

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-964**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** 21-964 / N000

**Drug Name:** Relistor (Methylnaltrexone Injection 0.15 mg/kg or 0.30 mg/kg)

**Indication(s):** Relief of constipation  opioid therapy in patients with advanced medical illness

**Applicant:** Progenics Pharmaceuticals, Inc.

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**Review Priority:** Standard

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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

The sponsor submitted two phase 3 studies to support the efficacy and safety of subcutaneous Methylbaltrexone (MNTX) sustained release (SR) in the treatment of opioid-induced constipation in patients with advanced medical illness receiving palliative therapy. Statistical evidence of the efficacy of MNTX SR at doses of 0.15 mg/kg and 0.30 mg/kg was supported by U.S. Study 301 as measured by rescue-free laxation within 4 hours of a single double-blind dose. U.S. and Canadian Study 302 provided evidence that MNTX SR 0.15 mg/kg was efficacious during the one-week treatment period. Study 302 secondary endpoints of rescue-free laxation within 4 hours after each of seven doses provided supportive evidence of efficacy in the two-week treatment period.

### **1.2 Brief Overview of Clinical Studies**

Study 301 was a multi-center, single-dose, double-blind, randomized, placebo-controlled study followed by a 28-day open-label period. MNTX doses under investigation were 0.15 mg/kg and 30 mg/kg. The study included 178 subjects from U.S. sites between the ages of 18 and 100 with advanced medical illness and opioid-induced constipation. A total of 155 subjects were randomized. The primary efficacy outcome was rescue-free laxation within 4 hours of one double-blind treatment dose.

Study 302 was a two-week, multi-center, double-blind, randomized, placebo-controlled and parallel group study of MNTX 15 mg/kg. The study included 174 subjects from U.S. and Canadian sites between the ages of 18 and 100 with advanced medical illness and opioid-induced constipation. A total of 134 subjects were randomized. The co-primary efficacy outcomes were rescue-free laxation within 4 hours after the first dose of double-blind treatment and rescue-free laxation within 4 hours after at least two of the first four doses of double-blind treatment.

### **1.3 Statistical Issues and Findings**

This reviewer confirmed the sponsor's results for studies 301 and 302 that MNTX 0.15 mg/kg and MNTX 0.30 mg/kg were effective in the treatment of opioid-induced constipation in patients with advanced medical illness as measured by laxation within 4 hours of one double-blind treatment dose. The results were consistent across subgroups of age and gender. Although the sponsor did not prespecify Type I error control for the multiple secondary endpoints, these results were supportive of primary efficacy. Study 302 provided evidence that MNTX 0.15 mg/kg was efficacious in one-week treatment period and showed supportive efficacy from secondary endpoints for the two-week period. Both studies had very low dropout rates and recruited an adequate number of subjects for the planned effect size to assess the efficacy of the doses under investigation with at least 90% power.

## 2. INTRODUCTION

### 2.1 Overview

According to the sponsor in section 7 on page 24 of the MNTX 301 study report:

Long-term administration of opioids is widely regarded as a mainstay approach for the treatment of pain associated with serious medical illness, such as cancer and acquired immune deficiency syndrome (AIDS), and in populations with chronic pain not associated with malignancies (e.g., sickle-cell anemia). Chronic opioid use may be complicated by a number of adverse effects, the most prevalent of which is constipation. Constipation affects many patients with metastatic malignancies who receive opioid pain medications. Virtually all of these patients require laxative therapy on a regular basis. Such treatment may be effective initially, but frequently loses its effect and becomes burdensome in advanced disease. Orally administered laxatives may not be tolerated when oral intake declines, and the number of tablets required, or their poor overall efficacy, may become problematic. In some cases, opioid-induced constipation may be severe enough to limit analgesic opioid use altogether.

Methylnaltrexone bromide (MNTX), a derivative of the opioid antagonist naltrexone, does not cross the blood-brain barrier in humans. This property allows MNTX to block the adverse effects of opioid pain medications mediated by peripherally located opioid receptors, while maintaining the centrally mediated analgesic effect.

The sponsor submitted two phase 3 efficacy studies and one phase 2 dose-ranging study to support the clinical utility of MNTX in the treatment of opioid-induced constipation. The focus of this review is on the two phase 3 studies, MNTX 301 and MNTX 302.

**Table 1: Brief Summary of Phase III Clinical Studies for Methylnaltrexone (MNTX)**

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Primary Endpoints	Treatments	Number Randomized (ITT)	Design <sup>2</sup>
MNTX 301 (17 / U.S.) Feb. 2003 to Feb. 2005	Patients with advanced medical illness and opioid-induced constipation who are poorly responsive to laxatives and have no bowel movement for 48 hours before treatment.	The primary endpoint was laxation response within 4 hours of DB dosing.	MNTX 0.15 mg/kg	47 (47)	DB, R, PC, PG, MC
			MNTX 0.30 mg/kg	55 (55)	
		Placebo	52 (52)		
		<b>Total</b>	<b>155<sup>1</sup> (154)</b>		
MNTX 302 (26 / U.S. & 1 / Canada) Feb. 2004 to Oct. 2005		1. laxation response within 4 hours of first DB dosing. 2. 2+ laxations within 4 hours post dosing over 4 DB doses in first week study.	MNTX 0.15 mg/kg (Days 1, 3, 5, 7)	63 (62)	
			Placebo (Days 1, 3, 5, 7)	71 (71)	
			<b>Total</b>	<b>134 (133)</b>	

<sup>1</sup> Patient 401 was randomized but the sponsor did not provide a treatment code for the patient

<sup>2</sup> DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

### 2.2 Data Sources

The study reports and additional information for this submission are available in electronic format. The SAS data sets are complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\EVSPROD\NDA021964.

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study MNTX 301 / MNTX 301EXT

###### 3.1.1.1 Objectives

The primary objective of study MNTX 301 was to determine the efficacy of MNTX administered as a single dose of 0.15 mg/kg or 0.30 mg/kg compared to placebo in inducing laxation within 4 hours in patients with opioid-induced constipation who respond poorly to laxatives. Patients in this trial had advanced medical illness with a life expectancy of 1 to 6 months.

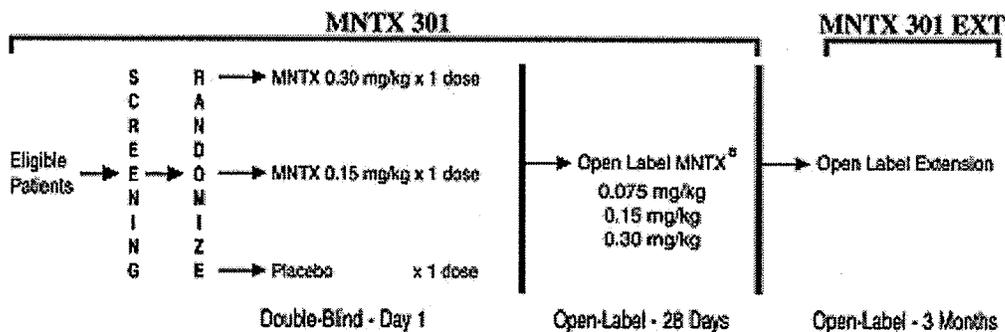
Secondary objectives of the study were to determine the safety of both MNTX doses compared to placebo based on adverse events, changes in pain scores, and opioid withdrawal symptoms and to determine the efficacy of MNTX at a single dose, either 0.15 mg/kg or 0.30 mg/kg, compared to placebo to induce laxation within 24 hours.

The primary objective of the 301 EXT open-label extension study was to provide access to continued treatment with MNTX administered subcutaneously to patients who completed Protocol MNTX 301. The secondary objective of the 301 EXT study was to obtain long-term safety and efficacy data of MNTX administered PRN for up to 3 months.

###### 3.1.1.2 Study Design

This was a multi-center, single-dose, double-blind, randomized, placebo-controlled, parallel group study in patients with opioid-induced constipation, and with an advanced medical illness (e.g. terminal illness such as incurable cancer or end-stage AIDS) and a life expectancy of 1 to 6 months. The one-week, double-blind portion of this study was followed by a 28-day open-label period. Study 301 was followed by a 3-month open-label extension study. This review will focus on the double-blind portion of study 301, whose design is illustrated in Figure 1.

Figure 1: Study MNTX 301/ 301 EXT Flow Chart



<sup>a</sup>Investigator had the option to modify dosing as appropriate.  
1st dose 0.15 mg/kg titrated to 0.075 or 0.30 mg/kg after.

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Figure 1, page 26)

Eligible patients must have been on a stable regimen of opioid medication for the control of pain/discomfort for at least 3 days before randomization and on a stable laxative regimen for at least 3 days before the first dose of study drug. Treatment with rescue laxatives and

enemas/suppositories was permitted during the study as clinically indicated, but the use of rescue laxatives, rectal suppositories, or enemas were not permitted within 4 hours before or after administration of the single treatment dose (no effective rescue intervention was administered for the preceding 48 hours).

After screening, eligible patients were randomized to one of three treatments: a single subcutaneous injection of either MNTX 0.15 mg/kg or 0.30 mg/kg or placebo. A total of 154 patients were treated (placebo: 52, 0.15 mg/kg: 47, and 0.30 mg/kg: 55) at 17 U.S. centers.

### **3.1.1.3 Efficacy Endpoints and Analyses**

The sponsor's efficacy analyses were performed on the intent-to-treat (ITT) analysis set, defined as all randomized patients who received the double-blind dose of the study drug.

#### Primary efficacy endpoint and analysis

The primary efficacy endpoint was a rescue-free laxation response within 4 hours of the single treatment dose (yes/no). A rescue-free laxation is defined as a bowel movement within the time window specified in a patient who had not received a rescue laxative (including enemas or disimpaction) between study drug administration and the bowel movement. Patients could not receive a rescue laxative within 4 hours prior to the dose.

A laxation response is defined as a clinically significant bowel movement, not the passing minimal amounts of hard stool or small amounts of liquid stool. If a laxation response is not documented or if any rescue medication or intervention is administered within 4 hours of study drug dosing, that response was not classified as a laxation response for analysis of the primary outcome.

The analysis of the primary endpoint comparing placebo to each MNTX dose was planned to first use a Cochran-Mantel-Haenszel test with study center (sites with fewer than four patients were pooled into one site) as a stratification factor to test the treatment-by-center interaction. If the treatment-by-center interaction was not significant ( $p > 0.10$  by the Breslow-Day test) a Chi-square test was to be used to compare each MNTX dose against placebo at the two-sided type I error level of 0.0249 - a Bonferroni multiplicity adjustment was applied to account for the two doses being tested and an alpha of 0.0002 spent at the interim analysis.

Estimates of laxation response rates within 4 hours of each single-dose treatment and 95% confidence intervals were calculated. Sensitivity analyses included testing the treatment-by-center interaction for several pooling schemes, and analysis using a Chi-square test without controlling for study center.

#### Secondary efficacy endpoints and analyses

Secondary endpoints included the following:

- Laxation responses within 24 hours of the single treatment dose (with and without rescue)
- Change in the 5-point constipation distress scale
- Change in bowel movement consistency: watery, soft-formed, slightly hard, hard, very hard
- Change in bowel movement difficulty: none, slight, moderate, considerable, great
- Change in pain scores
- Change in opioid withdrawal symptoms (Modified Himmelsbach scale)
- Global clinical impression of change ratings (patient and clinician)
- Use of rescue laxative medication (both double blind and open label period)

Analyses of laxation response within 24 hours of treatment used methods similar to the primary analysis. Other categorical endpoints were analyzed using the Chi-square test. Changes in bowel movement frequency were compared using ANOVA.

#### Additional subgroup analyses

The sponsor also conducted exploratory subgroup analyses by age (<65 and  $\geq 65$ ), gender, race (white/other), baseline constipation distress score, study site, primary disease, baseline opioids (mg equivalents <80, 80 to 200, >200), and baseline WHO Performance Scale (2, 3, 4). If any factor was significantly different between baseline treatment groups ( $p \leq 0.10$ ), it was to be included to test the treatment-by-factor interaction in an additional multivariate model.

#### Determination of Sample Size

The total sample size of 150 patients, or 50 patients per treatment group, was based on a 35% treatment difference in the proportion of laxation responders assuming various response rates, and applying a two-sided Chi-square test with an alpha level of 0.025. With actual sample size of 52, 47, and 55 for the placebo, MNTX 0.15 mg/kg and MNTX 0.30 mg/kg groups, respectively, there was at least 90% power to detect a 35% absolute effect size based on a placebo rate of .15%

#### Interim Analysis and Sample Size Re-estimation

An Interim Analysis was performed by an independent third party, \_\_\_\_\_ after approximately 50% of the patients ( $n=75$ ) completed the double-blind period to assess safety and evaluate if the study was adequately powered and, if not, to conduct a sample size re-estimation. The sample size re-estimation procedure was to be based on the conditional power method of Li, Shih, Xie, Lu (2002)<sup>1</sup>. There was no plan to terminate the study as a result of the interim efficacy findings.

A group sequential monitoring approach was used for the interim analysis. The primary efficacy endpoint, laxation within 4 hours of single treatment dose, was analyzed and presented by treatment group using the ITT population. Calculation of the boundary of 3.787 is based on the gamma spending function of Hwang, Shih, and deCani (1990)<sup>2</sup> with gamma equal to -10 and two-sided type 1 error rate of  $\alpha=0.0002$ .

The primary focus of the independent DSMB was to monitor the safety of short-term MNTX administration but it was also to convey future study conduct recommendations to the sponsor (e.g., continue as planned, early termination for serious safety concerns, or increase study sample size). The interim analysis was presented to the DSMB within 6 to 8 weeks of completion of the double-blind period of the 75<sup>th</sup> patient. The interim analysis results are discussed in Section 3.1.1.4.2.

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<sup>1</sup> Li, G., Shih, W.J., Xie, T. and Lu, J. A sample size adjustment procedure for clinical trials based on conditional power. *Biostatistics* 2002; 3(2):277-287.

<sup>2</sup> Hwang IK, Shih WJ, deCani JS. Group sequential designs using a family of type I error probability spending functions. *Stat in Med.* 1990; 9:1439-1445.

### 3.1.1.4 Efficacy Results

#### 3.1.1.4.1 Study Population

One hundred seventy eight (178) patients were screened of which 155 patients were randomized. Twenty patients were excluded from the randomization because they failed to meet the inclusion and exclusion criteria, and three patients requested withdrawal Patient 401 was initially considered qualified and was randomized but was later diagnosed with a bowel obstruction and was no longer eligible to participate.

A total of 154 patients completed screening. Fifty-two subjects received a single injection of placebo; 47 received MNTX 0.15 mg/kg, and 55 received MNTX 0.30 mg/kg. This is the ITT population and the safety population. The patient disposition is summarized in Table 2. Two MNTX 0.30 mg/kg group patients failed to complete the double blind period.

**Table 2: Patient Disposition by Treatment Group: MNTX 301 Double-Blind Period**

Category	Placebo (N=52)	0.15 mg/kg (N=47)	0.30 mg/kg (N=55)	Total
Number of Patients Entered				178
Number of Patients Randomized				155
Number of Patients Received DB Dose	52 (100.0%)	47 (100.0%)	55 (100.0%)	154 (100.0%)
Number of Patients Completed the DB Period	52 (100.0%)	47 (100.0%)	53 (96.4%)	152 (98.7%)
Number of Patients Discontinued the DB Period	0	0	2 (3.6%)	2 (1.3%)
Reason for Premature Discontinuation in 301 DB Period				
Non-Compliance	0	0	1 (1.8%)	1 (0.6%)
Death on Study	0	0	1 (1.8%)	1 (0.6%)

Percentages within the double-blind period are based on the number of patients entering that period.

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 6A, page 51)

Baseline demographic and disease characteristics of the ITT population are summarized in Appendix 1, Table 14. The mean age of patients was 65.3 years, with the majority being male (54.5%) and Caucasian (82.5%). The three treatment groups appeared balanced with regard to baseline demographic characteristics, baseline opioid use, and pain scores. The majority of patients had a primary diagnosis of cancer and most patients were using, on average, two laxatives per week at baseline.

#### 3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The proportion of patients with a positive rescue-free laxation response within 4 hours of treatment with the single treatment dose was the basis for the point estimates of efficacy for each treatment group. The sponsor's primary efficacy results are presented in Table 3. Because treatment-by-center interaction was not shown, the primary analysis was conducted using the Chi-squared test. This reviewer concurs with the sponsor's results. Both MNTX doses (0.15 mg/kg and 0.30 mg/kg) were effective compared to placebo ( $p < 0.0001$ ).

The purpose of the interim analysis, besides assessing safety, is to ascertain whether the study was adequately powered. The results of the interim analysis showed a highly significant effect of each MNTX compared to placebo ( $p < 0.001$ ), and it was concluded that a re-estimation of the sample size was not necessary.

**Table 3: Laxation Response by Treatment Group within 4 Hours: Double-Blind Patients**

Time	Placebo (n=52)	0.15 mg/kg (n=47)	0.30 mg/kg (n=55)
<b>Number of Patients with Rescue-Free Laxation Response within the Time Interval</b>			
24 Hours	14 (26.9%)	32 (68.1%)	35 (63.6%)
95% Confidence Interval	14.9% - 39.0%	54.8% - 81.4%	50.9% - 76.3%
P-Value [1]		<0.0001	0.0001

[1] p-values are nominal p-values in the pairwise comparison of each MNTX dose to placebo. Because of the interim analysis and comparison of each dose with placebo, p-values <0.0249 are considered statistically significant. (Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 11, page 65)

### 3.1.1.4.3 Sponsor's Efficacy Results for Secondary Endpoints

This section presents results for the two secondary efficacy endpoints which the clinical reviewer deemed useful: laxation response within 24 hours of double-blind dosing; and use of laxative medication/intervention. Additional secondary efficacy endpoint results are presented in Appendix 1.

#### Laxation Response within 24 Hours of Double-Blind Dosing

The results are shown in **Table 4**; both MNTX doses (0.15 mg/kg, and 0.30 mg/kg) had significantly greater laxation response rates compared to placebo and can be considered supportive to the primary efficacy conclusions.

**Table 4: Laxation Response by Treatment Group within 24 Hours: Double-Blind Patients**

Time	Placebo (n=52)	0.15 mg/kg (n=47)	0.30 mg/kg (n=55)
<b>Number of Patients with Rescue-Free Laxation Response within the Time Interval</b>			
24 Hours	14 (26.9%)	32 (68.1%)	35 (63.6%)
95% Confidence Interval	14.9% - 39.0%	54.8% - 81.4%	50.9% - 76.3%

(Source: Clinical Study Report: Study MNTX 301/301 EXT; extracted from Table 12, page 66)

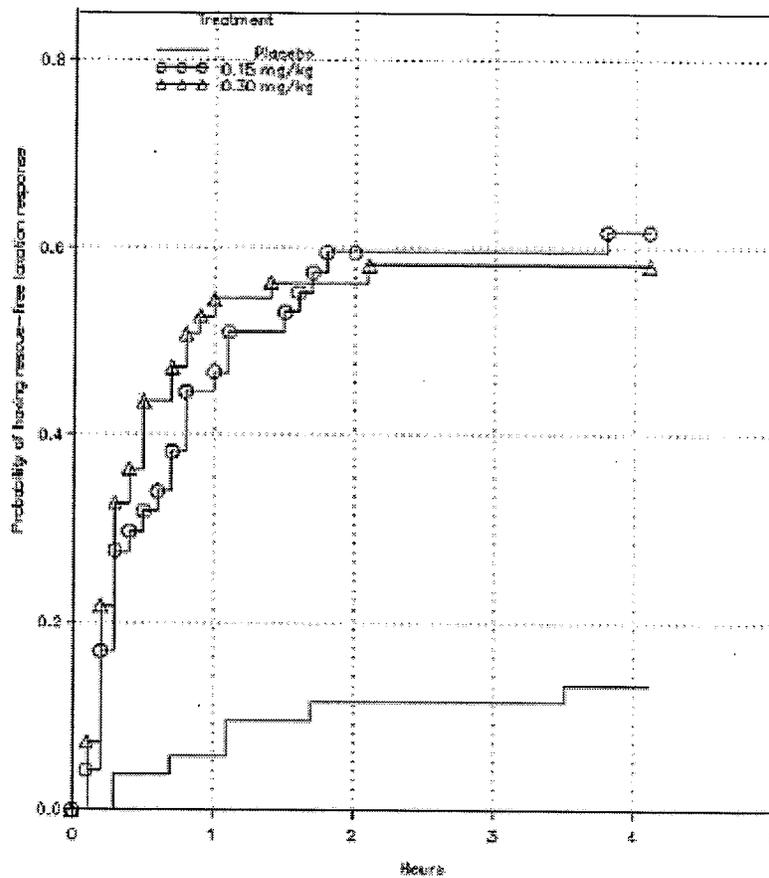
#### Use of Laxative Medication/Intervention

Data on laxative use was collected during the 1-day double-blind period. Routine general use of laxatives was comparable across the 3 treatment groups but not for use of rescue laxatives. 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.

### 3.1.1.4.4 Sponsor's Exploratory and Sensitivity Efficacy Analyses

The time to laxation within 4 hours and 24 hours after double-blind dosing was presented using Kaplan-Meier curves (see Figure 2). As presented in Table 5, patients in both MNTX groups had shorter median times to rescue-free laxation at 4 and 24 hours after dosing compared to the placebo group.

Figure 2: Kaplan-Meier Plot of Time to First Rescue-Free Laxatoin at 4 Hours for Double Blind Dose



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On Original

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Figure 2, page 69)

Table 5: Time to Rescue-Free Laxation Responses at 4 and 24 Hours: Double-Blind Patients

Treatment	Patients Treated	Patient Responders	Median Time to Rescue-Free Laxation (hr)
<b>4 Hour Interval <sup>a</sup></b>			
Placebo	52	7 (13.5%)	> 4
0.15 mg/kg	47	29 (61.7%)	1.10
0.30 mg/kg	55	32 (58.2%)	0.80
<b>24 Hour Interval <sup>b</sup></b>			
Placebo	52	14 (26.9%)	> 24
0.15 mg/kg	47	32 (68.1%)	1.10
0.30 mg/kg	55	35 (63.6%)	0.80

<sup>a</sup> Logrank test for time to first laxation censored at 4 hours or time of rescue medication performed in a pairwise manner to compare each MNTX dose with Placebo.

<sup>b</sup> Logrank test for time to first laxation censored at 24 hours or time of rescue medication performed in a pairwise manner to compare each MNTX dose with Placebo.

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 15, page 70)

#### **3.1.1.4.5 Statistical Reviewer's Results and Comments**

This reviewer confirmed the sponsor's findings for the primary endpoint. The findings on secondary endpoints, in general, support the primary finding. However, since there were no pre-planned adjustments to control Type I error for the multiple dose and multiple endpoint comparisons, the findings on secondary endpoints should not be considered confirmatory or useful for labeling purposes.

The sponsor's sensitivity analyses showed that efficacy conclusions are not affected by different pooling schemes or by using center as a controlling variable. I confirmed that there are no treatment-by-center interactions. Results are also similar when all bowel movements are considered, regardless of the use of rescue intervention given within 4 hours of the double-blind dose.

### **3.1.2 Study MNTX 302/ MNTX 302EXT**

#### **3.1.2.1 Objectives**

The two co-primary objectives of the double-blind period of study are as follow:

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

The secondary objectives of the double-blind portion of the study were as follows:

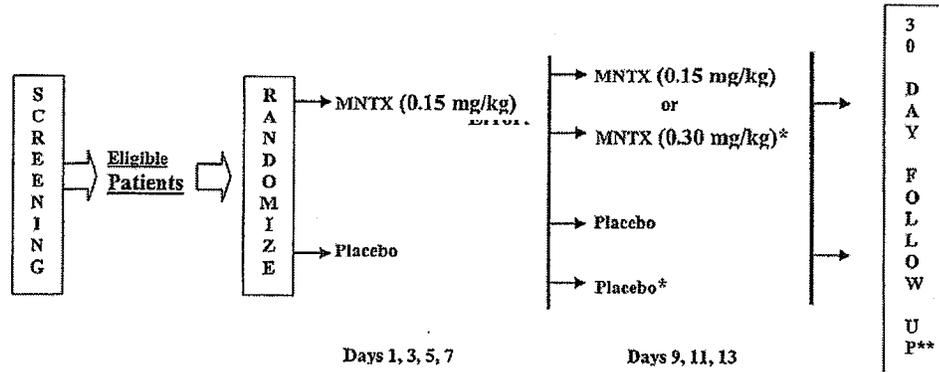
- To determine the efficacy of MNTX at a dose of 0.15 mg/kg QOD, with the option to escalate to 0.30 mg/kg, compared to placebo, over a 2-week period.
- To determine the safety of MNTX at a dose either of 0.15 mg/kg or escalating to 0.30 mg/kg QOD for a 2-week treatment period, compared to placebo.

The primary objective of extension study MNTX 302EXT was to provide access to treatment with MNTX to patients who completed study MNTX 302. The secondary objective was to obtain long-term safety and efficacy data on MNTX administered as needed for up to 3 months.

#### **3.1.2.2 Study Design**

MNTX 302 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study in patients with advanced medical illness and opioid-induced constipation, while MNTX 302EXT was an open-label, 3-month extension of Protocol MNTX 302. This review will focus primarily on the first week (Days 1 to 7) of the double-blind portion of study MNTX 302, whose design is illustrated schematically in Figure 3.

**Figure 3: MNTX 302 study design**



\* If the patient has < 3 bowel movements (not associated with rescue) by Day 8, patient will be eligible to escalate to a higher dose, in a blinded fashion by doubling the volume of study medication injected.

\*\* Patients who do not proceed to MNTX 302 extension will need to have a 30-day follow-up evaluation conducted.

(Source: Statistical Analysis Plan: Study MNTX 302; Section 2.2.2, page 6)

Eligible patients were randomly assigned to receive subcutaneous doses of either MNTX 0.15 mg/kg or matched placebo every other day during the first week (Days 1 to 7).

For the remainder of the study, any patient who had less than three bowel movements not associated with rescue medications or interventions by Day 8 was eligible for dose escalation, at the discretion of the investigator. Dose escalation was done in a blinded fashion by doubling the volume of study medication starting on Day 9 (i.e., 0.30 mg/kg MNTX or equivalent volume of placebo) and the treatment continued through Day 13.

On Day 14, eligible patients entered the open-label extension study, where dose administration continued on an as needed basis for up to 3 months. The investigator was permitted to increase the dose to 0.30 mg/kg or decrease the dose to 0.075 mg/kg at any time to attain the desired clinical effect or to ameliorate adverse effects.

### 3.1.2.3 Efficacy Endpoints and Analyses

The sponsor's efficacy analyses were performed on the intent-to-treat (ITT) analysis set, defined as all randomized patients who received the double-blind dose of the study drug.

#### Co-primary efficacy endpoints and analyses

The two co-primary efficacy endpoints of this study are: 1) the proportion of patients with a rescue-free laxation response within 4 hours after the first treatment dose (yes/no), and 2) the proportion of patients with a rescue-free laxation response within 4 hours after at least two of the first four treatment doses during the first week of double-blind treatment. A rescue-free laxation is defined as a bowel movement within the time window specified in a patient who had not received a rescue laxative (including enemas or disimpaction) between study drug administration and the bowel movement. Patients could not receive a rescue laxative within 4 hours before or after each treatment dose.

A laxation response is defined as a clinically significant bowel movement, not the passing minimal amounts of hard stool or small amounts of liquid stool. If a laxation response is not documented or if any rescue medication or intervention is administered within 24 hours of

study drug dosing, that outcome is not classified as a laxation response for purposes of the primary analysis.

The analyses of the co-primary endpoints comparing placebo to MNTX 0.15 mg/kg were planned to first use a Cochran-Mantel-Haenszel test with study center (sites with four or fewer patients were to be pooled into two separate sites) as a stratification factor to test the treatment-by-center interaction. If the treatment-by-center interaction was not significant ( $p > 0.10$ ) by the Breslow-Day test, a Chi-square test was to be applied to compare the MNTX dose against placebo at the two-sided type I error level of 0.0249. A Bonferroni multiplicity adjustment was applied to account for the two co-primary endpoint comparisons and also to account for an alpha (0.0000763) spent at the interim analysis.

Data imputation, as follows, was used. If a patient failed to receive any of the four scheduled doses of study drug, for any reason, before the end of the first week of treatment, the last value observed within 4 hours of the last dose of study drug was to be carried forward for the remaining doses (LOCF). During the 2-week double-blind treatment period, if any doses were missed or the patient discontinued treatment before the end of the 2-week double-blind treatment period, then the last value observed following the last dose administered was to be carried forward for the remaining doses until seven doses were observed or imputed per patient.

Estimates of response rates within 4 hours of each single-dose treatment and 95% confidence intervals were calculated. Sensitivity analyses of the co-primary efficacy endpoints were done by fitting a logistic regression model that accounts for treatment, study center, and baseline opioid medication use (converted to morphine equivalents). Further, a sensitivity analysis was performed on the second co-primary efficacy endpoint to support the LOCF imputation method. This analysis assumes a nonresponse for the missing values, irrespective of the last non-missing response. This analysis is equivalent to the observed case analysis.

#### Secondary efficacy endpoints and analyses

- Laxation responses within 4 hours after each dose of study medication
- Proportion of subjects with a total of at least 4 laxations each within 4 hours post dosing over the 7 doses of study drug (two-week treatment period)

Secondary endpoint analyses were similar to that used for the analysis of the primary endpoints. The sponsor assumed a nominal Type I error significance level of  $\alpha=0.05$  for each secondary endpoint comparison. The sponsor did not prespecify or conduct any adjustments for multiplicity for the secondary endpoints.

#### Tertiary efficacy endpoints and analyses

- Number of laxations per week for each study week (Week 1, Week 2)
- Number of rescue-free laxations per week during double-blind dosing
- Use of rescue laxative medication.
- Proportion of patients with at least 3 laxations per week during double-blind dosing.
- Time to laxation onset post-dosing
- Laxation responses within 24 hours following each dose
- Changes in bowel movement consistency
- Changes in bowel movement difficulty
- Changes in pain scores
- Changes in opioid withdrawal symptoms (modified Himmelsbach scale)
- Global Clinical Impression of Change ratings(patient and assessor)

The number of laxations per week for each patient was calculated as the number of laxations reported during the study period divided by the number of days observed times seven. The proportion of patients who reported at least 3 laxations per week and their respective 95% confidence intervals were calculated. The responses of the two treatment groups were compared using a Chi-square test. The other categorical endpoints were analyzed also using a Chi-square test. Changes in bowel movement frequency were compared using an analysis of variance model. The sponsor assumed a nominal Type I error significance level for the tertiary endpoints  $\alpha=0.05$  with no adjustments for multiplicity.

#### Determination of Sample Size

The total sample size of 130 patients, or 65 patients per treatment group, was based on a 30% to 35% treatment difference in the proportion of laxation responders under various assumptions of response rates, applying a two-sided Chi-square test, and an  $\alpha$ -level of 0.025. With the actual sample size of 71 and 63 for the placebo and MNTX 0.15 mg/kg groups, respectively, there was at least 90% power to detect an absolute treatment effect of 35% based on a placebo response rate of 15%.

#### Interim Analysis and Sample Size Re-estimation

An Interim Analysis was performed by a biostatistician external to both the sponsor and DSMB after approximately 50% of the patients ( $n=66$ ) completed the 2-week, double-blind period to assess safety and evaluate if the study was adequately powered and, if not, to conduct a sample size re-estimation if either of the co-primary efficacy endpoints failed the interim analysis. The sample size re-estimation procedure was to be based on the conditional power method of Li, Shih, Xie, Lu (2002)<sup>3</sup>. There was no plan to terminate the study as a result of the interim efficacy findings.

A group sequential monitoring approach was used for the interim analysis. The co-primary efficacy endpoints were analyzed and presented separately by treatment group using the ITT population. Calculation of the boundary value of 3.787 was based on the gamma spending function of Hwang, Shih, and deCani (1990)<sup>4</sup> with gamma equal to -10 and two-sided type I error rate of  $\alpha=0.000076$ .

The primary focus of the independent DSMB was to monitor the safety of short-term MNTX administration but it was also to convey future study conduct recommendations to the sponsor (e.g., continue as planned, early termination for serious safety concerns, or increase study sample size). The interim analysis was presented to the DSMB within 6 to 8 weeks of completion of the double-blind period of the 66<sup>th</sup> patient. Results of the interim analysis are discussed in Section 3.1.2.4.2.

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<sup>3</sup> Li, G., Shih, W.J., Xie, T. and Lu, J. A sample size adjustment procedure for clinical trials based on conditional power. *Biostatistics* 2002; 3(2):277-287.

<sup>4</sup> Hwang IK, Shih WJ, deCani JS. Group sequential designs using a family of type I error probability spending functions. *Stat in Med.* 1990; 9:1439-1445.

### 3.1.2.4 Efficacy Results

#### 3.1.2.4.1 Study Population

Patient disposition is presented in Table 6. One-hundred and seventy-four patients were screened of which 134 patients were randomized. Of the 40 patients not randomized, 26 patients failed to meet the inclusion/exclusion criteria; 8 patients requested withdrawal, 4 patients died, and 2 patients experienced pre-treatment adverse events.

A total of 134 patients completed screening: 71 were randomized to placebo and 63 to MNTX 0.15 mg/kg. More MNTX patients (84.1%) than placebo patients (76.1%) completed the study. The primary reasons for discontinuation were on-study death (4 placebo and 5 MNTX patients) and adverse events (3 placebo and 2 MNTX patients). Withdrawal was requested by 5 placebo patients.

One MNTX patient was excluded from the ITT analysis set due to that subject receiving open-label MNTX without being randomized. Thus the efficacy ITT analysis set consisted of 71 placebo patients and 62 MNTX patients

**Table 6: Patient disposition for MNTX 302 (ITT analysis set: all patients)**

Category	Placebo (N=71)	MNTX (N=63)	Total (N=134)
	n (%)	n (%)	n (%)
Number of Patients Screened			174
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)
Reason for Premature Discontinuation			
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 <sup>a</sup>	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)

(Source: Clinical Study Report: Study MNTX 302; Table 6, page 43)

Patient demographic and baseline information are summarized in Appendix 2, Table 17. The mean age was 67 years in the placebo group and 69 years in the MNTX group. More than half of the patients in each group were female and the majority were Caucasian (>90%). Both treatment groups appeared balanced with regard to baseline demographic characteristics,

baseline opioid use, and pain scores. The majority of patients had a primary diagnosis of cancer and most patients were using, on average, two to three laxatives per week at baseline.

### 3.1.2.4.2 Sponsor’s Efficacy Results for Primary Endpoint

The co-primary efficacy endpoints are: 1) the proportion of patients with a rescue-free laxation within 4 hours after the first dose of study drug, and 2) the proportion of patients who had a rescue-free laxation response within 4 hours after at least two of the first four doses of study drug (the first week of treatment). The sponsor’s co-primary efficacy results are presented in Table 7. This reviewer concurs with the sponsor’s results. MNTX 0.15 mg/kg is effective compared to placebo in providing a rescue-free laxation within 4 hours after the first dose of study drug and in providing a rescue-free laxation within 4 hours after at least two of the first four doses of study drug ( $p < 0.0001$ ).

**Table 7: Summary of results of the rescue-free laxation co-primary efficacy endpoints (ITT [LOCF] analysis)**

	Placebo ( 71)			MNTX ( 62)			p-value <sup>a</sup>
	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

<sup>a</sup> p-value comparing laxation response of MNTX versus placebo using the chi-square test. (Source: Clinical Study Report: Study MNTX 302; Table 9, page 51)

The purpose of the interim analysis, besides assessing safety, was to determine if the study was adequately powered. Because the results of the interim analysis based on the co-primary endpoints showed highly significant effects of MNTX 0.15 mg/kg compared to placebo, ( $p < 0.0001$ ), a re-estimation of the sample size was not deemed necessary. Because of the interim analysis, the significance level for testing was set at  $\alpha = 0.0249$ . Also, since no treatment-by-center interaction was demonstrated, the primary analysis was conducted using a Chi-squared test without adjusting for center effects.

### 3.1.2.4.3 Sponsor’s Efficacy Results for Secondary and Tertiary Endpoints

This section presents results for two secondary efficacy endpoints and three tertiary efficacy endpoints, which the clinical reviewer deemed clinically useful. These results are descriptive only, as the statistical significance of the comparisons was not prospectively adjusted for the multiple comparisons. Additional secondary and tertiary efficacy endpoint results are presented in Appendix 2.

#### Secondary: Rescue-free laxation response within 4 hours of each dose of study drug

Laxation responses within 4 hours of each of seven doses of study medication over the two-week period are summarized in Table 8. The absence of overlap between the group 95% confidence intervals for any dose suggests a treatment effect. However, results should be not

be considered confirmatory. Overall, 79.0% of the MNTX-treated patients and 46.5% of the placebo-treated patients had a rescue-free laxation response within 4 hours after at least 1 dose.

**Table 8: Rescue-Free Laxation Response Within 4 Hours After Each Dose (ITT Observed Case Analysis)**

	Placebo (N= 71)			MNTX ( N=62)		
	Patients Dosed	Patients with Laxation Response (%)	95% Confidence Interval (CI)	Patients Dosed	Patients with Laxation Response (%)	95% Confidence Interval (CI)
Dose 1 (Day 1)	71	11 (15.5)	7.1-23.9	62	30 (48.4)	35.9-60.8
Dose 2 (Day 3)	65	6 (9.2)	2.2-16.3	57	26 (45.6)	32.7-58.5
Dose 3 (Day 5)	63	8 (12.7)	4.5-20.9	58	27 (46.6)	33.7-59.4
Dose 4 (Day 7)	59	4 (6.8)	0.4-13.2	56	21 (37.5)	24.8-50.2
Dose 5 (Day 9)	58	8 (13.8)	4.9-22.7	56	23 (41.1)	28.2-54.0
Dose 6 (Day 11)	52	5 (9.6)	1.6-17.6	51	19 (37.3)	24.0-50.5
Dose 7 (Day 13)	51	4 (7.8)	0.5-15.2	47	18 (38.3)	24.4-52.2
Overall Response	71	33 (46.5)	34.9-58.1	62	49 (79.0)	68.9-89.2

(Source: Clinical Study Report: Study MNTX 302 – Amendment 7 – September 28, 2007; Table 10, page 53)

Secondary: At least 4 Laxations each within 4 hours post dose over 7 doses of study drug

Over all seven doses, 4 of 71 patients (5.6%) in the placebo group and 24 of 62 patients (38.7%) in the MNTX group had at least 4 rescue-free laxations within 4 hours post dose. This was based on the LOCF analysis. Based on the observed-case analysis, there were 1 (1.4%) and 19 (30.6%) patients, respectively, with at least 4 rescue-free laxations within 4 hours following at least four dose administrations. The results are similar when adjusted for baseline opioid use.

Tertiary: Laxation responses within 24 hours of the each dose of study medication

Laxation responses within 24 hours of each dose of study medication are summarized in Table 9. There was no overlap between the 95% confidence intervals for the 2 treatment groups following Doses 1 through 4. There was overlap for Doses 5 through 7, when the placebo response rate was greater than with previous doses. These results are considered to be descriptive only and not suggest a statistically significant difference.

**Table 9: Rescue-Free Laxation Response Within 24 Hours After Each Dose (ITT Observed-Case Analysis)**

	Placebo (N= 71)			MNTX (N=62)		
	Patients Dosed	Patients with Laxation Response (%)	95% Confidence Interval (CI)	Patients Dosed	Patients with Laxation Response (%)	95% Confidence Interval (CI)
Dose 1 (Day 1)	71	23 (32.4)	21.5-43.3	62	39 (62.9)	50.9-74.9
Dose 2 (Day 3)	65	20 (30.8)	19.5-42.0	57	35 (61.4)	48.8-74.0
Dose 3 (Day 5)	63	18 (28.6)	17.4-39.7	58	36 (62.1)	49.6-74.6
Dose 4 (Day 7)	59	18 (30.5)	18.8-42.3	56	35 (62.5)	49.8-75.2
Dose 5 (Day 9)	58	22 (37.9)	25.4-50.4	56	31 (55.4)	42.3-68.4
Dose 6 (Day 11)	52	19 (36.5)	23.5-49.6	51	30 (58.8)	45.3-72.3
Dose 7 (Day 13)	51	20 (39.2)	25.8-52.6	47	31 (66.0)	52.4-79.5
Overall Response	71	55 (77.5)	67.7-87.2	62	59 (95.2)	89.8-100

(Source: Clinical Study Report: Study MNTX 302 – Amendment 7 – September 28, 2007; Table 11, page 55)

Tertiary: Laxation Responses by Week

Table 10 presents the rescue-free laxation responses for each week of double-blind treatment.

**Table 10: Laxation response (rescue-free) per study week (analysis set: ITT [LOCF])**

	Placebo (N= 71)	MNTX (N=62)
<b>Laxations during Study Week 1</b>		
Number of Patients Dosed	71	62
Number (%) of Patients with Laxation Response	59 (83.1)	59 (95.2)
Mean (SD)	3 (2.19)	6 (3.71)
Median	3	5
Minimum - Maximum	1-9	1-16
<b>Laxations during Study Week 2</b>		
Number of Patients Dosed	58	57
Number (%) of Patients with Laxation Response	47 (81.0)	52 (91.2)
Mean (SD)	4 (2.38)	4 (2.91)
Median	4	3
Minimum - Maximum	1-12	1-14

(Source: Clinical Study Report: Study MNTX 302; Table 12, page 57)

Tertiary: Use of Laxatives

The percentage of patients using enemas increased relative to baseline in both groups, but 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%).

### 3.1.2.4.4 Sponsor's Exploratory and Sensitivity Analyses

The co-primary efficacy analyses were replicated by fitting a two-way logistic model that accounted for treatment and study center. Further, a sensitivity analysis was performed on the second co-primary efficacy endpoint to support the LOCF imputation method. This analysis is equivalent to the observed cases analysis.

Planned analyses based on a per-protocol analysis set, which was to exclude any patients with major protocol violations, were not performed because there was only one major protocol violation; this patient was treated but not randomized).

### 3.1.2.4.5 Statistical Reviewer's Results and Comments

This reviewer confirmed the sponsor's findings for the co-primary endpoints. The findings for secondary endpoints should be considered exploratory since Type I error was not controlled for the multiple doses and multiple endpoints.

The sponsor submitted Amendment 7 on September 28, 2007 which changed the methodology from using LOCF to OC (observed case) for the analysis of two secondary endpoints: laxation responses within 4 hours of the each dose of study medication and laxation responses within 24 hours of the each dose of study medication. The OC approach more accurately reflects the treatment effect of each dose of study medication since LOCF has the potential of carrying-over favorable earlier response. The change had no impact on the primary analysis.

Sensitivity analyses were performed by sponsor to test the treatment-by-center interactions for several pooling schemes; I confirmed that there were no treatment-by-center interactions. Baseline opioid medication use (converted to morphine equivalents), age group, gender and site were included as a covariate in the analysis of the two co-primary efficacy endpoints via logistic regression. None of the covariates were statistically significant.

Since missing laxation responses were considered to be no response for the co-primary efficacy endpoint of rescue-free laxation within 4 hours after the first dose of study drug, there was no issue with missing data. For co-primary endpoint of two or more laxations within 4 hours after dose administration over four doses, there is concern that the LOCF approach had potential to carry over biased responses. We conducted a sensitivity analysis based on complete cases and imputation which treated missing laxation responses as no response. As shown in Table 11, the results are consistent with the findings in LOCF model.

**Table 11: Study MNTX 302 - Sensitivity Analyses for Co-Primary Efficacy Endpoint of At Least 2 Rescue-Free Laxations Within 4 Hours Over the First Four Doses**

Population	Endpoint	N	% Responders (n)	Treatment Difference (95% C.I.)	p-value
<b>At least 2 laxations within 4 hours over the first 4 doses</b>					
Completers	Placebo	57	3.5 (2)		
	MNTX 0.15 mg/kg	54	51.8 (28)	48.3 (34.2, 62.5)	< 0.0001
Imputation	Placebo	71	4.2 (3)		
	MNTX 0.15 mg/kg	62	46.8 (29)	42.5 (29.3, 55.8)	< 0.0001
LOCF	Placebo	71	8.5 (6)		
	MNTX 0.15 mg/kg	62	51.6 (32)	43.2 (29.1, 57.2)	< 0.0001

(Source: Statistical Reviewer's results)

### 3.2 Evaluation of Safety

The reviewer also performed analyses of the QT study data (Refer to “Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review.” Dated 12-07-2007). Also refer to the clinical review for the full safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

#### 4.1.1 Gender

I conducted a gender stratified analysis of the primary efficacy outcomes in each study. As show in Table 12, the results suggest that the treatment effects on primary efficacy endpoint of rescue-free laxation within 4 hours on Day 1 were consistent across gender for both studies. For study MNTX 302, the second co-primary efficacy endpoint of at least two rescue-free laxations within 4 hours over the first four doses had a greater treatment effect for males (56.0%) compared to females (33.2%).

**Table 12: Summary of Efficacy Results by Gender**

Gender	Endpoint	N	% Responders (n)	Treatment Difference (95% C.I.)	p-value
<b>Study MNTX 301</b>					
<b><u>Laxation within 4 hours on Day 1</u></b>					
Male	Placebo	28	7.1 (2)		
	MNTX 0.15 mg/kg	25	52.0 (13)	44.9 (23.1, 66.6)	0.0003
	MNTX 0.30 mg/kg	31	58.1 (18)	50.9 (31.1, 70.7)	< 0.0001
Female	Placebo	24	20.1 (5)		
	MNTX 0.15 mg/kg	22	72.7 (16)	51.9 (27.2, 76.6)	0.0005
	MNTX 0.30 mg/kg	24	58.3 (14)	37.5 (11.9, 63.1)	0.0086
All	Placebo	52	13.5 (7)		
	MNTX 0.15 mg/kg	47	61.7 (29)	48.2 (31.5, 64.9)	< 0.0001
	MNTX 0.30 mg/kg	55	58.2 (32)	44.7 (28.7, 60.7)	< 0.0001
<b>Study MNTX 302</b>					
<b><u>Laxation within 4 hours on Day 1</u></b>					
Male	Placebo	31	12.9 (4)		
	MNTX 0.15 mg/kg	27	44.4 (12)	31.5 (9.4, 53.7)	0.0079
Female	Placebo	40	17.5 (7)		
	MNTX 0.15 mg/kg	35	51.4 (18)	33.9 (13.6, 54.2)	0.0020
All	Placebo	71	15.5 (11)		
	MNTX 0.15 mg/kg	62	48.4 (30)	32.9 (17.9, 47.9)	< 0.0001
<b><u>At least 2 laxations within 4 hours over the first 4 doses</u></b>					
Male	Placebo	31	3.2 (1)		
	MNTX 0.15 mg/kg	27	59.3 (16)	56.0 (36.5, 75.6)	< 0.0001
Female	Placebo	40	12.5 (5)		
	MNTX 0.15 mg/kg	35	45.7 (16)	33.2 (13.9, 52.6)	0.0015
All	Placebo	71	8.5 (6)		
	MNTX 0.15 mg/kg	62	51.6 (32)	43.2 (29.1, 57.2)	< 0.0001

(Source: Statistical Reviewer’s results)

#### 4.1.2 Race and Age

For age, the subjects in both studies were between 21 and 100 year old. I conducted analyses stratified by age group, < 65 and ≥ 65 years of age. These results suggest that the treatment effects based on the primary efficacy endpoints were consistent across age groups for both studies.

I conducted an analysis by race only for study 301 using the categories of Caucasian and non-Caucasian. As shown in Table 13, trends in responder rates were not consistent between Caucasians and non-Caucasians, especially for MNTX 0.15 mg/kg, which had a negative treatment effect due to the high placebo response rate. However, no conclusion can be drawn due to the small sample size. A similar analysis was not conducted for Study 302 because there were only two non-Caucasian patients per treatment group.

**Table 13: Summary of Efficacy Results by Race; Review's Results**

Race	Endpoint	N	% Responders (n)	Treatment Difference (95% C.I.)
<b>Study MNTX 301</b>				
<b>Laxation within 4 hours on Day 1</b>				
	Placebo	43	7.0 (3)	
Caucasian	MNTX 0.15 mg/kg	38	68.4 (26)	61.4 (44.8, 78.1)
	MNTX 0.30 mg/kg	46	56.5 (26)	49.5 (33.3, 65.8)
Non-Caucasian	Placebo	9	44.4 (4)	
	MNTX 0.15 mg/kg	9	33.3 (3)	-11.1 (-33.6, 55.9)
	MNTX 0.30 mg/kg	9	66.7 (6)	22.2 (-22.5, 67.0)
All	Placebo	52	13.5 (7)	
	MNTX 0.15 mg/kg	47	61.7 (29)	48.2 (31.5, 64.9)
	MNTX 0.30 mg/kg	55	58.2 (32)	44.7 (28.7, 60.7)

(Source: Statistical Reviewer's results)

#### 4.2 Other Special/Subgroup Populations

There were no other special or subgroup populations of interest in this submission.

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

The sponsor submitted two phase 3 efficacy studies to demonstrate the superiority of efficacy of Methylnaltrexone SR over placebo. U.S. Study MNTX 301 provided evidence that one injection of MNTX SC 0.15 mg/kg or of MNTX SC 0.30 mg/kg was effective in the treatment of opioid-induced constipation in patients with advanced medical illness as measured by rescue-free laxation within 4 hours of the single dose. The findings of study 301 at doses 0.15mg/kg SR and 0.30mg/kg SR were consistent across age and gender group. Study 302, conducted in U.S. and Canada, confirmed efficacy for 0.15 mg/kg MNTX SC as measured by laxation within 4 hours of the double-blind dose. The co-primary endpoint at least two laxations within 4 hours after dose administrated over four doses provided evidence that MNTX SC 0.15 mg/kg was efficacious in the one-week treatment period. Study 302 secondary endpoints at least 4 laxations each within 4 hours post dose over seven doses and laxation response within 4 hours of each dose provided supportive evidence of efficacy in the two-week treatment period.

### **5.2 Conclusions and Recommendations**

The results of both MNTX 301 and MNTX 302 provide evidence that MNTX SC 0.15 mg/kg and MNTX SC 0.30 mg/kg are efficacious in treating opioid-induced constipation in patients with advanced medical illness receiving palliative therapy.

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## APPENDIX 1 - STUDY MNTX 301

**Table 14: Demographic and Baseline Characteristics for MNTX 301 Study: Double-Blind Patients**

Characteristic <sup>a</sup>	Statistic/ Category	Placebo (N=52)	MNTX 0.15 mg/kg (N=47)	MNTX 0.30 mg/kg (N=55)	Total (N=154)
Age (years)	N	52	47	55	154
	Mean (SD)	64.7 (16.20)	65.9 (15.51)	65.3 (13.43)	65.3 (14.96)
	Median	62.5	67.0	68.0	66.0
	Min-Max	21-100	26-96	34-89	21-100
Sex, n (%)	Male	28 (53.8%)	25 (53.2%)	31 (56.4%)	84 (54.5%)
	Female	24 (46.2%)	22 (46.8%)	24 (43.6%)	70 (45.5%)
Race, n (%)	Caucasian	43 (82.7%)	38 (80.9%)	46 (83.6%)	127 (82.5%)
	Black	3 (5.8%)	5 (10.6%)	4 (7.3%)	12 (7.8%)
	Hispanic	5 (9.6%)	3 (6.4%)	4 (7.3%)	12 (7.8%)
	Asian	1 (1.9%)	1 (2.1%)	0	2 (1.3%)
	Other	0	0	1 (1.8%)	1 (0.6%)
Weight (kg)	N	51 <sup>b</sup>	47	55	153
	Mean (SD)	67.1 (19.12)	70.4 (21.08)	65.5 (16.03)	67.6 (18.71)
	Median	68.1	70.0	64.0	65.9
	Min-Max	29-133	31-135	31-110	29-135
Primary diagnosis, n (%)	Cancer	43 (82.7%)	37 (78.7%)	45 (81.8%)	125 (81.2%)
	Cardiovascular	2 (3.8%)	4 (8.5%)	2 (3.6%)	8 (5.2%)
	HIV/AIDS	0	1 (2.1%)	0	1 (0.6%)
	Other	7 (13.5%)	5 (10.6%)	8 (14.5%)	20 (13.0%)
WHO Performance Status <sup>c</sup> , n (%)	0	0	1 (2.1%)	0	1 (0.6%)
	1	2 (3.8%)	2 (4.3%)	1 (1.8%)	5 (3.2%)
	2	17 (32.7%)	13 (27.7%)	15 (27.3%)	45 (29.2%)
	3	21 (40.4%)	19 (40.4%)	30 (54.5%)	70 (45.5%)
	4	12 (23.1%)	12 (25.5%)	9 (16.4%)	33 (21.4%)
Oral morphine equivalents (mg/day)	N	52	47	55	154
	Mean (SD)	617.3 (1559.86)	3289.8 (17855.3)	1220.4 (4585.74)	1648.3 (10263.5)
	Median	150.0	207.0	188.0	186.5
	Min-Max	8-9720	10-122560	12-33120	8-122560

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 9A, page 59)

**Table 14 (cont'd) : Demographic and Baseline Characteristics for MNTX 301 Study: Double-Blind Patients**

Characteristic <sup>a</sup>	Statistic/ Category	Placebo (N=52)	MNTX 0.15 mg/kg (N=47)	MNTX 0.30 mg/kg (N=55)	Total (N=154)
Current Pain Score <sup>d</sup>	N	49	45	54	148
	Mean (SD)	3.2 (2.67)	3.2 (2.82)	3.1 (2.84)	3.2 (2.76)
	Median	3.0	3.0	2.5	3.0
	Min-Max	0-9	0-9	0-10	0-10
Worst Pain Score <sup>d</sup>	N	49	44	54	147
	Mean (SD)	5.6 (2.77)	6.4 (2.75)	5.3 (2.92)	5.7 (2.83)
	Median	6.0	7.0	6.0	6.0
	Min-Max	0-10	0-10	0-10	0-10
Constipation Distress	None	4 (8.2%)	4 (8.7%)	4 (7.4%)	12 (8.1%)
	A Little Bit	9 (18.4%)	7 (15.2%)	5 (9.3%)	21 (14.1%)
	Somewhat	10 (20.4%)	9 (19.6%)	13 (24.1%)	32 (21.5%)
	Quite a Bit	18 (36.7%)	14 (30.4%)	21 (38.9%)	53 (35.6%)
	Very Much	8 (16.3%)	12 (26.1%)	11 (20.4%)	31 (20.8%)
	Missing	3	1	1	5
Number of Laxatives Taken by Drug Class	N	52	47	55	154
	Mean (SD)	1.8 (0.96)	1.7 (0.92)	1.7 (1.15)	1.7 (1.01)
	Median	2.0	2.0	2.0	2.0
	Min-Max	0-4	0-4	0-5	0-5
Number of Laxatives Taken by Generic Term	N	52	47	55	154
	Mean (SD)	2.1 (1.25)	1.9 (1.12)	2.0 (1.52)	2.0 (1.31)
	Median	2.0	2.0	2.0	2.0
	Min-Max	0-6	0-5	0-7	0-7

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 9B, page 61)

### Additional Secondary Efficacy Endpoint Results for Study 301

#### Constipation Distress:

Patients assessed the level of constipation distress baseline (on study Day 1 prior to dosing) and again 4 hours after administration of the single treatment and at the end of the double-blind period. The sponsor put emphasis on results from the double-blind period for which the most data were available. As shown in Table 15, at 4 and 24 hours after double-blind dosing, more patients had a change for the better in constipation distress in both treatment groups compared to the placebo group.

**Table 15: Changes from Baseline in Constipation Distress: Double-Blind Patients**

	Placebo (N=52)	MNTX 0.15 mg/kg (N=47)	MNTX 0.30 mg/kg (N=55)
<b>4 Hours after Double-Blind Dosing</b>			
Better	17 (34.0%)	29 (64.4%)	33 (63.5%)
No Change	29 (58.0%)	16 (35.6%)	17 (32.7%)
Worse	4 (8.0%)	0 ( 0.0%)	2 (3.8%)
Missing	2	2	3
<b>24 Hours after Double-Blind Dosing</b>			
Better	15 (29.4%)	29 (64.4%)	29 (56.9%)
No Change	25 (49.0%)	14 (31.1%)	19 (37.3%)
Worse	11 (21.6%)	2 (4.4%)	3 (5.9%)
Missing	1	2	4

Baseline: Double Blind Day 1 pre-dose value or screening value if pre-dose value is missing.  
 (Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 17, page 74)

#### Bowel Movement Consistency and Difficulty

Assessments of bowel movement consistency and difficulty can be made only if bowel movements actually occur. Given that few patients in the placebo group had bowel movements, the sponsor stated that it was not very useful to compare the treatment groups in terms of the change in bowel movement consistency and difficulty.

#### Pain Scores:

Assessments of current and worst pain levels were recorded at baseline, 4 hours and 24 hours after double-blind dosing. Little change was observed in either current or worst pain scores for all 3 treatment groups in double-blind dosing period.

#### Modified Himmelsbach Scale:

Assessments of Opioid Withdrawal Symptoms scores were recorded at baseline, 4 hours and 24 hours after double-blind dosing. At 4 hours after double-blind dosing, the three treatment groups had similar mean decreases from baseline in opioid withdrawal symptoms. 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.

#### Global Clinical Impression of Change Ratings (GCIC):

Patient and Clinician GCIC ratings recorded at the end of the double-blind period and at the end of the open-label period of the study (Day 28) to assess changes in bowel status. As shown in Table 16, at the end of the double-blind period, the percent of patients who were better (as assessed by the patient) was 22% in the placebo group compared to 59% in each of the MNTX groups. Within-group patient and investigator assessments of each treatment group were very similar, and patients and clinicians had more favorable impressions of MNTX than of placebo.

**Table 16: Global Clinical Impression of Change (Patient and Clinician) at the End of Double Blind by Treatment Group: Double-Blind Patients**

	Placebo (N=52) n (%)		0.15 mg/kg (N=47) n (%)		0.30 mg/kg (N=55) n (%)	
	Patient	Clinician	Patient	Clinician	Patient	Clinician
Better <sup>a</sup>	11 (21.6)	10 (19.6)	27 (58.7)	28 (60.9)	30 (58.8)	30 (57.7)
No change	34 (66.7)	38 (74.5)	19 (41.3)	18 (39.1)	18 (35.3)	20 (38.5)
Worse <sup>b</sup>	6 (11.8)	3 (5.9)	0 (0.0)	0 (0.0)	3 (5.9)	2 (3.8)
Missing	1	1	1	1	4	3

<sup>a</sup>Better=Patients with ratings of Somewhat Better, Slightly Better or Much Better

<sup>b</sup>Worse= Patients with ratings of Much Worse, Somewhat Worse, and Slightly Worse

(Source: Clinical Study Report: Study MNTX 301/301 EXT; Table 21, page 78)

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## APPENDIX 2 - STUDY MNTX 302

**Table 17: Demographic and baseline characteristics by treatment group for MNTX 302 (analysis set: all patients)**

Characteristics	Statistics	Placebo (N=71)	MNTX (N=63)
Age (years)	N	71	63
	Mean (SD)	66.8 (15.39)	68.9 (14.33)
	Median	70.0	72.0
	Min-Max	39-98	34-93
Gender, n (%)	Male	31 (43.7)	27 (42.9)
	Female	40 (56.3)	36 (57.1)
Race, n (%)	Caucasian	65 (91.5)	61 (96.8)
	Black	5 (7.0)	1 (1.6)
	Asian	0	1 (1.6)
	Other	1 (1.4)	0
Ethnicity, n (%)	Hispanic/Latino	1 (1.4)	2 (3.2)
	Not Hispanic/Latino	70 (98.6)	61 (96.8)
Weight (kg)	N	71	63
	Mean (SD)	71.3 (23.94)	68.9 (17.79)
	Median	68.2	68.2
	Min-Max	34-189	39-123
Primary Diagnosis, n (%)	Cancer	41 (57.7)	37 (58.7)
	Cardiovascular	7 (9.9)	8 (12.7)
	HIV/AIDS	0	0
	Alzheimer/AD/Dementia	4 (5.6)	4 (6.3)
	COPD, COPD/Emphysema, Other	5 (7.0)	9 (14.3)
	Others	14 (19.7)	5 (7.9)
WHO Performance Status <sup>a</sup> , n (%)	1	6 (8.5)	3 (4.8)
	2	16 (22.5)	14 (22.2)
	3	36 (50.7)	28 (44.4)
	4	13 (18.3)	18 (28.6)
Number of Laxatives Taken: by Drug Class	N	71	62 <sup>b</sup>
	Mean (SD)	2.4 (1.12)	2.1 (1.00)
	Median	2	2
	Min-Max	1-5	1-4
Number of Laxatives Taken: by Generic Term	N	71	62 <sup>b</sup>
	Mean (SD)	2.7 (1.32)	2.5 (1.35)
	Median	3	2
	Min-Max	1-6	1-5
Opioid Dose (mg/day) (Oral morphine equivalents)	N	71	63
	Mean (SD)	338.8 (1213.06)	417.0 (787.35)
	Median	100.0	150.0
	Range	10.0-10160.0	9.0-4160.0
Current Level of Pain <sup>c</sup>	N	71	60
	Mean (SD)	3.5 (2.6)	3.6 (2.7)
	Median	3	3
	Min-Max	0-10	0-9
Constipation Distress, n (%)	None	8 (11.3)	7 (11.1)
	A little bit	6 (8.5)	6 (9.5)
	Somewhat	11 (15.5)	9 (14.3)
	Quite a bit	18 (25.4)	16 (25.4)
	Very much	27 (38.0)	22 (34.9)
	Not reported	1 (1.4)	3 (4.8)

(Source: Clinical Study Report: Study MNTX 302; Table 8, page 49)

## Additional Tertiary Efficacy Endpoint Results for Study 302

### Laxation Responses for Patients with Dose Escalation:

A total of 41 patients (21 in the placebo group and 20 in the MNTX group) had escalation of the dose to 0.30 mg/kg during the second week of the study. Table 18 shows the cumulative rescue-free laxation responses within 4 hours after all doses for these patients, by dose level. There was a modest increase in the response rate for the MNTX-treated patients but not for the placebo-treated patients following dose escalation.

**Table 18: Laxation response (rescue-free) within 4 hours after 0.15 mg/kg doses and 0.30 mg/kg doses for patients with dose escalation (analysis set: ITT [observed cases])**

Group	Number with Escalation	Dose Level (mg/kg)	Number of Doses	Number (%) of Doses with Laxation Response
Placebo	21	0.15	85	7 (8.2)
		0.30	54	4 (7.4)
MNTX	20	0.15	85	13 (15.3)
		0.30	49	12 (24.5)
Total	41	0.15	170	20 (11.8)
		0.30	103	16 (15.5)

(Source: Clinical Study Report: Study MNTX 302; Table 13, page 57)

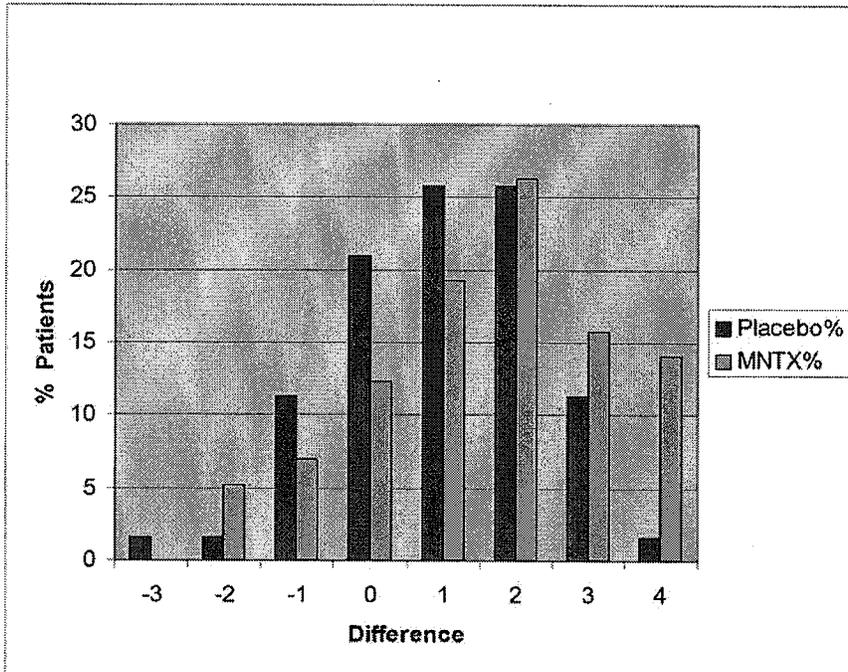
### Time to Laxation:

Based on patients who had laxation, the median time to laxation was 1.0 hour in the MNTX group and 11.2 hours in the placebo group after the first dose. The median times to laxation after subsequent doses ranged from 1.1 to 2.6 hours in the MNTX group and from 7.2 to 22.0 hours in the placebo group. Based on all patients, the median time to laxation was significantly shorter in the MNTX group than in the placebo group after each of the 7 doses of study medication ( $p \leq 0.0018$ ).

### Bowel Movement Consistency and Difficulty:

Figure 4 shows the distribution of the patients in each group according to the change in bowel movement difficulty between the baseline rating and the average on-therapy rating. The figure demonstrates that greater levels of improvement occurred in larger percentages of patients in the MNTX group than in the placebo group.

**Figure 4:** Difference between baseline and average on-therapy bowel movement difficulty ratings (analysis set: ITT)



(Source: Clinical Study Report: Study MNTX 302; Figure 4, page 59)

**Constipation Distress:**

The patients assessed the level of constipation distress at the screening visit (baseline), before study drug administration on Days 1 and 7, and on Day 14. As shown in Table 19, at each evaluation, higher percentages of patients in the MNTX group than in the placebo group had improvement in constipation distress, whereas lower percentages of patients in the MNTX group than in the placebo group had worsening constipation distress.

**Table 19: Changes in constipation distress (analysis set: ITT)**

Day	Placebo (N=71) N (%)				MNTX (N=62) N (%)			
	N <sup>a</sup>	Improved	No Change	Worsened	N <sup>a</sup>	Improved	No Change	Worsened
1	64	19 (29.7)	40 (62.5)	5 (7.8)	55	29 (52.7)	24 (43.6)	2 (3.6)
7	48	24 (52.1)	12 (25.0)	12 (25.0)	45	29 (64.4)	12 (26.7)	4 (8.9)
14	54	29 (53.7)	15 (27.8)	10 (18.5)	53	32 (60.4)	13 (24.5)	8 (15.1)

(Source: Clinical Study Report: Study MNTX 302; Table 14, page 60)

**Pain Scores:**

Assessments of current and worst pain levels were recorded at baseline and on Days 1, 7, and 14. The mean pain scores at each evaluation were similar in the 2 treatment groups, and there was little change in the scores over time in either group.

Modified Himmelsbach Scale (Opioid Withdrawal Symptoms):

Assessments of Opioid Withdrawal Symptoms scores were recorded at baseline, Days 1, 7, and 14. There were no meaningful changes in group mean or median values or in the range of changes from baseline on Days 1, 7, and 14, when the MNTX group was compared with the placebo group.

Global Clinical Impression of Change:

Table 20 summarizes the GCIC ratings of bowel status provided by the Investigators and the patients on Days 7 and 14. On Day 7, a majority of the patients and Investigators considered bowel status unchanged in the placebo group, whereas a majority of the patients and Investigators considered bowel status improved in the MNTX group. On Day 14, bowel status was considered improved by a larger proportion of the patients and Investigators in the MNTX group (68%) than in the placebo group (45% to 50%).

**Table 20: Global Clinical Impression of Change (GCIC) ratings (analysis set: ITT)**

Statistics	Placebo (N=71)		MNTX (N= 62)	
	Patient	Clinician	Patient	Clinician
<b>Day 7</b>				
N <sup>a</sup>	57	57	49	49
Better	20 (35.1%)	20 (35.1%)	36 (73.5%)	34 (69.4%)
No Change	34 (59.6%)	35 (61.4%)	12 (24.5%)	15 (30.6%)
Worse	2 (3.5%)	2 (3.5%)	0 (0%)	0 (0%)
<b>Day 14</b>				
N <sup>a</sup>	56	56	53	53
Better	25 (44.6%)	28 (50.0%)	36 (67.9%)	36 (67.9%)
No Change	27 (48.2%)	25 (44.6%)	14 (26.4%)	16 (30.2%)
Worse	2 (3.6%)	3 (5.4%)	2 (3.8%)	1 (1.9%)

(Source: Clinical Study Report: Study MNTX 302; Table 14, page 60)

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/s/

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Kate L Dwyer  
3/7/2008 03:16:44 PM  
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Mike Welch  
3/7/2008 03:34:54 PM  
BIOMETRICS  
Concur with review.

**Screening of New NDA for Statistical Filing  
Division of Biometrics III**

**NDA #:** 21-964 (Serial 000)

**Applicant:** Progenics Pharmaceuticals, Inc.

**Trade/Generic Name:** Methylnaltrexone (MNTX)

**Indication:** Relief of Constipation ~~in~~ Opioid Therapy in Patients with Advanced Medical Illness

**Date of Submission:** March 30, 2007

**Filing Meeting Date:** May 29, 2007

**User Fee Goal Date:** January 30, 2008

**Project Manager:** Brian K Strongin (DGP)

**Medical Reviewer:** Keith St. Amand, M.D.

**Statistical Reviewer:** Kate Dwyer, Ph.D.

**Comments:** This NDA is fileable from a statistical perspective.

**Brief Summary of Phase III Clinical Studies for Methylnaltrexone (MNTX)**

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population / Primary Endpoints	Treatment	Number Randomized (ITT <sup>1</sup> )	Design <sup>3</sup>
MNTX 301 (17 / U.S.) Feb. 2003 to Feb. 2005	Patients with advanced medical illness and opioid-induced constipation who are poorly responsive to laxatives and have no bowel movement for 48 hours before treatment. The primary endpoint was laxation response within 4 hours of DB dosing.	MNTX 0.15 mg/kg MNTX 0.30 mg/kg Placebo <b>Total</b>	47 (47) 55 (55) 52 (52) <b>155<sup>2</sup> (154)</b>	DB, R, PC, PG, MC
MNTX 302 (26 / U.S. & 1/ Canada) Feb. 2004 to Oct. 2005	Patients with advanced medical illness and opioid-induced constipation who are poorly responsive to laxatives and have no bowel movement for 48 hours before treatment. The co-primary endpoints were laxation response within 4 hours of first DB dosing and 2+ laxations within 4 hours post dosing over 4 DB doses in first week study.	MNTX 0.15 mg/kg (Days 1, 3, 5, 7) Placebo (Days 1, 3, 5, 7) <b>Total</b>	63 (62) 71 (71) <b>134 (133)</b>	

<sup>1</sup> ITT = Intent To Treat

<sup>2</sup> Patient 401 was randomized but the sponsor did not provide a treatment code for the patient

<sup>3</sup> DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

The Sponsor still needs to provide additional information that will be included in the 74-day letter:

1. For Study MNTX 301, provide either the location within the application of the pre-specified Interim Analysis Plan for sample size re-estimation, or submit the plan with the sign-off sheet with signatures and dates.
2. For Study MNTX 302, please provide both the pre-specified Interim Analysis Plan with the sign-off sheet with signatures and dates and the Interim Analysis Report.

3. Provide a data file with the following information for each Phase III Study: Subject I.D., Treatment Group and Flag to identify which subjects were used in the interim analysis.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	Need More Info (See Comment above)
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	EDR data present
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	NA

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Mike Welch  
6/13/2007 11:25:53 AM  
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