	54.6 (35.29)

<sup>1</sup>Total Number of Doses is the total number of MNTX doses with date and time recorded within the study interval for all patients.

<sup>2</sup>Total Number of Laxation Responses is the total number of doses with a laxation response within 4 hours of dose for all patients for that study interval. Average Laxation Response Rate is calculated for each patient as the number of laxation responses/number of doses x100 for doses within the study interval. The patient's average response rates are then summarized.

Source: CSR, MNTX 301/301EXT, Page 68

### Efficacy Conclusions MNTX 301/301EXT

Results of Study MNTX 301/301EXT show that a single SC injection of MNTX at doses of either 0.15 mg/kg or 0.30 mg/kg was significantly more effective than placebo in inducing laxation in the patients studied (Table 10).

Rescue-free laxation occurred for 62% of MNTX 0.15 mg/kg patients and 58% of MNTX 0.30 mg/kg patients compared with 13.5% of placebo patients 4 hours after double-blind dosing and for 68% of MNTX 0.15 mg/kg patients and 64% of MNTX 0.30 mg/kg patients compared with 27% of placebo patients 24 hours after double-blind dosing ( $p \leq 0.0001$ ). Similar results were observed when bowel movements that occurred after rescue intervention was given were also included.

The percentage of patients with laxation response to the 1<sup>st</sup> open-label dose of MNTX 0.15 mg/kg was similar to the response rate for patients who received MNTX as their double-blind dose (Table 14). Four hours after the 1<sup>st</sup> open-label dose of MNTX 15 mg/kg, the rescue-free laxation response rates were 54% for patients who had been randomized to the placebo group, 62% for patients who had been in the MNTX 0.15 mg/kg group, and 52% for patients who had been randomized to the MNTX 0.30 mg/kg group during the double-blind period. By 24 hours after the 1<sup>st</sup> open-label dose of MNTX, rescue-free laxation rates were 71% for patients who received placebo as their double-blind dose, 76% for patients randomized to MNTX 0.15 mg/kg, and 59% for patients randomized to MNTX 0.30 mg/kg during the double-blind period.

When used on a PRN basis, MNTX continued to be effective with 56% and 68% of patients having rescue-free laxation 4 and 24 hours after their first PRN dose (Table 14). These results were consistent over time such that the average laxation response ranged from 55% to 64% over the 3-month EXT study (Table 18).

As one might expect, with a decrease in constipation (four times as many MNTX-treated patients had bowel movements compared with placebo-treated patients), there were improvements in the constipation associated symptoms of distress and pain. Both patients and clinicians rated MNTX at both the 0.15 mg/kg and 0.30 mg/kg dose more favorably on the Global Clinical Impression of Change Scale, and the patient and clinician ratings were consistent.

#### **Medical Reviewer's Comments**

- *MNTX demonstrated efficacy in treating opioid-induced constipation for both the primary endpoint and secondary endpoints that directly measured laxation as well as on other measures of constipation such as constipation distress and Global Clinical Impression of Change. Despite the background use of laxatives, MNTX had a significant effect.*
- *There was no evident superiority of the MNTX 0.30 mg/kg dose over the MNTX 0.15 mg/kg dose. The patient response rates and the dose response rates achieved with MNTX were consistent for the first open-label dose and over the 3 months of open-label treatment for both patients originally randomized to MNTX and to placebo.*
- *Laxation response rates after conversion to open-label MNTX were similar to the rates achieved with double-blind MNTX.*
- *MNTX 0.15 mg/kg was very effective in treating OIC in the terminally ill patients studied.*

### **MNTX 302: A Double-Blind, Phase 3, Two-Week, Placebo Controlled Study of Methylnaltrexone (MNTX) for the Relief of Constipation Due to Opioid Therapy in Advanced Medical Illness**

**Treated Patients: 134**

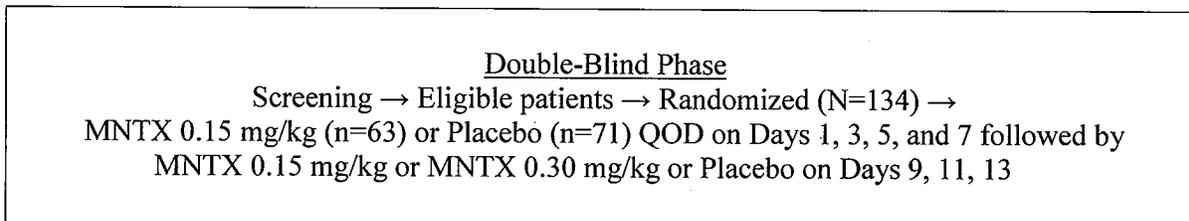
#### **Study Design**

This was a multi-center, double-blind, randomized, placebo-controlled study conducted in patients with advanced medical illness and OIC. Eligible patients (N=134) were randomly assigned to receive SC doses of either MNTX 0.15 mg/kg (n=63) or matched placebo (n=71) QOD for 2 weeks. In the second week, the patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Dose escalation was achieved in a blinded fashion by doubling the volume of study medication given SC starting after 4 doses on Day 9 (i.e., 0.30 mg/kg MNTX or the equivalent volume of placebo).

Efficacy was assessed both objectively based on laxation response during the first 4 hours and the first 24 hours following each dose and subjectively by patient evaluations of consistency/difficulty of bowel movements and constipation distress. Other efficacy assessments included opioid withdrawal symptoms, patient and Investigator global ratings, and pain. Safety assessments included adverse events, clinical laboratory evaluations, and vital signs.

Patients who completed the study were eligible to enter a 3-month open-label extension of the study (Protocol MNTX 302EXT). Patients who did not enter Study MNTX 302EXT were contacted by the Investigator or a study staff member 30 days after the last dose of study drug for follow-up of adverse events and concomitant medications associated with those adverse events.

#### **Figure 4 Study Design Double-Blind Phase: MNTX 302**



Source: Adapted from CSR, MNTX 302, Adapted from Figure 1, Page 26

#### **Medical Reviewer's Comment**

- *Patients in this study all had advanced illness and were located in nursing homes, hospice facilities and palliative care programs.*

#### **Protocol Amendments**

The original study protocol was dated 10/24/2003. There were 3 amendments submitted to the original study protocol.

Amendment 1 (3/30/2004): This amendment clarified the inclusion criterion regarding opioid use required for study entry, specified that subsequent doses should be given according to the protocol schedule if a patient missed a dose, clarified the timing of some of the study evaluations, and made administrative changes. After the original protocol was written, the DEA Drug changed the classification of MNTX from a schedule II controlled substance to a non-controlled substance.

Amendment 2 (10/28/2004): This amendment consisted of typographical corrections and administrative changes.

Amendment 3 (6/8/2005): This amendment expanded the entry criterion regarding the definition of opioid-induced constipation, which could be defined either as a) <3 bowel movements during the previous week and no clinically significant laxation within 24 hours before the first dose or as b) no clinically significant laxation within 48 hours prior to the first dose. The purpose of this amendment was to ensure that the same basis for inclusion was used in Protocol MNTX 302 as had been used in Protocol MNTX 301.

#### **Medical Reviewer's Comment**

- *Some of the participating hospices, required intervention after 2 days in any patient without a bowel movement.*

In MNTX 302, 6 patients were enrolled by the time of Amendment 1; an additional 20 patients were enrolled under Amendment 2; and 111 patients were enrolled under Amendment 3.

The two co-primary objectives of this study were:

- To determine the efficacy of a single dose of SC MNTX 0.15 mg/kg, compared with placebo, in inducing laxation within 4 hours in patients with advanced medical illness and OIC.
- To determine the efficacy of SC MNTX at a dose of 0.15 mg/kg every other day over a 1-week treatment period compared with placebo, in relieving OIC in patients with advanced medical illness.

The secondary objectives of this study were as follows:

- To determine the efficacy of SC MNTX at a dose of 0.15 mg/kg QOD, with the option to escalate to a dose of 0.30 mg/kg, compared with placebo, over a 2-week treatment period.
- To determine the safety of SC MNTX at a dose either of 0.15 mg/kg or of 0.15 mg/kg escalating to 0.30 mg/kg QOD for a 2-week treatment period, compared with placebo.

#### **Inclusion Criteria**

1. 18 years of age or older;
2. Patients or their legal representatives had to be able to understand the potential risks and benefits of the study and provide signed informed consent before initiation of study-specific procedures.
3. Females of childbearing potential had to use an effective method of birth control, which may have included abstinence, during the course of the study.
4. Negative pregnancy test (serum or urine) at screening for all women of childbearing potential. This was changed to a negative urine pregnancy test by Protocol Amendment 2.
5. Advanced medical illness, i.e., terminal illness such as incurable cancer or end-stage AIDS, with a life expectancy of  $\geq 1$  month.

6. Patients must have been taking opioid medication for the control of pain/discomfort for at least 2 weeks before the first dose of study drug (not including PRN or rescue pain medication), and the opioid regimen must have been stable for at least 3 days. "Stable" means no reduction in the opioid dose of  $\geq 50\%$ . Increases to the opioid regimen were permitted within 3 days of randomization, e.g., an increase in dosage or the addition of another opioid to the regimen.
7. Opioid-induced constipation was defined by either of the following criteria:
  - $< 3$  bowel movements during the previous week, by history, and no clinically significant laxation within 24 hours before the first dose of study drug. Small amounts of "leakage" of liquid stool or "pellets" may not have been considered significant, at the discretion of the Investigator.
  - No clinically significant laxation within 48 hours prior to the first dose of study drug. Small amounts of "leakage" of liquid stool or "pellets" may have been considered insignificant, at the discretion of the Investigator.
8. On a stable laxative regimen, e.g., stool softener and SENNA or equivalent, for at least 3 days before the first dose of study drug. If a rescue laxative (or enema/suppository) was given and laxation was induced, an additional 24 hours (if the first definition of opioid-induced constipation from Inclusion Criterion 7 was used) or 48 hours (if the second definition of opioid-induced constipation from Inclusion Criterion 7 was used) without laxation had to elapse for the patient to be eligible to start the study. Rescue laxatives within 4 hours before the study drug dose were to be avoided.
9. Stable vital signs; systolic blood pressure  $\geq 85$  mm Hg and diastolic blood pressure  $\geq 45$  mm Hg (supine or sitting).

#### Exclusion Criteria

A patient was not eligible for the study if any of the following criteria were met:

1. Women who were pregnant and/or nursing.
2. Previous treatment with MNTX.
3. Participation in any other studies involving investigational products within 30 days before screening.
4. Any disease process suggestive of mechanical gastrointestinal obstruction, e.g., tumor adhesion.
5. Any potential non-opioid cause of bowel dysfunction.
6. Current peritoneal catheter for intraperitoneal chemotherapy or dialysis.
7. Clinically significant active diverticular disease.
8. Evidence of fecal impaction.
9. Surgically acute abdomen.
10. Fecal ostomy.
11. Any other condition, including mental illness or sensitivities or allergies to similar compounds (naloxone, naltrexone), that may have interfered with a patient's participation in or compliance with the study, in the opinion of the Investigator.

#### Medical Reviewer's Comment

- *Eligible patients had a life expectancy of less than six months and had less than three laxations in the prior week or no laxation within 48 hours. All patients were on stable laxatives and opioids. No rescue laxatives were allowed within four hours of dosing.*

### Study Procedures

All patients were evaluated for study eligibility at a screening visit conducted within 5 days before the first dose of study drug was administered. A detailed medical history and medication use within the preceding week were recorded. A physical examination (including recording of vital signs) was performed, and the patient's status was assessed on the World Health Organization (WHO) Performance Scale. Laboratory assessments (serum chemistry and hematology for all patients; urine pregnancy test for women of childbearing potential) were performed. Baseline assessments of pain, opioid withdrawal, bowel movements, and constipation were made. The screening procedures were performed on Day 1 of the study, before the patient received study drug.

During 2 weeks of double-blind treatment, bowel movements, adverse events, and concomitant medications were assessed each day. Study drug was administered on Days 1, 3, 5, 7, 9, 11, and 13. Vital signs were recorded before dose administration and at 30 minutes, 60 minutes, and 4 hours after administration on Day 1 (all patients) and Day 9 (patients whose doses were escalated). Physical examinations and laboratory assessments were performed before dose administration on Day 7, and evaluations of pain, opioid withdrawal, and constipation were performed before dose administration and 4 hours after administration on that day. On Day 14, physical examinations, vital sign measurements, laboratory assessments, and evaluations of pain, opioid withdrawal, and constipation were repeated. In addition, the Investigator and the patient both completed the Global Clinical Impression of Change (GCIC) scale on Days 7 and 14. Patients who completed the double-blind study were eligible to enter a 3-month open-label extension study (Protocol MNTX 302EXT). Patients who did not enter the extension study were contacted by telephone 30 days after the last dose of study drug was administered. At that time, the Investigator or a designated study staff member asked each patient about adverse events and the use of concomitant medication associated with those adverse events.

### Demographics

The mean age was about 67 years in the placebo group and 69 years in the MNTX group. More than half of the patients in each group were females and nearly all were Caucasians. The median weight at baseline was 68.2 kg in each group. More than half of the patients in each group had cancer. Approximately 6% in each group had dementia, including Alzheimer's dementia. A higher percentage of patients in the MNTX group (14.3%) than in the placebo group (7.0%) had chronic obstructive pulmonary disease and/or emphysema. Most patients in both treatment groups had WHO performance status ratings of 3 or 4 at screening.

The patients in both groups were receiving a median of 2 or 3 laxatives when they entered the study, and more than 70% were experiencing constipation pain and distress at baseline. The mean current level of pain was 3.5 in the placebo group and 3.6 in the MNTX group, on a scale

of 0 (no pain) to 10 (worst possible pain). The median baseline dose of opioid medication was 100 mg/day in the placebo group and 150 mg/day in the MNTX group, expressed as oral morphine equivalents.

**Table 19 Demographics and Baseline Characteristics: MNTX 302**

Characteristics	Category	Placebo (n=71)	MNTX (n=63)
Age (years)	Mean	66.8	68.9
	Median	70.0	72.0
Gender (%)	Male	43.7	42.9
	Female	56.3	57.1
Race (%)	Caucasian	91.5	96.8
	Black	7.0	1.6
	Asian	0	1.6
	Other	1.4	0
Ethnicity (%)	Hispanic	1.4	3.2
	Non-Hispanic/Latino	98.6	96.8
Weight (kg)	Mean	71.3	68.9
Primary Diagnosis (%)	Cancer	57.7	58.7
	Cardiovascular	9.9	12.7
	HIV/AIDS	0	0
	Other	7.0	14.3
Oral Morphine Equivalents (mg/day)	Mean	338.8	417.0
	Median	100.0	150.0
Current Pain Score (1-10)	Mean	3.5	3.6
Constipation Distress (%)	None	11.3	11.1
	Somewhat	15.5	14.3
	Very Much	38.0	34.9
Number of Laxatives Taken by Generic Term	Mean	2.1	1.9

Source: CSR, Study MNTX 302, Table 8, Pages 49-50

Subject Disposition

A total of 134 patients completed the screening procedures and were treated with either placebo (n=71) or MNTX (n=63). A higher percentage of patients in the MNTX group (84.1%) than in the placebo group (76.1%) completed the study. The primary reason for noncompletion was death during the study (4 placebo-treated patients and 5 MNTX-treated patients). Adverse events were the reason for noncompletion in 5 patients, 3 in the placebo group and 2 in the MNTX group. Withdrawal was requested by 5 patients, all in the placebo group. There were no subject withdrawals in the MNTX arm of the study.

**Table 20 Patient Disposition: MNTX 302**

Category	Placebo (n=71) n (%)	MNTX (n=63) n (%)	Total (N=134) N (%)
Number of Patients Screened			174

Category	Placebo (n=71) n (%)	MNTX (n=63) n (%)	Total (N=134) N (%)
Number of Patients Treated	71 (100.0)	63 (100.0)	134 (100.0)
Number of Patients With Dose Escalated	21 (29.6)	20 (31.7)	41 (30.6)
Number of Patients Completed the Study	54 (76.1)	53 (84.1)	107 (79.9)
Number of Patients Discontinued Prematurely	17 (23.9)	10 (15.9)	27 (20.1)

Source: CSR, MNTX 302, Table 6, Page 43

### Subject Discontinuations

**Table 21 Patient Discontinuations: MNTX 302**

Reason for Premature Discontinuation	Placebo (n=71)	MNTX (n=63)	Total (N=134)
Administrative/Investigator decision	0	1 (1.6)	1 (0.7)
Adverse event	3 (4.2)	2 (3.2)	5 (3.7)
Death on study	4 (5.6)	5 (7.9)	9 (6.7)
Disease progression while on study	0	1 (1.6)	1 (0.7)
Lost to follow-up	1 (1.4)	0	1 (0.7)
Noncompliance	3 (4.2)	0	3 (2.2)
Protocol violation*	1 (1.4)	1 (1.6)	2 (1.5)
Withdrawal requested by patient	5 (7.0)	0	5 (3.7)

\*Patients who missed more than 2 doses of study drug were withdrawn from the study.

Source: CSR, MNTX 302, Table 6, Page 43

### Primary Efficacy Endpoints

The co-primary efficacy endpoints of this study were:

- The proportion of patients with laxation within 4 hours after the first dose of study drug
- The proportion of patients with laxation within 4 hours after 2 of the first 4 doses (the first week of double-blind treatment).

The significance level for the co-primary endpoints was  $\alpha=0.025$ , to account for the 2 comparisons.

### Primary Efficacy Analysis

Efficacy analyses were performed on the ITT analysis set using a Cochran-Mantel-Haenzel test. The ITT analysis set included all randomized patients who received at least 1 dose of study drug, and was comprised of 71 patients randomized to the placebo group and 62 patients randomized to the MNTX group. Only 1 of the 134 patients who received study drug was excluded from the

ITT analysis set. Patient 301 (MNTX arm), was an 88-year-old female with a primary diagnosis of adult failure to thrive. She was the first patient enrolled at study site #3 but was incorrectly entered into the study without being randomized, and was given unblinded MNTX from a supply of open-label medication intended for the extension of Protocol 302. She received 0.15 mg/kg for the first four doses and no laxation data were recorded. For the purpose of analysis, it is assumed that no laxations occurred. She subsequently received 0.30 mg/kg for Dose 5, but the dose was decreased to 0.15 mg/kg for Doses 6 and 7 because of adverse events. She did complete the study however.

Of the 133 patients in the ITT analysis set, the percentage of patients who had a rescue-free laxation within 4 hours of receiving the first dose of study medication was higher in the MNTX 0.15 mg/kg group (48.4%) than in the placebo group (15.5%). The percentage of patients who had a rescue-free laxation within 4 hours after dose administration following at least 2 of the first 4 doses was also higher in the MNTX 0.15 mg/kg (51.6%) than in the placebo group (8.5%).

**Table 22 Summary of Results of Primary Efficacy Endpoints: MNTX 302**

	Placebo (n=71)			MNTX 0.15mg/kg (n=62)			p-value
	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

Source: CSR, MNTX 302, Table 9, Page 51

**Medical Reviewer's Comments**

- *MNTX 302 initially studied 134 subjects each taking one double-blind dose of MNTX (0.15 mg/kg) or placebo every other day for a total of seven doses.*
- *Rescue-free laxation occurred within 4 hours after the first dose in 30 (48.4%) MNTX-treated patients and 11 (15.5%) placebo-treated patients (p<0.0001).*
- *Thirty-two (51.6%) MNTX-treated patients and 6 (8.5%) placebo-treated patients had a rescue-free laxation within four hours after at least two of the first four doses (p<0.0001).*
- *The results of the co-primary endpoints remained statistically significant when baseline opioids use was included as a covariate.*

**Secondary and Tertiary Efficacy Endpoints**

Twenty-four (38.7%) MNTX-treated patients and 4 (5.6%) placebo-treated patients had a rescue-free laxation within 4 hours after at least four of the maximum seven doses (p<0.0001). After administration of any individual dose, higher percentages of patients in the MNTX group (range,

48.2-57.4%) than in the placebo group (range, 11.9-19.2%) had rescue-free laxations within 4 hours.

Likewise, higher percentages of patients in the MNTX group (range, 62.9-85.1%) than in the placebo group (range, 33.3-51.0%) had rescue free laxations within 24 hours after administration of any individual dose. The median time to rescue-free laxation after the first dose was 1.0 hour in the MNTX group and 11.2 hours in the placebo group, based on the patients who had laxation before receiving the second dose. Following subsequent doses, the median time to laxation ranged from 1.1 to 2.6 hours in the MNTX group and 7.2 to 22.0 hours in the placebo group based on patients who had laxation before receiving the next dose. At least 3 rescue-free laxations per week, regardless of the time after dose administration, occurred in 42 (67.7%) MNTX-treated patients and 32 (45.1%) placebo-treated patients ( $p=0.0087$ ). Higher percentages of MNTX-treated patients than placebo-treated patients had at least one rescue-free laxation at some time during the first week of treatment (95.2% and 83.1%, respectively) and during the second week of treatment (91.2% and 81.0%, respectively).

Twenty-one patients in the placebo group and 20 patients in the MNTX group had dose escalation from 0.15 mg/kg (or the equivalent volume of placebo) during the first week of the study to 0.30 mg/kg (or the equivalent volume of placebo) during the second week. There was a slight increase in laxation response in the MNTX-treated patients following escalation (24.5%, versus 15.3% before escalation) but not in the placebo-treated patients (7.4% versus 8.2%).

Higher percentages of patients in the MNTX group than in the placebo group had improvement in constipation distress on Day 1 (53% versus 30%), Day 7 (64% versus 52%), and Day 14 (60% versus 54%).

Global rating scales showed that higher percentages of patients in the MNTX group than in the placebo group rated their bowel status improved on Day 7 (73.5% versus 35.1%) and Day 14 (67.9% versus 44.6%). Likewise, the Investigators rated bowel status improved for higher percentages of patients in the MNTX group than in the placebo group on Day 7 (69.4% versus 35.1%) and Day 14 (67.9% versus 50.0%).

Baseline use of laxatives was comparable in the 2 groups. The percentage of patients using enemas increased during double-blind treatment in both groups, but the magnitude of the increase was greater in the placebo group (from 14.1% at baseline to 35.2% during the study) than in the MNTX group (from 12.7% to 23.8%). There was also a larger increase in the use of osmotic agents in the placebo group (from 33.8% at baseline to 40.8% during the study) than in the MNTX group (from 30.2% to 33.3%).

Pain scores were similar in the 2 treatment groups at baseline, and both groups showed only small mean changes in pain scores over the course of the study.

Most patients had ratings of none, mild, or moderate for opioid withdrawal symptoms at all evaluations. Upward shifts to ratings of severe occurred in only one MNTX-treated patient

(perspiration), compared with 4 placebo-treated patients (yawning, restlessness, and perspiration).

### **MNTX 302EXT: A Three-Month Open-Label Treatment Extension of Protocol MNTX 302**

**Treated Patients: 82**

#### **Study Design**

MNTX 302EXT was an open-label extension of MNTX 302. Patients from either treatment group who had completed the double-blind study could enter MNTX 302EXT and receive open-label MNTX on an as needed basis up to once daily for up to three months. The first dose of MNTX in the open-label extension was 0.15 mg/kg for all patients and subsequent dose adjustments to 0.75 or 0.30 mg/kg were permitted at the discretion of the investigator. The first dose was to be given >14 days after the first dose was received in Protocol MNTX 302 and >24 hours after the last dose was received in Protocol MNTX 302.

Because Protocol MNTX 302 was still ongoing and still blinded when the first patient entered the extension study, the starting dose of 0.15 mg/kg was again chosen. This dose was expected to be effective in patients who were receiving MNTX for the first time, i.e., those who had received placebo in the double-blind study, and in patients who had completed the double-blind study while receiving MNTX 0.15 mg/kg. Patients who had their dose escalated to 0.30 mg/kg in the double-blind study may not have responded to a lower dose, but the protocol allowed for that possibility by permitting the Investigator to increase the dose to 0.30 mg/kg as early as the second dose. A dose of 0.075 mg/kg was chosen as one that could minimize drug-related adverse events, and might still be effective in some patients, based on the phase 2 data.

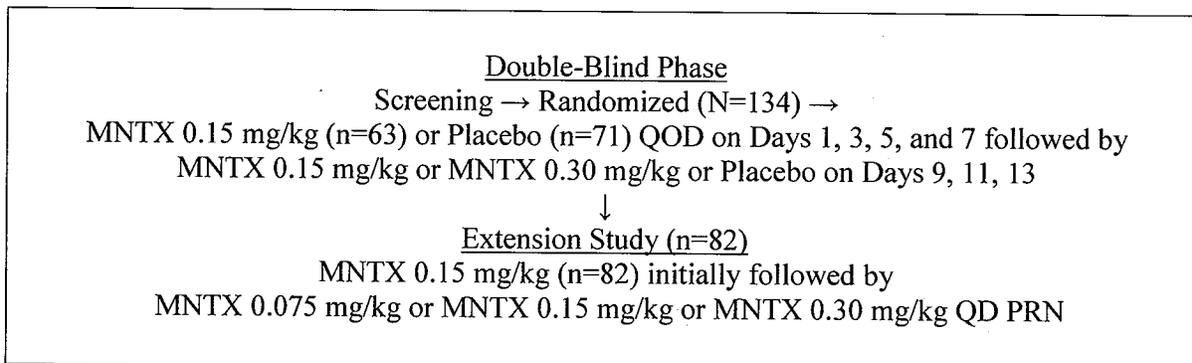
There were 2 amendments to the original study protocol, which was dated 10/24/2003.

Amendment 1 (3/30/2004): This amendment clarified the inclusion criteria regarding the time between completion of Protocol MNTX 302 and enrollment on Protocol MNTX 302EXT.

Amendment 2 (10/28/2004): This amendment changed the description of when end-of-study data from Protocol MNTX 302 could serve as baseline data for Protocol MNTX 302EXT.

One patient had enrolled in the extension study by the time of Amendment 1, and an additional 13 patients had enrolled by the time of Amendment 2.

**Figure 5 Study Design: MNTX 302EXT**



Source: Adapted from CSR, MNTX 302EXT, Page 36

Inclusion Criteria

1. Completed Protocol MNTX 302
2. Enrolled and signed informed consent within 28 days after the end-of-study visit in Protocol MNTX 302 and 14 days or more after receiving the first dose of study drug in Protocol MNTX 302
3. Stable vital signs

Exclusion Criteria

A patient was not eligible for the study if any of the following criteria were met:

1. Women who were pregnant and/or nursing.
2. Participation in any other studies involving investigational products other than MNTX within 30 days before screening.
3. Any disease process suggestive of mechanical gastrointestinal obstruction, e.g., tumor adhesion.
4. Clinically significant active diverticular disease.
5. Evidence of fecal impaction.
6. Surgically acute abdomen.

Study Procedures

**Table 23 Study Flow Chart: MNTX 302EXT**

	Screening	Daily	Monthly (Weeks 4, 8, and 12/End of Study) <sup>1</sup>
Patient Informed Consent	X		
Inclusion/ Exclusion Criteria	X		
Medical History	X		
Pregnancy Test	X		

	Screening	Daily	Monthly (Weeks 4, 8, and 12/End of Study) <sup>1</sup>
Physical Examination	X		X
Vital Signs	X		X
Hematology	X		X
Serum Chemistry	X		X
Global Clinical Impression of Change (GCIC)			X
Pain Evaluation	X		X
Modified Himmelsbach (Opioid Withdrawal Scale)	X		X
Assessment of Bowel Movement	X	X	X
Constipation Evaluation	X		X
WHO Performance Scale	X		X
Concomitant Medications	X	X	X
Adverse Events	X	X	X <sup>a</sup>
SC Injection MNTX <sup>2</sup>		PRN <sup>3</sup>	

<sup>1</sup>All treated patients were contacted 30 days after the last dose of study drug was administered for follow-up of adverse events and concomitant medications associated with those events.

<sup>2</sup>The first dose was 0.15 mg/kg and it was not to be administered less than 24 hours after the last dose of MNTX 302 study drug.

<sup>3</sup>The maximum dose of 0.30 mg/kg and the maximum dose frequency of 1 dose per 24-hour period could not be exceeded without prior approval from the Sponsor. The dose was to be calculated monthly based on the patient's current body weight.

Source: CSR, MNTX 302EXT, Page 28

### Demographics

Table 24 summarizes baseline information about all treated patients combined and by the double-blind treatment received in Protocol MNTX 302EXT. The demographic and baseline characteristics of the entire safety analysis set were similar to the characteristics of the 2 subsets of patients based on their double-blind treatment. The mean age of the 82 treated patients was 67.9 years (range, 34 to 98 years). More than half of the patients were females and most were Caucasian. The mean weight was 69.2 kg.

A majority of the patients (54.9%) had cancer. Approximately 10% of the patients had primary diagnoses of cardiovascular diseases, 11% had primary diagnoses of chronic obstructive pulmonary disease and/or emphysema, and 8.5% had primary diagnoses of dementia, including Alzheimer's dementia. Most patients had WHO performance status ratings of 3 or 4 at screening.

The patients were receiving a median of 3 laxatives when they entered the study, and approximately 70% were experiencing some degree of constipation distress at baseline. The

mean current level of pain was 3.2, on a scale of 0 (no pain) to 10 (worst possible pain). The median baseline dose of opioid medication was 146.8 mg/day, expressed as oral morphine equivalents.

**Table 24 Demographic and Baseline Characteristics: MNTX 302EXT**

Characteristics	Statistics	Double-Blind Treatment		
		Placebo (n=40)	MNTX (n=42)	Total (N=82)
Age (Years)	Mean (SD)	68.9 (15.53)	66.9 (15.35)	67.9 (15.38)
	Median	71.5	67.5	70.0
Gender, n (%)	Male	18 (45.0)	14 (33.3)	32 (39.0)
	Female	22 (55.0)	28 (66.7)	50 (61.0)
Race, n (%)	Black	3 (7.5)	1 (2.4)	4 (4.9)
	Caucasian	37 ( 92.5)	41 ( 97.6)	78 ( 95.1)
Ethnicity, n (%)	Hispanic/Latino	0	2 (4.8)	2 (2.4)
	Not Hispanic/Latino	40 (100.0)	40 (95.2)	80 (97.6)
Weight (kg)	Mean (SD)	69.9 (26.58)	68.5 (20.12)	69.2 (23.36)
Primary Diagnosis, n (%)	Cancer	20 (50.0)	25 (59.5)	45 (54.9)
	Cardiovascular	4 (10.0)	4 (9.5)	8 (9.8)
	COPD/Emphysema	3 (7.5)	6 (14.3)	9 (11.0)
	Dementia, including Alzheimer's Dementia	4 (10.0)	3 (7.1)	7 (8.5)
	Other	9 (22.5)	4 (9.5)	13 (15.9)
WHO Performance	1	1 ( 2.5)	3 (7.1)	4 (4.9)
Status, n (%)	2	8 (20.0)	10 (23.8)	18 (22.0)
	3	22 (55.0)	16 (38.1)	38 (46.3)
	4	9 (22.5)	13 (31.0)	22 (26.8)
Number of Laxatives Taken by Generic Term	Mean (SD)	3.3 (1.62)	3.4 (1.80)	3.4 (1.70)
Opioid Dose (mg/day)	N	40	42	82
(Oral morphine equivalents)	Mean (SD)	213.8 (309.26)	852.4 (1531.15)	540.9 (1155.80)
	Median	95.9	205.8	146.8
Current Level of Pain	N	40	40	80
	Mean (SD)	2.7 (2.9)	3.7 (2.7)	3.2 (2.8)
	Min-Max	0-10	0-9	0-10
Constipation Distress, n (%)	None	10 (25.0)	5 (11.9)	15 (18.3)
	Somewhat	11 (27.5)	7 (16.7)	18 (22.0)
	Very much	6 (15.0)	15 (35.7)	21 (25.6)

Characteristics	Statistics	Double-Blind Treatment		
		Placebo (n=40)	MNTX (n=42)	Total (N=82)
	Not reported	0 (0.0)	2 (4.8)	2 (2.4)

Source: CSR, MNTX 302EXT, Table 8, Page 43

### Subject Disposition

One hundred seven subjects completed Protocol MNTX 302. Eighteen decided not to enter Protocol 302EXT. Eighty-nine patients who completed MNTX 302 were enrolled in the extension study and 82 of the 89 patients received at least one open-label dose of MNTX. Seven patients were not treated. One of the 7 (Patient 3810) completed the study without receiving a single dose of open-label MNTX. Of the remaining 6 untreated patients, 2 (Patients 402 and 2603) died, 2 (Patients 2416 and 3812) requested withdrawal, one was withdrawn by the Investigator (Patient 3301), and one (Patient 1101) was discharged from hospice care. Of the 82 patients treated in MNTX 302EXT, Forty-two had received MNTX in MNTX 302 and 40 patients received placebo in that study. Thirty-one of the 82 treated patients in MNTX 302EXT completed the study and 51 patients discontinued. The study sites obtained 30-day follow-up information about 58 patients, including 55 of the treated patients and 3 of the untreated patients. Table 25 provides an overview of the disposition of the patients in this study.

**Table 25 Subject Disposition: MNTX 302EXT**

Category	MNTX 302 (N=89)		MNTX 302EXT
	Placebo (n=42) n (%)	MNTX (n=47) n (%)	Total Enrolled (N=89) n (%)
Number of Patients Entered MNTX 302EXT	42 (100.0)	47 (100.0)	89 (100.0)
Number of Patients Took Extension Medication	40 (95.2)	42 (89.4)	82 (92.1)
Number of Patients Completed the Study	15 (35.7)	17 (36.2)	32 (36.0)
Number of Patients Discontinued Prematurely	27 (64.3)	30 (63.8)	57 (64.0)

Source: CSR, MNTX 302EXT, Table 6, Page 37

### Subject Discontinuations

Fifty-seven patients discontinued MNTX 302EXT prematurely. Patient 3301 (MNTX arm) was withdrawn by Investigator decision prior to getting the first dose due to a staff shortage at the nursing home.

**Table 26 Subject Discontinuations: MNTX 302EXT**

Reason for Premature Discontinuation	MNTX 302 Treatment		MNTX 302EXT
	Placebo (N=42)	MNTX (N=47)	Total Enrolled (N=89)
Number of Patients Who Took MNTX 302EXT Medication	40 (95.2)	42 (89.4)	82 (92.1)
Number of Patients Discontinued Prematurely	27 (64.3)	30 (63.8)	57 (64.0)
Administrative/Investigator decision	1 (2.4)	1 (2.1)	2 (2.2)
Adverse event	2 (4.8)	1 (2.1)	3 (3.4)
Death on study	13 (31.0)	13 (27.7)	26 (29.2)
Disease progression while on study	2 (4.8)	0	2 (2.2)
Noncompliance	0	1 (2.1)	1 (1.1)
Other	0	3 (6.4)	3 (3.4)
Unresponsive to treatment	2 (4.8)	0	2 (2.2)
Withdrawal requested by patient	7 (16.7)	11 (23.4)	18 (20.2)

Source: CSR, MNTX 302EXT, Table 6, Page 37

Of the 18 patients who withdrew due to “patient request”, 11 were in the MNTX arm. One of these patients (Patient 2416) never took study drug. Four patients (Patients 1109, 1119, 1902, 1903) withdrew because they were unresponsive to treatment. The remaining 6 patients withdrew for various other reasons none of which were related to adverse events.

#### Efficacy Assessments and Endpoints

The main efficacy endpoint was: Laxation response, i.e., occurrence of rescue-free laxation within 4 hours after administration of a dose of MNTX, expressed as a patient response rate and a dose response rate.

The patient response rate is defined as the number of doses per patient with laxation response within 4 hours divided by total number of doses taken per patient.

For the subset of patients who had received MNTX in the double-blind study and continued to receive MNTX during the extension, the response rate remained fairly constant from the end of double-blind treatment (45.3%) through the first 2 months of the extension (40.8% and 50.2%); the rate increased to 59.8% during the third month of the extension, but the number of patients still receiving MNTX at that time was small (12 patients).

For the subset of patients who had received placebo in the double-blind study, the response rate increased from 10.8% at the end of double-blind treatment to 46.2% during the first month of open-label MNTX treatment. This rate is comparable to the rate achieved with MNTX at the end of double-blind treatment. The rate was similar during the second month of the extension (47.7%) and lower during the third month (38.2%) when the number of patients still receiving MNTX was small (13). Table 27 summarizes the patient response rates.

**Table 27 Rescue-Free Patient Response Rates, All Doses By Month: MNTX 302EXT**

Visit		Placebo (N=40)			MNTX (N=42)		
		# Doses per Patient	# Doses with Laxation Response per Patient <sup>1</sup>	Response Rate per Patient <sup>2</sup> (%)	# Doses per Patient	# Doses with Laxation Response per Patient	Response Rate per Patient <sup>2</sup> (%)
End of MNTX 302 DB	N <sup>3</sup>	40	40	40	42	42	42
	Mean	6.9	0.8	10.8	6.8	3.1	45.3
302EXT Month 1	N <sup>3</sup>	40	40	40	42	42	42
	Mean	7.4	3.6	46.2	7.9	3.6	40.8
302EXT Month 2	N <sup>3</sup>	23	23	23	25	25	25
	Mean	6.4	3.0	47.7	6.2	3.6	50.2
302EXT Month 3	N <sup>3</sup>	13	13	13	12	12	12
	Mean	7.2	3.8	38.2	8.0	4.6	59.8

Note: Percentages are based on the number of patients with non-missing data

<sup>1</sup>Number of doses per patient with laxation response within 4 hours post-dose..

<sup>2</sup>Response rate per patient = Doses with laxation response per patient /Total number of doses per patient.

<sup>3</sup>Number of patients dosed.

Source: Adapted from CSR, MNTX 302EXT, Table 9, Page 44

The dose response rate is defined as the number of doses with rescue-free laxation response for all patients divided by total number of doses taken by all patients.

Table 28 summarizes the laxation response expressed as the dose response rate. Following conversion from placebo in the double-blind study to MNTX in the extension study, the response rate for the original placebo-treated group increased to the response rate for the original MNTX-treated group. The response rates for the original placebo-treated and MNTX-treated groups were essentially the same throughout the extension study.

**Table 28 Rescue-Free Dose Response Rates, All Doses by Month: MNTX 302EXT**

Visit	Placebo (N=40)				MNTX (N=42)			
	Number of Patients Dosed	# Doses Over All Patients	Doses with Laxation Response <sup>1</sup>	Response Rate per Dose <sup>2</sup> (%)	Number of Patients Dosed	# Doses Over All Patients	Doses with Laxation Response <sup>1</sup>	Response Rate per Dose <sup>2</sup> (%)
End of MNTX 302 DB	40	277	30	10.8	42	287	130	45.3
EXT Month 1	40	294	142	48.3	42	330	150	45.5
EXT Month 2	23	147	70	47.6	25	156	90	57.7
EXT Month 3	13	94	49	52.1	12	96	55	57.3

<sup>1</sup>Number of doses with laxation response within 4 hours post-dose.

<sup>2</sup>Response rate = Doses with laxation response /Total number of doses.

Source: Adapted from CSR, MNTX 302EXT, Table 10, Page 45

### **Medical Reviewer's Comment**

- *Both the patient response rates and the dose response rates show that the efficacy of MNTX is sustained during this 3-month study period.*

Other efficacy endpoints included:

2) Time to laxation response:

- For patients who had a rescue free laxation response within 4 hours or less after dose administration, the median time to laxation was 45 minutes or less with every open-label dose taken during the extension study.

3) Bowel movement consistency and difficulty whether or not associated with the use of rescue medication:

- Bowel movement difficulty was rated moderate, considerable or great after 243 (33.3%) of the 736 doses followed by rescue-free laxation within 4 hours.

4) Constipation distress:

- Absence of constipation distress was reported by 37 of 67 patients (67%) on Day 1 of the study and by 15 of 44 patients (18%) after 12 weeks of treatment.

5) Pain:

- There was little change in the pain scores throughout the course of the open-label extension.

6) Opioid withdrawal symptoms:

- There were no significant changes in pain scores.

7) Use of rescue laxatives:

- All patients used both concomitant and/or rescue laxatives during the study.

8) Patient and Investigator Global Clinical Impression of Change in bowel status:

- At Week 12, 56.8% of the patients rated themselves better in terms of the GCIC ratings.

### **Medical Reviewer's Comment**

- *In general, similar percentages of the patients used rescue laxatives, rescue pain medications, and other concomitant medications.*

## **MNTX 251: A Phase 2 Double-Blind, Randomized, Parallel-Group, Dose-Ranging Study of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Bowel Dysfunction**

**Treated Patients: 33**

### **Study Design**

MNTX 251 was a phase 2, double-blind, randomized, dose-ranging (Week 1) and open-label (Weeks 2-4) study. In order to enroll in this study, patients must have been on a constant, stable dose of a laxative for at least 5 days (prior to Amendment 2) or 4 days or longer (following Amendment 2) and on a constant, stable dose of opioid medication for at least 2 weeks. The