CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208271Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208,271
Priority or Standard	Standard
Submit Date(s)	6/19/2015
Received Date(s)	6/19/2015
Original PDUFA Goal Date	4/19/2016
Amended PDUFA Date	7/19/2016
Division / Office	Division of Gastroenterology and Inborn Errors Products/ Office of Drug Evaluation III
Reviewer Name(s)	Dina J. Zand M.D.
Review Completion Date	June 2, 2016
Established Name	Methylnaltrexone bromide
(Proposed) Trade Name	Relistor®
Therapeutic Class	Peripherally acting mu-opioid receptor antagonist (PAMORA)
Applicant	Salix Pharmaceuticals, Inc
Formulation(s)	Oral Tablet
Dosing Regimen	3 tablets once daily (450 mg/day)
Indication(s)	Opioid-induced constipation in adult patients with chronic non-cancer pain
Intended Population(s)	≥18 years of age

Template Version: March 6, 2009

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 9

1.1 Recommendation on Regulatory Action 9
1.2 Risk Benefit Assessment 9
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 13
1.4 Recommendations for Postmarket Requirements and Commitments 15

2 INTRODUCTION AND REGULATORY BACKGROUND 15

2.1 Product Information 17
2.2 Tables of Currently Available Treatments for Proposed Indications 18
2.3 Availability of Proposed Active Ingredient in the United States 18
2.4 Important Safety Issues with Consideration to Related Drugs 19
2.5 Summary of Presubmission Regulatory Activity Related to Submission 19
2.6 Other Relevant Background Information 24

3 ETHICS AND GOOD CLINICAL PRACTICES 24

3.1 Submission Quality and Integrity 24
3.2 Compliance with Good Clinical Practices 25
3.3 Financial Disclosures 27

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 28

4.1 Chemistry Manufacturing and Controls 28
4.2 Clinical Microbiology 29
4.3 Preclinical Pharmacology/Toxicology 30
4.4 Clinical Pharmacology 31
4.4.1 Mechanism of Action 31
4.4.2 Pharmacodynamics 32
4.4.3 Pharmacokinetics 32

5 SOURCES OF CLINICAL DATA 35

5.1 Tables of Studies/Clinical Trials 36
5.2 Review Strategy 37
5.3 Discussion of Individual Studies/Clinical Trials 38

6 REVIEW OF EFFICACY 56

Efficacy Summary 56
6.1 Indication 57
6.1.1 Methods 57
6.1.2 Demographics 58
6.1.3 Subject Disposition 61
6.1.4 Analysis of Primary Endpoint(s) 67
6.1.5 Analysis of Secondary Endpoints(s) 68

6.1.7 Subgroup Analyses 75
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 83
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 84
6.1.10 Additional Efficacy Issues/Analyses 86

7 REVIEW OF SAFETY 88

Safety Summary 88
7.1 Methods 89
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 90
7.1.2 Categorization of Adverse Events 92
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 94
7.2 Adequacy of Safety Assessments 95
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 95
7.2.2 Explorations for Dose Response 98
7.2.3 Special Animal and/or In Vitro Testing 102
7.2.4 Routine Clinical Testing 102
7.2.5 Metabolic, Clearance, and Interaction Workup 102
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 103
7.3 Major Safety Results 105
7.3.1 Deaths 105
7.3.2 Nonfatal Serious Adverse Events 105
7.3.3 Dropouts and/or Discontinuations 109
7.3.4 Significant Adverse Events 114
7.3.5 Submission Specific Primary Safety Concerns 115
7.4 Supportive Safety Results 119
7.4.2 Laboratory Findings 122
7.4.3 Vital Signs 123
7.4.4 Electrocardiograms (ECGs) 124
7.4.5 Special Safety Studies/Clinical Trials 124
7.4.6 Immunogenicity 124
7.5 Other Safety Explorations 125
7.5.1 Dose Dependency for Adverse Events 125
7.5.2 Time Dependency for Adverse Events 128
7.5.3 Drug-Demographic Interactions 130
7.5.4 Drug-Disease Interactions 133
7.5.5 Drug-Drug Interactions 134
7.6 Additional Safety Evaluations 135
7.6.1 Human Carcinogenicity 135
7.6.2 Human Reproduction and Pregnancy Data 136
7.6.3 Pediatrics and Assessment of Effects on Growth 136
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 137
7.7 Additional Submissions / Safety Issues 137

8 POSTMARKET EXPERIENCE 137

9 APPENDICES 142

Source: Modified from Section 1.16.1 Module 1 Administrative Information NDA 208271 146

4 NOVEMBER 2014 MEETING CLINICAL COMMENTS: 147

9.1 Literature Review/References 155
9.2 Labeling Recommendations 155
9.3 Advisory Committee Meeting 155

Table of Tables

Table 1: FDA Approved Prescription Drugs for use in Chronic OIC 18
Table 2: Summary of Meeting Requests for IND 067452 22
Table 3: Clinical Site Inspections 25
Table 4: Components and Composition of Methylnaltrexone Bromide Tablets, 150 mg 28
Table 5: Components and Composition of Methylnaltrexone Bromide: Tablets 150 mg – (b) (4) and (b) (4) Formulations 29
Table 6: Additional Pre-clinical Studies Completed to support NDA 208271 30
Table 7: Summary of Clinical Trials Included in PK/PD, Bioavailability (BA) and Bioequivalence (BE) Analyses 32
Table 8: Single-Dose Pharmacokinetic Parameters for Oral Methylnaltrexone Bromide and Subcutaneous Methylnaltrexone Bromide 33
Table 9: MNOC1111 comparison of Cmax and AUC in Phase 3 and TBM formulations of Oral Methylnaltrexone Bromide 34
Table 10: Overview of Clinical Development Program Supporting Efficacy of MNTX Tablets for Chronic OIC 36
Table 11: MNTX3201 Schedule of Assessments and Procedures 45
Table 12: MNTX3201 Schedule of Assessments and Procedures - continued 46
Table 13: Definition of Analysis Sets for MNTX3201 58
Table 14: Demographic Characteristics (ITT) for Study MNTX3201 59
Table 15: Baseline Disease Characteristics (ITT Population) 60
Table 16: Analysis Populations by Treatment Groups Study MNTX3201 61
Table 17: Subject Disposition by Dosing Period (All subjects and PRN Subjects) 62
Table 18: Study MNTX3201 Summary of the Incidence of Major Protocol Deviations by Category (Deviations Reported During the QD/PRN Phases) in Randomized Subjects 64
Table 19: Statistical Concerns with Analysis of Study MNTX3201 65
Table 20: Percentage of Subjects using Laxatives during Study MNTX3201 (total subjects and %) 65
Table 21: Episodes of Reported Laxative use by Concomitant Medication Dataset Variables 66
Table 22: Percentage of Dosing Days that Resulted in RFBMs within 4 hours of Dosing during Weeks 1-4 68
Table 23: First Key Secondary Endpoint (Responder Endpoint) - Defined as ≥ 3 RFBM/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 out of the first 4 weeks of the treatment period. (ITT Population) 69
Table 24: Second Key Secondary Efficacy Endpoint: Change in Weekly Number of RFBMs from Baseline over the First 4 Weeks of Dosing in Study 3201 (ITT Population) 70
Table 25: Proportion (%) of Subjects Achieving at Least 3 RFBMs per Week (LOCF) during Weeks 1-4 of Study MNTX3201 (Exploratory Endpoint) 72

Table 26: Overall Responders with Durability for the Last Month – Proportion (%) of Subjects Responding to Study Drug for ≥9 of 12 Weeks Including ≥ 3 of the Final 4 Weeks of Treatment (ITT Population) 74
Table 27: Overall Responders-Proportion (%) of Subjects Responding to Study Drug for ≥9 of 12 Weeks of the treatment Period (ITT Population)....75
Table 28: Key Secondary Efficacy Endpoint 1 (Responder Endpoint): Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Gender Population: ITT 79
Table 29: Key Secondary Efficacy Endpoint 1 (Responder Endpoint) : Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Age Group Population: ITT 80
Table 30: Key Secondary Efficacy Endpoint 1 (Responder Endpoint) : Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Race: ITT....81
Table 31: Key Secondary Efficacy Endpoint 1 (Responder Endpoint): Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Baseline Opioid morphine equivalent dose groups: 82
Table 32: Key Secondary Efficacy Endpoint 1 (Responder Endpoint) Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Baseline primary pain condition using the Responder Endpoint....83
Table 33: Overall Responders with Durability for the Last Month- Proportion (%) of Subjects Responding to Study Drug for ≥9 of 12 weeks Inclusive of ≥3 of the Final 4 Weeks of Treatment (ITT Population) 85
Table 34: Analysis of Coprimary Endpoints (ITT Population) 86
Table 35: Safety Populations and Definitions 90
Table 36: Description of the Phase 3 Study Primarily Reviewed in Safety Review....90
Table 37: Additional Studies used in Analysis for the Integrated Summary of Safety ...91
Table 38: Summary of Adverse Event Variables 93
Table 39: AEDECOD Terms Re-assigned by Medical Officer....94
Table 40: Treatment Groups from Oral Methylnaltrexone bromide-only OIC pool 95
Table 41: Extent of Exposure: Oral Placebo-Controlled OIC Pool 96
Table 42: Extent of Exposure: Oral MNTX-only OIC Pool 97
Table 43: Study Drug Exposure MNTX3201 97
Table 44: Overview of Adverse Events: Oral Placebo-Controlled OIC Pool 99
Table 45: Adverse reactions that occurred in ≥2% of subjects and more frequently in the MNTX Treatment Group Than the Placebo Group in SC MNTX 3356 and in Oral MNTX Study 3201 100
Table 46: Comparison of the Applicant's Recoded AEs (Study MNTX3356) and Medical Officer's Recoded (b) (4) in 4 Week Double-Blind Portions of Studies MNTX and MNTX3201....101
Table 47: Serious Adverse Event Criteria 106
Table 48: Summary of SAEs for Study MNTX3201 for full 12 week duration 107
Table 49: Disposition of Subjects: Oral Placebo-controlled OIC Pool 110
Table 50: Study MNTX3201 Subject Disposition by Dosing Period (All Subjects and PRN Subjects)....111

Table 51: Treatment-Emergent Adverse Events Leading to Study Discontinuation During 12 weeks of study (Randomized Subjects Population) 112
Table 52: Medical Officer Review of the Most Commonly Reported AEs in Study MNOC1111 114
Table 53: Cardiovascular Disorder AEs reported in the Oral Placebo-controlled OIC Pool (Recoded by Medical Officer) 115
Table 54: Summary of Adverse Events (Safety Population) of Study MNTX3201 120
Table 55: Treatment-Emergent Adverse Events in Subjects Treated with MNTX or Placebo (Safety Population) in Study MNTX3201 over 4 weeks 121
Table 56: Clinical Chemistry Parameters: Clinically Relevant Shifts from Baseline To the End of Treatment in ≥5% of Subjects in MNTX3201 Study Patients 122
Table 57: TEAEs Associated with Abnormal Laboratory Results in 1% of MNTX3201 Study Patients 123
Table 58: Dose Dependency for Adverse Events in Oral Placebo-Controlled OIC pool 126
Table 59: Summary of Adverse Events – Study MNTX3201 127
Table 60: Related Treatment-Emergent Adverse Events by system Organ Class and Preferred Term: Oral Placebo-Controlled OIC Pool (3200A3-200-WW, 3200A3-2201-US, 3200A3-2202-WW, MNTX3201, MNOC1111) 128
Table 61: TEAEs with Incidence ≥5% by Age: Oral Placebo-Controlled OIC Pool 131
Table 62: TEAEs with Incidence ≥5% by Gender: Oral Placebo-Controlled OIC Pool 132
Table 63: Concomitant Medications Taken by ≥15% of Subjects in any Treatment Group (Safety Population) for Study MNTX3201 135
Table 64: Labeling Revisions for Relistor® SC 138
Table 65: Overview of Relistor® SC Postmarketing Adverse Events (28 March 2008 through 27 March 2015) 139
Table 66: SAEs During Post-marketing use of Relistor 140

Table of Figures

Figure 1: Structural formula: 17
Figure 2: MNTX3201 Study Design 39
Figure 3: Proportion of subjects responding (responder/nonresponder) to study drug over the entire 12-week treatment period 73
Figure 4: Subgroup Analysis of Key Secondary Efficacy Endpoint #1: Proportion of Drug Responders (ITT Population) MNTX 3201 77
Figure 5: (continued): Subgroup Analysis of Key Secondary Efficacy Endpoint #1: Proportion of Drug Responders (ITT Population) MNTX 3201 78
Figure 6: Proportion of Subjects with ≥ 3 Rescue-Free Bowel Movements per Week and an Increase of ≥1 Rescue-Free Bowel Movement from Baseline (ITT Population, LOCF Analysis) 85
Figure 7: Pairwise Correlations Among the Primary and Key Secondary Efficacy Endpoints During the QD and PRN Treatment Periods (ITT Population) 87
Figure 8: Categorical Changes in Hemodynamic Parameters at 1 Hour following the First Dose of Study Drug by Treatment Group (Safety Population) 124
Figure 9: Time Dependency of Reported AEs in the Oral Placebo Controlled OIC Pooled Data 129
Figure 10: Time Dependency of Reported AEs in Study MNTX 3201. 130

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the opinion of this reviewer that methylnaltrexone bromide tablets 450 mg may be approved for marketing in the United States for the treatment of opioid-induced constipation (OIC) in adult patients with chronic, non-cancer pain. It is also the opinion of this reviewer that methylnaltrexone bromide 150 mg once daily may also be approved for patients with hepatic impairment (See Pharmacology Review) for the same indication. These recommendations are based on the Applicant's demonstration of efficacy for their pre-specified primary endpoint at the proposed dose for marketing and the demonstration of statistical significance over placebo with the Applicant's key secondary endpoint. While there were limitations to the data provided, the oral formulation of methylnaltrexone bromide may have slightly better tolerability, and there are benefits to the availability of an oral formulation for patients who may not be able to use the subcutaneous formulation.

Because the duration of the double blind treatment phase in the pivotal phase 3 trial submitted for NDA 208271 was 4 weeks and the efficacy was not as robust as that demonstrated with subcutaneous methylnaltrexone bromide (Relistor® SC; NDA 021964), this reviewer recommends the label should state that the durability of effect of Relistor® tablets has been established for 3 of 4 weeks.

1.2 Risk Benefit Assessment

Worldwide, opioid induced constipation is the most common adverse reaction associated with the use of opioids. A recent study estimated that 47% of patients with chronic opioid use reported associated constipation.[1] As compared with other adverse reactions associated with opioid use, the associated constipation does not improve with time.[2,3] Overall, OIC significantly affects patients' quality of life, for example, by increasing the number of visits to health care providers and decreasing a patients' ability to work and performance at work.[4]

---

[1] Tujeta AK, Biskupiak J, Stoddard GJ et al. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil* 2010;22:424-420

[2] Manchikanti L Helm S, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV, Opioid epidemic in the United
States. Pain Physician. 2012 Jul;15(3 Suppl):ES9-38.

[3] Warner EA. Opioids for the Treatment of Chronic Noncancer Pain, *Am J of Med* 2012;125:1155-1161.

[4] Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *J Opioid Manag* 2009;5:137-44.

Management of chronic OIC includes use of dietary fiber, increased fluid intake and physical activity. When these measures do not help, usually pharmacologic means are added including laxatives, stool softeners, and use of enemas. Opioid antagonists have been used for the treatment of OIC[5] and currently there are three approved medications specifically indicated for the treatment of adults with OIC due to chronic, non-cancer pain: subcutaneous (SC) methylnaltrexone bromide (subsequently referred to as Relistor® SC) injection, naloxegol (Movantik®) oral tablets and lubiprostone (Amitiza®) oral tablets. As Relistor® SC is currently only approved as a subcutaneous (SC) injection, approval of methylnaltrexone bromide tablets would provide an alternative route of administration for patients currently receiving the SC injection, as well as an alternative to the currently approved oral products indicated for the treatment of OIC in adults with chronic non-cancer pain.

Efficacy: A single Phase 3 clinical trial (MNTX3201) was conducted to evaluate the efficacy of oral methylnaltrexone bromide at 450 mg once daily for the treatment of OIC in adults. Data from this study, in conjunction with the methylnaltrexone SC clinical data and the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of SC, intravenous and oral dosage forms of methylnaltrexone combined to support the efficacy of the oral methylnaltrexone bromide for the proposed indication.

As noted in pre-NDA meetings (07March2012 and 04November2014), support for the approval of oral methylnaltrexone bromide would require the results of the pre-specified analyses supporting the proposed dose to first be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product. In addition, the results of these key analyses of clinical endpoints considered suitable for purposes of labeling would need to be robust (e.g., analyses comparable to the analyses presented in subcutaneous methylnaltrexone product labeling for the indication of OIC in chronic pain.)

The Phase 3 oral methylnaltrexone bromide clinical trial is the primary subject of the current review. Study MNTX3201 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of oral methylnaltrexone for the treatment of OIC in 803 subjects with chronic, non-malignant pain. The pre-specified primary endpoint in this study was the percentage of dosing days that resulted in rescue free bowel movements (RFBMs) within 4 hours of dosing during weeks 1-4. This endpoint was not acceptable to the Division; however, the applicant proposed that approval be based on results of the first key secondary endpoint, also known as the responder endpoint. The responder endpoint was pre-specified as the proportion of subjects who responded to study drug during weeks 1-4, where a responder is defined as ≥3 RFBM/week, with an increase of ≥1 RFBM/week over baseline, for ≥3 out of the first 4 weeks of the treatment period.

[5] Nelson AD and Camilleri M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. *Therap Adv Gastroenterol* 2015;8:206-220

The current standard for approvability for drugs intended to be used chronically in the management of OIC in adults with chronic, non-cancer pain (CNCP) includes two Phase 3 studies of at least 12 weeks in duration. The recommended primary endpoint for such studies is the proportion of subjects who are weekly responders for at least 9 of the 12 weeks, including 3 of the last 4 weeks of the 12-week study period, where a weekly responder is defined as ≥ 3 RFBMs/week for each week of the study, with an increase of ≥ 1 RFBM/week over baseline

However, Relistor® SC was previously approved based on a Phase 3 study of only 4 weeks in duration. For approval of oral methylnaltrexone bromide, NDA 208271 is relying on the comparability of the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of subcutaneous (SC), intravenous (IV) and the oral dosage form and the clinical data from the Relistor® SC development program (NDA 021964), in addition to the oral clinical data from the Phase 3 MNTX3201 study. As such, the Division determined that the applicant's 4 week primary analysis period was sufficient

The development programs for Relistor® SC and methylnaltrexone bromide tablets were initiated and completed prior to the current standards for approvability for drugs intended to be used chronically in the management of OIC in adults with CNCP. These programs were short in duration, 4 weeks, for the double blind, placebo controlled portion of each study. The key responder endpoints for the Relistor® SC OIC Phase 3 study and the oral methylnaltrexone bromide Study MNTX3201 were:

- **Relistor® SC:** Proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as ≥ 3 RFBMs/week for each week of the 4 week study,
- **Oral Tablets:** proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as ≥ 3 RFBMs/week for 3 of the 4 weeks of the study with an increase of ≥ 1 RFBM/week over baseline.

While these responder endpoints are slightly different, the Applicant did find substantial statistical significance at 450 mg for both the primary and Responder endpoints so that the totality of evidence does support that methylnaltrexone bromide tablets (450 mg) is effective in the treatment of OIC in adults with chronic, non-cancer pain.

Safety: In the clinical development program, 1057 subjects with OIC and chronic, non-cancer pain were enrolled in a placebo-controlled clinical trial and received at least 1 dose of methylnaltrexone bromide tablets. The most commonly reported AEs were complaints of abdominal pain, nausea and diarrhea.

In the methylnaltrexone tablet development program one death of a patient receiving 450 mg occurred and was interpreted as related to atherosclerotic disease and not study drug (Refer to section 7.3.1). The largest percentage of Serious Adverse Events

(SAEs) was noted at >450 mg (7.7%) which was studied in phase 2 studies, in comparison to ≤150 mg (1.8%), 300 mg (2.1%), 450 mg (2.1%) and placebo (2.3%).

Overall, the incidence rates for adverse events (AEs) with 450 mg methylnaltrexone bromide tablets were similar to the labeled adverse events reported for Relistor® SC 12 mg, with the exception of GI adverse events of abdominal pain, nausea, and diarrhea. The most commonly reported AEs for both oral and subcutaneous methylnaltrexone bromide were abdominal pain, nausea and diarrhea, which occurred more frequently in the SC methylnaltrexone formulation in comparison to oral tablets (21.3% vs.13.5%). The rates of these AEs in the placebo arms were similar at 6.2% (SC) and 6.0% (tablet) over a 4 week period. Adverse events of vomiting and abdominal distension occurred more frequently with oral methylnaltrexone bromide. In review of TEAEs from the double blind period of sNDA 21-964[6] there was one report of vomiting (0.6%) and one report of abdominal distention (0.7%) at the approved dosage in comparison to placebo (4.9% and 1%, respectively). In Study MNTX3201, 3% of subjects who received methylnaltrexone bromide tablets at 450 mg complained of vomiting and 3.5 % noted abdominal in comparison to placebo (1.5% and 2.0% respectively).

The oral Phase 3 Study MNTX3201 was conducted with a different formulation than is to-be-marketed ((b) (4) vs. (b) (4) tablets). The to-be-marketed formulation was evaluated only in Study MNOC1111, a single dose, double blind, placebo controlled study. In this study, there were more GI complaints reported in patients receiving the to-be-marketed formulation ((b) (4) compared with the phase 3 study formulation ((b) (4) These increased GI complaints included 7 ((b) (4) vs. 2 ((b) (4) complaints of abdominal pain.

There were no deaths reported during the Phase 3 study MNTX3201. One death was reported in the methylnaltrexone bromide tablet clinical development program, but was not attributed to the study drug but rather to underlying atherosclerotic cardiovascular disease (Refer to section 7.3.1). Overall the rates of serious AEs were similar between oral methylnaltrexone bromide 450 mg (2.1%) and placebo (2.3%) and were comparable to rates noted in the SC methylnaltrexone clinical development program.

Methylnaltrexone is a peripherally acting mu-opioid receptor antagonist (PAMORA). Risk for major adverse cardiac events (MACE), bowel perforation, and opioid withdrawal have been identified as potential risks with this class of agents. No signal for increased risk of MACE was identified during the oral methylnaltrexone bromide clinical development program, and no bowel perforations were reported. However, the short duration of the Phase 3 trial and relatively small sample size limits the ability to draw any conclusion about the risk for MACE in the oral clinical development program. There were cases consistent with opioid withdrawal reported. See Section 7.3.5 for additional details.

[6] sNDA 21,964 Medical Officer Review (Helen Sile, M.D., 16 March 2012) Table 73, page 101

Summary: Overall, it is the assessment of this reviewer that the benefits of methylnaltrexone bromide tablets 450mg outweigh the risks in the treatment of adult patients with OIC due to chronic, non-cancer pain, when used as labeled. The safety profile of oral methylnaltrexone bromide was comparable to that of the approved formulation of Relistor® SC. The oral formulation used during the phase 3 study appeared to have less associated reports of GI related adverse events in comparison to Relistor® SC. , While the formulation used in the Phase 3 Study MNTX3201 is not the to-be-marketed (TBM) formulation, based upon PK/PD comparability of the two oral formulations should be comparable and demonstrate improvedtolerability of the oral tablets compared with Relistor® SC. No signal for MACE was identified during this clinical development program; however, a post-marketing requirement for an observational study to evaluate for MACE, similar to that of the approved formulation Relistor® SC, is needed to determine if there is an increased risk for cardiovascular events in patients receiving PAMORAs for chronic, non-cancer pain.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

After a complete safety review and analysis, this clinical reviewer does not believe a formal post-marketing Risk Evaluation and Mitigation Strategy (REMS) is required for oral methylnaltrexone bromide. The Applicant provided a non-REMS Risk Management Plan which included the following goals:

- Identify potential safety issues in a prompt and proactive manner in order to protect patients and appropriately inform prescribers and regulatory authorities.
- Identify changes in the adverse reaction profile as more patients are exposed to Relistor. This profile will be characterized by the class of drugs to which Relistor belongs, specific characteristics of the molecule, and the target treatment population, inclusive of patients with comorbidities and concomitant medicinal treatment not represented in premarketing clinical trials.
- Prospectively assess data from clinical trials and safety surveillance and identify appropriate risk minimization interventions as needed.
- Implement specific post-marketing risk minimization interventions, if needed.
- Monitor safety issues continuously and implement appropriate risk minimization to maximize benefit for patients.
- Assess risk minimization activities and update the RMP as needed.

The Applicant's risk minimization strategy to inform patients and educate prescribers includes the Full Prescribing Information, routine pharmacovigilance and planned surveillance for opioid withdrawal and cardiovascular events. A full description of the risk minimization strategy offered by the Applicant is outlined in Appendix A:

Full Prescribing Information: The full Prescribing Information contains information about the risk messages related to gastrointestinal perforation in the Contraindications (methylnaltrexone bromide is contraindicated in patients with known or suspected mechanical or gastrointestinal obstruction and at increased risk for recurrent obstruction). The Warnings and Precaution further instructs prescribers on the risk of gastrointestinal effects (severe or persistent diarrhea), gastrointestinal perforation (instructs prescribers to consider the overall risk benefit in patients with known or suspected lesions as well as the signs or symptoms consistent with diagnosis) and Opioid Withdrawal Symptoms (instructs the prescriber that symptoms, such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety and yawning have been seen in treated patients).

Post-marketing Monitoring: Routine monitoring for adverse events to include gastrointestinal effects, gastrointestinal perforation, opioid withdrawal symptoms, off label usage, lactation and pregnancy will be conducted and reported in periodic reports. In addition, the Applicant commits to evaluate adverse events of special interest on an ongoing basis. This will focus on the known risks of gastrointestinal perforation, opioid withdrawal syndrome (OWS) and the potential risks of misuse, off-label usage and major adverse cardiovascular events (MACE). Any new safety information concerning risks identified via routine pharmacovigilance and analysis of reported adverse events will be communicated through updates to the product label.

Reviewer comments: This reviewer does not believe a formal post-marketing Risk Evaluation and Mitigation Strategy (REMS) is required for oral methylnaltrexone bromide and agrees that the full Prescribing Information sufficiently addresses the risk of MACE as related to the PAMORA drug class. The routine post-marketing monitoring proposed is acceptable.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review, the following Postmarket Requirement is recommended for methylnaltrexone bromide tablets due to a potential risk of major adverse cardiovascular events (MACE) in patients receiving PAMORAs.

A post-marketing, observational epidemiologic study comparing oral Relistor (methylnaltrexone bromide) to other treatments of opioid induced constipation in patients with chronic non-cancer pain is recommended. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Relistor (methylnaltrexone bromide)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among oral Relistor (methylnaltrexone bromide) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the Relistor (methylnaltrexone bromide)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of oral Relistor (methylnaltrexone bromide) exposure at the end of the study.

Reviewer Comments: The same postmarketing requirement (Study 2787-1) was issued for Relistor® SQ in its approval letter 29September2014, (b) (4) *As this serious risk has not yet been fully assessed for PAMORAs, this reviewer concurs that a PMR for a postmarketing observational study with oral methylnaltrexone bromide is needed in order to assess for the risk of MACE in patients receiving chronic methylnaltrexone bromide for the treatment of OIC in chronic, non-cancer pain.*

2 Introduction and Regulatory Background

Opioid induced bowel dysfunction describes a constellation of adverse effects on the gastrointestinal (GI) system associated with chronic opioid therapy. Opioid induced constipation (OIC) is one of the most common and symptomatic complaints of patients on chronic opioids. The prevalence of OIC can vary from 15% to as high as 90% of all patients and, in general, the constipation associated with opioid use does not improve over time. Symptoms can be severe and result in discontinuation or moderation of

therapy. The National Health and Wellness Survey (Patient Reports of Opioid-related Bothersome Effects [PROBE 1 Survey], reported that constipation was the leading adverse side effect reported by opioid users (81%).[7]

Opioids mediate their effects via binding to opioid receptors (mu, delta, and kappa), but are primarily active at mu-receptors. Mu-opioid receptors are located in both the central and peripheral nervous system. In the GI tract mu-opioid receptors are localized to the mesenteric and submucosal plexus. Activation via exogenous opioids provides analgesia, but may also result in significant adverse effects, including sedation, bowel dysfunction, respiratory depression and dependence.

Opioid therapy tends to inhibit gastric motility and emptying, increases absorption and decreases fluid secretion in both the large and small intestine. Opioids also cause delay in transit from both the small intestinal and colon and increases in internal anal sphincter tone. The compounding secondary effects of exogenous opioids on the GI tract is a generalized sequence of dysfunctional transit, which results in increased gastroesophageal reflux, hard dry stools, incomplete evacuation, straining, and abdominal distension.

Standard treatments for OIC include non-pharmacologic therapies such as dietary modification with increased fluid and fiber intake, over the counter laxatives and stool softeners. Opioid dose reduction is another strategy to treat OIC, but may result in suboptimal pain control. Opioid rotation, or the use of an alternative opioid has also been considered for OIC treatment, however, there is insufficient evidence on the effectiveness or safety of opioid rotation in patients with chronic, non-cancer pain.[8,9]

Currently, the FDA has approved three therapies for the indication of OIC treatment in adult patients with chronic, non-cancer pain (CNCP). They include lubiprostone (Amitiza®), subcutaneous methylnaltrexone bromide (Relistor® SQ) and naloxegeol (Movantik®). Two, (Relistor® and Movantik®), are peripherally acting mu-opioid receptor antagonists, also referred to as PAMORA, and Amitiza® is a locally acting chloride channel activator (Table 1).

Relistor® SC was initially approved on 24 April 2008 for use in OIC for adult patients with advanced illness and receiving palliative care, when response to laxative therapy has not been sufficient under NDA 21,964. Supplemental approval for adult patients with OIC due to chronic non-cancer pain (CNCP) was given on 29 September 2014. Clinical development for the oral methylnaltrexone bromide tablets began on 28 May

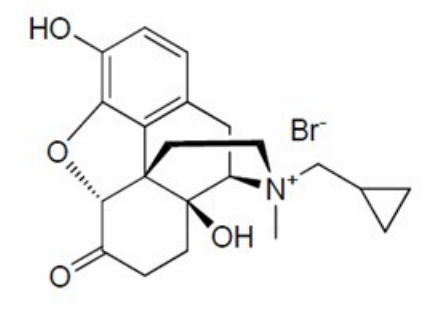
[7] Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The Prevalence, severity and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1), *Pain Med* 2009 19:35-42
[8] Smith HS and Peppin JF. Toward a systematic approach to opioid rotation. Journal of Pain Research 2014:7;589-608
[7] Nalamachu SR. Opioid rotation in clinical practice. 2012:29(10)849-863.

2003 under IND 067452. This NDA submission includes a single Phase 3 multicenter, double-blind, placebo controlled study to support the approval of methylnaltrexone bromide tablets in adult patients with OIC due to CNCP. In this NDA, the Applicant relies on data from the Relistor® SC studies and the comparability of the PK/PD relationship of the subcutaneous (SC) and oral dosage forms.

2.1 Product Information

Trade Name:	Relistor®
Generic Name:	methylnaltrexone bromide (MNTX)
Chemical Name:	17-Cyclopropylmethyl-4,5-α-exposy-3,14-dihydroxy-17-methyl-6-oxomorphinan-17-ium bromide

Figure 1: Structural formula:



Molecular Formula:	$C_{21}H_{26}NO_4Br$
Molecular Weight:	436.34
Therapeutic Class:	Mu-opioid receptor antagonist
Formulation:	Film coated oral tablet containing 150 mg methylnaltrexone bromide. Inactive ingredients are silicified microcrystalline cellulose, microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, crospovidone, poloxamer 407, stearic acid (vegetable source), colloidal silicon dioxide, edetate calcium disodium, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

Proposed indication: Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Proposed dosing regimen: 3 tablets (150 mg) once daily on an empty stomach

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: FDA Approved Prescription Drugs for use in Chronic OIC

Name of Drug/ (Sponsor)	Drug Class	Approval Date	Indication
Relistor® (methylnaltrexone bromide) subcutaneous (SC) injection Progenics Pharmaceuticals, Inc and Salix Pharmaceuticals	Peripherally acting μ-opioid receptor antagonist (PAMORA)	**4/24/08** **9/29/14**	- Original FDA approval (NDA 021964) for treatment of OIC in adults with advanced illness and receiving palliative care who are unresponsive to laxative therapy - FDA approval in 2014 (sNDA 021964) for treatment of chronic OIC in adults with non-cancer pain
Movantik® (naloxegol) oral tablet AstraZeneca Pharmaceuticals	Peripherally acting μ-opioid receptor antagonist (PAMORA)	**9/6/14**	- FDA approval in 2014 (NDA 204760) for treatment of chronic OIC in adults with non-cancer pain
Amitiza® (lubiprostone) oral tablets Sucampo Pharma Americas, LLC	Locally acting CIC-2 chloride channel activator which promotes fluid secretion into intestinal lumen.	**1/31/06** **4/19/13**	- Original FDA approval (NDA 021908) for treatment of adults with chronic idiopathic constipation. - FDA approval in 2013 (sNDA 021908) for treatment of adults with OIC and non-cancer pain

Source: Reviewer's table from info derived from Drugs@FDA.com

2.3 Availability of Proposed Active Ingredient in the United States

Methylnaltrexone bromide tablets are not currently approved or marketed in the US. However, Relistor® SC was originally approved in 2008 for patients with OIC who had advanced illness and in palliative care and were unresponsive to available therapy (Table 1). In 2014, Relistor® SC injection received an indication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Relistor® SC injection is currently marketed in 29 countries, including the United States, and the Applicant states that it has been prescribed to over (b) (4) patients worldwide, representing over 25,000 patient-years of exposure.

2.4 Important Safety Issues with Consideration to Related Drugs

Peripherally acting mu-opioid receptor antagonists (PAMORA) are have been indicated for the treatment of OIC in adults with OIC who have advanced illness and are in palliative care, unresponsive to available therapy, OIC in chronic non-cancer pain and indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis.. The most common adverse effects reported for PAMORA include GI related disturbances such as abdominal pain, flatulence, diarrhea and nausea. In addition, cases of gastrointestinal perforation have been reported with PAMORAs, as well as symptoms consistent with opioid withdrawal. Symptoms of opioid withdrawal include hyperhidrosis, chills, anxiety, yawning along with dizziness, abdominal cramping prior to bowel movements, muscle spasm and an increase in body temperature.

The major safety concern associated with PAMORA is a potential risk for increased cardiovascular adverse events, initially identified during a 12 month controlled trial of Entereg® (alvimopan) (b) (4) A numerical imbalance in myocardial infarctions (7 alvimopan vs. 0 placebo, in the context of a 2:1 randomization) was observed during the 12 month trial, and the majority of cardiac adverse events occurred during months 1 – 4 of exposure. Although this finding may have represented a chance occurrence, the serious nature of the risk prompted the Gastrointestinal Drugs Advisory Committee in January 2008 to recommend that Entereg® be approved for the indication sought (postoperative ileus) only if measures were implemented to restrict its use to short-term in-hospital administration. Consequently, Entereg® was approved with a Risk Evaluation and Mitigation Strategy (REMS) that limits its use to in-hospital postoperative administration for no more than seven days.

The cardiovascular safety concerns with PAMORA led to the convening of an FDA Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) on 11 June 2014 (Section 9.3). At that time, the Advisory Committee recommended that premarket cardiovascular outcomes trials (CVOT) not be required. The committee recommended a 52 week premarket placebo controlled general safety study to support new PAMORA for this chronic indication as well as one or more post-marketing observational studies to further characterize the risk of MACE in users of this class of drugs. The oral methylnaltrexone bromide clinical development program did not include a 52 week placebo controlled, general safety study; however, this was determined to be acceptable, as the applicant is relying, in part, on the safety of the approved subcutaneous formulation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relistor® SC injection was developed under IND 064583 and initially approved on 24April2008 under NDA 021964 for the treatment of OIC in patients with advanced illness receiving palliative care and inadequate response to laxatives. A supplemental NDA was submitted on 27June2011 for the indication of treatment of OIC in adults with chronic non-cancer pain. This submission received a Complete Response (CR) on 27July 2012 due to lack of sufficient safety data to assess the potential for cardiovascular risks (Appendix B). Given previous concern for MACE in other PAMORA and the inability to assess risk for Relistor® SC methylnaltrexone bromide due to the brevity of the randomized, double-blind, placebo-controlled portion of study MNTX3356 (4 weeks in duration), sNDA 021964 was given a Complete Response (CR) by DGIEP on 27July2012. In the CR letter, the FDA indicated that a powered premarket cardiovascular safety trial (CVOT) to assess cardiovascular risk would be required prior to consideration for approval. This request led to a dispute resolution over the need for a premarket CVOT and a subsequent meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) on 11June 2014 to discuss how to adequately assess cardiovascular safety of the five peripherally active mu-opioid receptor antagonists that were in various stages of drug development at that time, including alvimopan and Relistor® SC injection.

The Advisory Committee members were split regarding whether a CVOT would be needed, based upon the evidence of whether the imbalance in myocardial infarctions seen with Entereg® represented a real cardiac signal. Ultimately the AC recommended that a premarket CVOT should not be required for PAMORA; however, the committee recommended that a 12 month controlled trial of modest size would be a useful addition to the safety database of new members of the class, although it was recognized that such a trail may not detect modest increases in MACE risk.

Dispute resolution for sNDA 021964 was completed on 10July2014 by Dr. Julie Beitz, Director of the Office of Drug Evaluation III, who concluded that a cardiovascular outcomes trial (CVOT) was not required at that time for the approval of Relistor® SC usage in chronic OIC; however, at least one post-marketing observational study to further characterize the risk of MACE in SC methylnaltrexone bromide injection users was required. Approval was formally granted on 29 September 2014.

The approval of Relistor® for OIC in adults with chronic, non-cancer pain included a PMR to conduct a postmarketing observational study to address concerns of a potential risk for MACE (see section 1.4). (b) (4)

IND 067452 was originally submitted by Progenics Pharmaceuticals, Inc. on 27 May 2003 for methylnaltrexone bromide oral tablets for the management of OIC. Changes in Sponsorship are summarized below:

- Changed on 8 March 2006 to Wyeth Pharmaceuticals, Inc.
- Changed on 24 November 2009 to Progenics Pharmaceuticals, Inc.
- Changed on 1 June 2011 to Salix Pharmaceuticals, Inc.

Since the initial submission, the Sponsor has had 5 communications and 2 formal meetings with the FDA summarized in Table 2 below:

Table 2: Summary of Meeting Requests for IND 067452

	Meeting Type	Meeting Purpose	Regulatory Comments
26 June 2006	Type C	To obtain guidance on proposed development plan for oral MNTX for OIC with chronic pain	- Eligibility criteria were defined as a history of constipation related to opioid usage for at least 1 month prior to screening visit. Constipation was defined as <3 spontaneous bowel movements per week on average associated with hard or lumpy stools (>25% of time); a sensation of incomplete evacuation following at least 25% of bowel movements; straining during at least 25% of bowel movements. - Endpoints were not agreed upon. (b) (4) . - The Agency felt a 4-week study was too short to receive a long-term OIC indication, did not address a range of opioid-induced GI adverse events (b) (4). The Agency recommended that to obtain an indication for OIC long term, the Sponsor was to perform and demonstrated efficacy over 12 weeks in two 12-week OIC trials. - (b) (4) - Statistical modeling was not agreed upon. - Recommendation of at least 1500 multiple-dose exposures to MNTX to be completed for evaluation of significant safety signals. - Recommendations for mandatory f/u safety visits after completion of studies to assess for AE.
17 May 2010	Type C	Request to discuss a potential degradant	- The Sponsor cancelled the meeting after receipt of the preliminary meeting comments and state that the pre-meeting correspondence addressed concerns. - **(The Sponsor inquired if a specifically identified degradation product ((b) (4) at the lower range of normal was reasonable. The agency concurred.)**
4 April 2011	Type C	Drug Product Impurity Specifications	- The Sponsor cancelled the meeting after receipt of the preliminary meeting comments and state that the pre-meeting correspondence addressed concerns. - **(The Sponsor offered that as their in silico data for the degradation product ((b) (4) was at the lower range of normal (MNT (b) (4) % or (b) (4) ng total daily intake (TDI)) and so should be reasonable. The Agency concurred and stated that based upon the expectation that the human daily dose of MNTX will not be more than 2g , however for daily doses greater than 2 g MNTX the limit of NMT should be (b) (4) %.)**
7 March 2012	Type B	Pre-NDA submission	- The Agency did not feel that the data from phase 3 study 3201, double blind efficacy study 3356 and open-label study 3358 were sufficient to allow a substantive review of the NDA. The sponsor provided additional discussion points relative to these comments, but no agreements were reached. - The Agency felt that a clinically relevant endpoint was not evaluated over an adequate treatment duration (12 weeks), relative bioavailability studies had not been completed and that bioequivalence studies had not been completed. Additionally, in vivo drug interaction potential had not been addressed. - **(The Sponsor concurred with studies for the transporter interactions)**

4 November 2014	Type B	Pre-NDA submission	- The Sponsor cancelled the meeting after receipt of the preliminary meeting comments and stated that the pre-meeting correspondence addressed their concerns. - Key concerns expressed by the Division were focused upon primary endpoints and concern for persuasive safety data that the oral formulation is better tolerated than the SC formulation. - The Agency reiterated that they did not agree with the pre-specified primary endpoint of Study 3201 (**The pre-specified primary endpoint in this study was the percentage of dosing days that resulted in rescue free bowel movements (RFBMs) within 4 hours of dosing during weeks 1-4**.) However, the Agency acknowledged that Relistor SC was approved based on a primary endpoint of the proportion of patients with ≥3 SBMs per week during the 4-week period (key secondary endpoint of Study 3201). The Agency stated that in order for Study 3201 to support the approval of an oral Relistor formulation, the results of the pre-specified analyses supporting the proposed dose would first need to be statistically valid, allowing for the evaluation of key secondary analyses of interest for the purposes of approval and labeling the product. - The Division did not agree (b) (4) - A new NDA will be required for MNTX (oral) as it is a new dosage form.

Source: Reviewer's Table summarized from FDA Meeting Minutes

2.6 Other Relevant Background Information

There is no other relevant background information, other than that discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity are acceptable. The electronic application was organized and easy to navigate. The datasets were complete and navigable.

As noted in Table 2, pre-NDA conversations with the FDA demonstrated disagreement over the following:

- Use of the primary endpoint (Section 5.3.7) as the Division did not feel that this endpoint was clinically significant, and therefore should not be considered.
- Concerns regarding the statistical analysis plan (SAP) for Study MNTX3201. Specifically, the FDA had consistently recommended against using the Hochberg gate–keeping procedure as well as the Hochberg multiplicity testing procedure, in addition to removal of the pre specified primary endpoint.

Ultimately, the Division decided to base review of NDA 208271 upon the responder endpoint (1st key secondary endpoint as noted in Section 5.3.7) to determine efficacy due as this endpoint was found to be more clinically meaningful, and a 4-week responder endpoint was found to be acceptable for approval of Relistor® SQ under NDA 021964.

Both the Adverse Events (AE) dataset and Concomitant Medication (CM) data sets were noted to have multiple typographical errors requiring recoding, and the coding of medications used for laxation was not consistent throughout the entire study period. These concerns were sufficiently addressed by the Applicant during the review period.

Reviewer Comments: In the context of the available efficacy and safety information for SC methylnaltrexone bromide for use as a context for evaluation of Study MNTX3201, the submission was of sufficient quality to review. However, if this submission had been a new molecular entity (NME) the totality of concerns regarding the use of a primary endpoint without clinical meaningfulness, the changes in SAP during the development program, the limit of duration of the placebo-controlled study phase, may have resulted in concerns for the quality of the submission for review.

3.2 Compliance with Good Clinical Practices

The Applicant responded to an information request (IR) from 10 August 2015, confirming that the Phase 3 clinical studies were performed by Salix Pharmaceuticals, Inc. with (b) (4) as the main partnering contract research organization (CRO) for the diary data, randomization and treatment dispensing. (b) (4) is now known as (b) (4).

The Applicant reports that standard operating procedures, quality control measures, and audit programs were followed to provide reassurance that the clinical studies presented in this summary were carried out in accordance with the Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonization (ICH) and the FDA.

The Office of Scientific Investigations (OSI) performed site investigations of 5 clinical sites for Study which are summarized in Table 3 below.

Table 3: Clinical Site Inspections

Principal Investigator/Location	Clinical Site Number	Number of Subjects	Site Selection Rationale	Inspection Date(s)	Final Classification
Adams, Atoya Las Vegas, NV	001	29	No inspections High # INDs	October 19-22, 2015	NAI
Mirkil, Jerome Las Vegas, NV	025	28	Complaint	October 12-19, 2015	VAI
Choi, Steve Dayton, OH	039	25	High # INDs	October 19 to 36 2015	NAI
Chiu, Echo Singla, Sonia Pasadena, CA	062	39	High enroller	November 17,18, 20, 23, 30 and December 30, 2015	NAI
Rosenberg, Robert Phoenix, AZ	143	29	High enroller	October 13-16, 2015	NAI

Source: reviewed created from OSI inspection summaries

Overview of Inspection Findings:

Clinical Site 001:
34 subjects were screened, 29 subjects were enrolled, and 23 subjects completed study MNTX3201. Source documents were reviewed for all six subjects who discounted early, protocol deviations were checked for ten subjects, adverse event listings were verified for five subjects and test article verification was conducted for four subjects. IVRS diary data at the site were compared to line listings submitted for the primary endpoints for five subjects. No discrepancies were identified and the data generated by this site was acceptable for use.

Clinical Site 025:
45 subjects were screened, 28 subjects were enrolled, and 24 subjects completed the study. IVRS diary data were reviewed for 11 subjects and compared to the line listings provided in the background material. Source records for the11 subjects who were screen failures or discontinued were also reviewed. Source records for five subjects were reviewed for adverse events, and source records for four subjects were reviewed for concomitant medications.

Form FDA 483 was issued as subject 023-030, randomized to placebo, should have been excluded due to use of laxative within the 72 hours after a bowel movement (exclusion criterion at baseline during visit #2). This was noted in the NDA as a protocol violation and the clinical investigator both acknowledged the observation and adequately responded to the inspection findings in a letter dated October 20, 2015. It was determined that the violation appeared as isolated and did not impact data integrity. The data generated by this site was acceptable for use.

Clinical Site 039:
50 subjects were screened, 25 subjects were enrolled, and 20 subjects completed the study. The records for ten enrolled subjects were reviewed and compared with data listings for primary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.

There was no evidence of under-reporting of adverse events. No violations were noted. The study appears to have been conducted adequately, and the data generated by this study appeared acceptable in support of the respective indications

Clinical Site 062:
97 subjects were screened, 39 subjects were enrolled, and 33 subjects completed the study. The records for 20 enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points provided with the assignment. The Clinical Investigator (CI) Dr. Echo Chiu was replaced by Dr. Sonia Singla on 16 January 2012. In addition, Subject 003 (randomized to MNTX 150 mg) and Subject 009 (randomized to MNTX 450 mg) both ingested rescue medication prior to study drug. The CI provided these study deviations to the Field Investigator and the Sponsor also submitted this information in the NDA. The Field Officer determined that the study appeared to have been conducted adequately, and the data generated study acceptable.

Clinical Site 143:
64 subjects were screened, a total of 29 subjects were enrolled, and 19 subjects completed the study. The records for 11 enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. The study appears to have been conducted adequately, and the data generated study acceptable.

Observations for the Clinical Investigator (CI) inspections for Sites 039 and 062 were based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

Reviewer Comments: Five clinical investigator sites were chosen and inspected for this application on the basis of high enrollment, numbers of INDs in the OSI database, and previous inspectional history. Four of the inspections have a final classification of NAI. One site received a classification of VAI, however, the violation is considered minor and does not affect data reliability. The study appears to have been conducted adequately, and the data generated by the study are acceptable in support of the respective indication.

3.3 Financial Disclosures

The applicant provided a single signed copy of FDA Form 3454 with a full list of investigator names from studies MNTX3201 and MNOC1111. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No FDA Form 3455s were provided, as no investigators reported financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Methylnaltrexone bromide tablets, 150 mg, are white, round, biconvex, film-coated tablets, debossed with "REL" on one side and plain on the other side. The drug product will be packaged in 6-, 60-, and 90-count high-density polyethylene bottles (b) (4) and each bottle will include 2 silica gel desiccants. Table 4 below provides the components and composition of methylnaltrexone bromide tablets.

Table 4: Components and Composition of Methylnaltrexone Bromide Tablets, 150 mg

Ingredient	Quality Standard	Function	Theoretical Quantity	
			mg/tablet	%w/w[a]
Methylnaltrexone bromide[b]	In house	Active	150.00	(b) (4)
Microcrystalline cellulose[c]	NF	(b) (4)	(b) (4)	
Crospovidone	USP			
Edetate calcium, disodium	USP			
Sodium lauryl sulfate	NF			
Colloidal silicon dioxide	NF			
Croscarmellose sodium	NF			
Poloxamer 407 (b) (4)	NF			
Silicified microcrystalline cellulose	NF			
Stearic acid (vegetable source)	NF			
(b) (4)				
Total Theoretical Weight			533.59	100.0

Source: Applicant Description and Composition of the Drug Product, Table 1, Section 2.3P.1
Abbreviations: DMF = drug master file, NF = National Formulary, USP = United States Pharmacopeia, w/w = weight/weight

a (b) (4)
b
c
d
e (b) (4)

The Phase 3 study MNTX3201 utilized a (b) (4) formulation of methylnaltrexone bromide tablets. In contrast, the to-be-marketed (TBM) product is a (b) (4) tablet formulation which was compared to the Phase 3 formulation in a single dose, double-blind, placebo controlled study MNOC1111. Table 5 compares the components and composition of the (b) (4) formulation used in the Phase 3 clinical trial with the (b) (4) formulation (TBM tablet). Oral methylnaltrexone bromide will be sourced from (b) (4). The drug product will be manufactured and packaged by (b) (4). Salix Pharmaceuticals, Inc., the NDA holder, will be responsible for final release of the drug product.

Table 5: Components and Composition of Methylnaltrexone Bromide: Tablets 150 mg – (b) (4) and (b) (4) Formulations

Ingredient	Function	mg/150 mg Tablets (b) (4)	mg/150 mg Tablets (b) (4)
Methylnaltrexone bromide	Active	150.00	150.00
Microcrystalline cellulose	(b) (4)		(b) (4)
Crospovidone			
Edetate calcium, disodium			
Sodium lauryl sulfate			
Poloxamer 407 (b) (4)			
(b) (4)			
Silicified microcrystalline cellulose			
Crospovidone			
(b) (4)			
Croscarmellose sodium			
Talc			
Colloidal silicone dioxide			
(b) (4)			
Stearic acid			
(b) (4)			
(b) (4)			
Total Theoretical Weight		533.59	533.59

Source: MNOC111 Clinical Study Report Table 2
a (b) (4)

Reviewer comments: Please see complete OPQ Integrated Quality Assessment review.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Complete nonclinical studies to assess the pharmacology, safety pharmacology, pharmacokinetics, metabolism and toxicology of methylnaltrexone bromide were previously submitted to support the approval of Relistor® SC (NDA 021964) for the treatment of OIC in adult patients with advanced illness, receiving palliative care, when response to laxative therapy has not been sufficient and for the treatment of OIC in adult patients with chronic non-cancer pain. For the submission of NDA 208271, the following additional nonclinical studies were completed:

Table 6: Additional Pre-clinical Studies Completed to support NDA 208271

Study	Assay	Test System	Substrate Tested	Result
Primary Pharmacodynamics				
Study MNIV0101	*In vitro* binding assay (Mu-, Kappa- and Delta-Opioid receptors	-- CHO-KI cells transfected with human mu opioid receptor. -- HEK293 cells transfected with human kappa or delta opioid receptor	Analysis of: -- MNTX -- MNTX sulfate (M2) -- Methyl-6α-naltrexol (M4) -- Methyl-6β-naltrexol (M5)	MNTX and metabolites were shown to bind the human opioid receptors according to the following rank order of potency: Mu: M4>MNTX>M5>> M2 Kappa:MNTX≈M4≈M5 >>M2 Delta: MNTX≈M4≈M5 >M2
Secondary Pharmacodynamics				
Study MNIV0102	*In vitro* platelet aggregation assay	Human platelet rich plasma	Analysis of: --MNTX --Naloxone --Naltrexone	No compounds induced platelet aggregation. At low concentrations, there was no inhibition of platelet aggregation. At 500 µM, naloxone inhibited PAF-induced platelet aggregation by 68%. MNTX and naltrexone did not inhibit platelet aggregation > 50%
Study MNIV0105	*In vitro* evaluation of effects on hERG channels	Cloned hERG channels expressed in human embryonic kidney (HEK293) cells	Analysis of: --MNTX sulfate --methyl-6α-naltrexol --methyl-6β-naltrexol,	Superfusion of the vehicle, PSS, produced no meaningful change in mean hERG- mediated potassium currents. Superfusion of the test articles, Methyl-6α-Naltrexol, Methyl-6β-Naltrexol, and MNTX Sulfate, at concentrations of 0.1, 1, 10, and 100 µM, also produced no meaningful change in mean hERG-mediated potassium currents. Consistent with prior experience, the positive control article, 0.1 µM cisapride in PSS containing 0.1% DMSO produced approximately 80% inhibition of hERG channel mediated potassium currents.

Source: Reviewer's table summarized from Pharmacology Tabulated Summary (Module 2.6.3) NDA 208271

No additional toxicology, toxicokinetic, single- or multiple-dose toxicology, genotoxity, carcinogenicity, reproductive and developmental toxicity, juvenile animal, local tolerance or other toxicity studies were completed by the Applicant in association with this NDA submission.

Reviewer comments: *There are no major safety or efficacy issues from the nonclinical review team, which recommends approval. For more information see the nonclinical review by Sushanta Chakdar Ph.D.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Methylnaltrexone bromide (MNTX) is a peripherally acting μ-opioid receptor antagonist, and a quaternary derivative of naltrexone. As a quaternary amine the ability to cross the blood brain barrier is limited. Methylnaltrexone bromide primarily functions as a selective antagonist in the gastrointestinal tract, and is used with the intention of decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

Model development for plasma PK parameters and PD endpoints were obtained from the 6 studies noted in Table 7

Table 7: Summary of Clinical Trials Included in PK/PD, Bioavailability (BA) and Bioequivalence (BE) Analyses

Study (PK/PD or BA or BE)	Route	Dose	Patient Population
3200A3-2201-US (PK/PD)	PO	Multiple dose; placebo or 150 mg, 300 mg, 450 mg, 600 mg QD (PK on Day 1)	CNCP
MNPK1117 (PK/PD)	SC and PO	Randomized crossover study to evaluate the comparative bioavailability of 150, 300, 450 mg methylnaltrexone tablets compared to 12 mg single subcutaneous doses of methylnaltrexone bromide	Healthy Subjects
MNPK1001 (PK)	PO	Randomized, open-label, multiple-cohort, single-dose, two-way crossover	Healthy Subjects
MNOC1111 (PK/PD)	SC and PO	Single dose; 12 mg SC open label followed by placebo PO or 450 mg PO (TBM formulation)	CNCP
MNFE1001 (BA and BE)	PO	Two-arm, randomized, open-label, crossover study to evaluate the pharmacokinetics of a single 450 mg oral dose of methylnaltrexone bromide tablets after a high fat meal or fasting (TBM formulation)	Healthy Subjects
MNPK1114 (BE)	PO	Single dose, randomized, crossover study to evaluate the PK of a single dose of 450 mg after high fat meal or fasting	Healthy Subjects
MNPK10004 (PK/PD)	PO	Single dose, open-label study to evaluate the PK of methylnaltrexone tablets in patients with hepatic impairment (TBM formulation)	Hepatic Impairment and Healthy Subjects

Source: Reviewer's Modification from Applicant's Tabular Listing of All Clinical Trials, NDA208271, Section 5.2 and individual study reports
TBM – to-be-marketed formulation

4.4.2 Pharmacodynamics

No significant efficacy or safety issues related to pharmacodynamics were identified.

4.4.3 Pharmacokinetics

Methylnaltrexone bromide is absorbed rapidly with a median Tmax of approximately 1.5 to 2 hours after ingestion. The bioavailability of oral methylnaltrexone bromide is lower (<5%) in comparison to the SC methylnaltrexone bromide. (b) (4) Ingestion of food decreases bioavailability, and the Applicant recommends ingestion of the oral tablets on an empty stomach.

The Applicant compared single dose systemic exposure parameters between (b) (4) tablets (used in Phase 3 Study MNTX3201) and Relistor ® SC dosing in study MNPK1117. Study MNPK1117 was a randomized, open-label, crossover study

used to compare PK/PD between the oral tablets and subcutaneous dosing in healthy adults. The C_{max} of the oral tablets was proportional to dosage, and the C_{max} of the 450 mg oral tablet was notably about four-fold lower than the C_{max} of the Relistor® SC 12 mg. The AUC of oral methylnaltrexone bromide 450mg was about 1.3x higher than that of Relistor® SC 12 mg. The C_{max} and AUC of both tablet and subcutaneous formulations were interpreted as comparable and are summarized in Table 8.

Table 8: Single-Dose Pharmacokinetic Parameters for Oral Methylnaltrexone Bromide and Subcutaneous Methylnaltrexone Bromide

	MNTX 150 mg Tablet[a] (N = 16)	**MNTX 300 mg Tablet[a] (N = 16)**	**MNTX 450 mg Tablet[a] (N = 16)**	**MNTX 12 mg SC Injection (N = 48)**
Cmax (ng/mL) Mean (standard deviation)	13.22 (15.17)	26.22 (18.40)	39.89 (32.11)	174.01 (61.42)
AUC0–∞ (ng.h/mL) Mean (standard deviation)	106.87 (64.77)	231.24 (115.98)	373.32 (207.36)	269.09 (45.14)
AUC0–t (ng.h/mL) Mean (standard deviation)	104.65 (64.66)	229.37 (116.27)	366.68 (205.71)	267.87 (44.94)
Tmax (h) Median (minimum, maximum)	2.00 (0.45, 6.00)	1.50 (0.50, 6.00)	2.00 (0.50, 6.00)	0.25 (0.25, 6.68)
CL/F (L/h) Mean (standard deviation)	1735 (683)	1565 (627)	1664 (1036)	45.7 (6.90)
t½ (h) b Mean (standard deviation)	13.95 (5.51)	14.16 (4.71)	16.57 (4.42)	9.16 (2.03)
Relative Bioavailability	3.2%	3.4%	3.7%	--

Source: Applicant's Clinical pharmacology overview Study MNPK 1117 CSR Table 1, Module 2.5 CSR
Abbreviations: AUC0–∞ = area under the plasma concentration versus time curve (AUC) from time 0 (predose) to time infinity; AUC0–t = AUC from time 0 (predose) to the last quantifiable concentration-time point; Cmax = maximum observed plasma concentration; CL/F = apparent oral clearance; MNTX = methylnaltrexone; SC = subcutaneous; Tmax = time to Cmax; t½ = terminal or disposition half-life.
Note: Mean values are arithmetic means unless otherwise specified.
a Phase 3 formulation. The phase 3 formulation includes (b) (4) and was manufactured by (b) (4) A (b) (4) l film coating was applied to the tablets in this study.
b Expressed as harmonic means and pseudo standard deviation based on jackknife variance.

The (b) (4) formulation used in the Phase 3 pivotal study for methylnaltrexone bromide tablets differs from the proposed TBM formulation. However, study MNPK 1001 established bioequivalence (BE) between the Phase 3 (b) (4) formulation and 6 different test formulations, including the to-be- marketed formulation in healthy subjects. The PK/PD of the to-be-marketed formulation was further characterized in Study MNOC1111. Study MNOC1111 compared C_{max} and AUC of only the Phase 3 ((b) (4) formulation to the to-be-marketed (TBM) (b) (4) formulation in patients with OIC and chronic, non-cancer pain, after demonstrated response to Relistor® SC. Both formulations demonstrated almost identical Cmax and similar AUC. The results are shown below in Table 9.

Table 9: MNOC1111 comparison of Cmax and AUC in Phase 3 and TBM formulations of Oral Methylnaltrexone Bromide

	Subcutaneous MNTX 12 mg (N=72	(b) (4) (TBM))MNTX 450 mg (N=37)	(b) (4) MNTX 450 mg (N=36)	(b) (4) to (b) (4) Comparison p-value
Cmax (ng/ml)	132.82 (78.996)	34.58	35.35	0.95
AUC 0-inf (ng.h/ml)		203.53	228.65	
AUC_{0-t} (ng.h/mL)	186.03 (89.596)	183.50 (97.882)	204.86 (136.109)	-
AUC_{0-4} (ng.h/mL)	187.05 (89.024)	84.95 (58.538)	89.19 (70.364)	-
$AUC_{0-\infty}$ (ng.h/mL)	NC	203.53 (104.617)	228.65 (150.498)	0.53
CL/F (L/h)	NC	3324.13 (3109.837)	2865.03 (1985.385)	-
$t_{1/2b}$ (hours)	NC	6.63 (2.352)	7.20 (2.301)	-

Source: Table 11 MNOC1111 CSR

Abbreviations: AUC0-t = area under the plasma concentration versus time curve from time 0 (predose) to the last quantifiable plasma concentration-time point; AUC0-4 = AUC from time 0 (predose) to 4 hours post-dose; AUC0-∞ = AUC from time 0 (predose) to time infinity; CL/F = apparent oral clearance; Cmax = maximum observed plasma concentration (b) (4) = (b) (4) MNTX = methylnaltrexone; NC = not calculated; SD = standard deviation; Tmax = time to Cmax; (b) (4) = (b) (4)
Note: Three subjects in the (b) (4) MNTX and 1 subject in the (b) (4) MNTX groups experienced vomiting. However, the vomiting did not affect the determination of pharmacokinetic parameters for these subjects.
a Reported as median (range).
b Expressed as harmonic mean and pseudo standard deviation based on jackknife variance.
c Cmax and AUC0-∞ were compared between oral MNTX formulations by using analysis of variance.

Study MNPK1004 evaluated the PK, T_{max}, AUC, and safety of oral methylnaltrexone bromide in patients with OIC due to CNCP in healthy adults and subjects with underlying hepatic impairment who did not have OIC. Twenty-four (24) subjects with a Child-Pugh score of A, B, or C were compared to healthy subjects. Subjects with Child-Pugh Scores B and C demonstrated C_{max} of 4.8 and 3.7 fold higher than healthy subjects. Median T_{max} was shorter in patients with liver impairment.

For additional details, please see reviews by Dr. Dilara Jappar (pharmacokinetics) and Dr. Justin Earp (phamacometrics).

Reviewer Comments: According to the clinical pharmacology reviewer, the applicant demonstrated comparability between the subcutaneous and oral formulation used in the phase 3 study. The Phase 3 and TBM formulations were subsequently demonstrated to have comparable PK in study MNOC1111. Results from study MNPK1004 demonstrated a higher Tmax for patients with hepatic impairment. Clinical pharmacology team recommend that doses for patients with moderate to severe hepatic impairment (Child-Pugh score B and C) should be decreased to 150 mg daily.

5 Sources of Clinical Data

The Applicant's submission of NDA 208271 is based upon the development program of an oral dosage form of methylnaltrexone bromide as an alternative to the subcutaneous injection which was approved by the FDA for use in OIC related to chronic non-cancer pain on 29 September 2014. The Sponsor submits that the relevant data to support this NDA submission include the following:

- Pharmacokinetic (PK) /pharmacodynamic (PD) relationship of subcutaneous, intravenous and oral dosage forms.
- Subcutaneous clinical data (NDA 021964 and associated postmarketing studies)
- Oral clinical data from phase 3 Study MTNX3201.

The results of the PK/PD studies are summarized in Section 4.4 and reviewed in detail in the clinical pharmacology reviews. The Relistor® SC clinical data supporting the approved indication were not reviewed in detail in this review. For detailed information on the efficacy of Relistor® SC, see the clinical reviews from Helen Sile, M.D. dated 10 August 2011 and 27 July 2012. The oral clinical data is further described below.

5.1 Tables of Studies/Clinical Trials

Table 10: Overview of Clinical Development Program Supporting Efficacy of MNTX Tablets for Chronic OIC

Study ID	Study Design	Study Population	Study Enrollment and Treatment Arms	Endpoints
PHASE 3				
MNTX3201 9/2010 to 11/2011	*28 day, multicenter, randomized, double blind, placebo controlled, parallel–group dose ranging, study with a 56 day open arm continuation study*	Adult patients using opioids for at least 30 days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD).	804 Total enrollment: 150 mg QD (201) 300 mg QD (201) 450 mg QD (200) Placebo (201)	**Primary**: Average percentage of dosing days that resulted in RFBMs within 4 hours of dosing during Weeks1 - 4 **Secondary:** - ≥ 3 RFBMs per week with an increase of ≥1 from baseline for ≥3 out of the first 4 weeks of the treatment period. -Bristol Stool Form Scale -Straining Scale -Abdominal pain and cramping scale -Abdominal bloating scale -Appetite assessment scale
PHASE 1				
MNOC1111 8/2014 to 6/2015	Single dose, randomized, double-blind, placebo-controlled, single-dose, parallel group study to evaluate the clinical efficacy and safety of oral methylnaltrexone tablets in subjects with chronic non-cancer pain and OIC who initially responded to single doses of subcutaneous methylnaltrexone bromide	Adult patients with chronic OIC for non-cancer pain responding to subcutaneous MNTX for at least 30 days.	*112 Total enrollment*: 450 mg QD (b) (4) tabs (37) 450 mg QD (b) (4) tabs (38) Placebo (37)	**Primary:** RFBM within 4 hours after oral dose of study drug **Secondary:** -PK -Clinical equivalence of (b) (4) to (b) (4) tablets with regard to the primary endpoint. -RFBM within 24 hours of study drug -Bristol Stool Form Scale -Straining Scale -Abdominal pain and cramping scale -Abdominal bloating scale -Appetite assessment scale
MNPK 1117 3/2012 to 4/2012	Randomized, open-label, single-dose, , crossover	Healthy subjects 18-45 years of age	*48 total enrollment*	**Primary:** To evaluate the BA and PK of 150 mg, 300 mg, 450 mg tablets with 12 mg SC MNTX
PHASE 2				
3200A3-200-WW	28 day, multicenter, randomized, double blind, placebo	Adult patients using opioids for at least 30 days with chronic	236 Total enrollment:	-Change in the number of spontaneous bowel movement (SBM) from

8/2006 to 2/2007	controlled, dose ranging, adaptive design study	non-malignant pain with opioid induced bowel dysfunction (OIBD).	10mg QD (31) 50 mg QD (36) 150 mg QD (33) 300 mg QD (45) 450 mg QD (47) Placebo (44)	baseline -Bristol Stool Form Scale (BSFS) **(Study terminated due to lack of efficacy)**
3200A3-2202-WW 1/2008 to 6/2008	28 day, multicenter, randomized, double blind, placebo controlled, parallel–group dose ranging, study	Adult patients using opioids for at least 30 days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD).	128 Total enrollment: 150 mg QD (19) 300 mg QD (20) 450 mg QD (30) 600 mg QD (30) Placebo (39)	**Primary:** Proportion of individuals demonstrating a spontaneous bowel movement (SBM) within 3 hours of dosage **Secondary:** -Bristol Stool Form Scale -Straining Scale -Abdominal pain and cramping scale -Abdominal bloating scale -Appetite assessment scale
3200A3-2201-US 12/2009 to 3/2010	28 day, multicenter, randomized, double blind, placebo controlled, dose ranging, adaptive design study	Adult patients using opioids for at least 30 days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD)	125 Total enrollment: 150 mg QD (7) 300 mg QD (14) 450 mg QD (35) 600 mg QD (35) Placebo (34)	**Primary:** Proportion of individuals demonstrating a spontaneous bowel movement (SBM) within 3 hours of dosage **Secondary:** -Bristol Stool Form Scale -Straining Scale -Abdominal pain and cramping scale -Abdominal bloating scale -Appetite assessment scale

Source: Reviewer's summary from Applicant's Summary of Clinical Efficacy, Module 2.7.3

5.2 Review Strategy

For this NDA submission Phase 3 Clinical Trial MNTX3201 was reviewed in detail. Details of the study design and conduct for MNTX3201 are contained in Section 5, and study results are discussed in Section 6 (efficacy) and 7 (safety). Phase 2 Clinical Trials 3200-A3-200-WW, 3200-A3-2201-US, and 3200-A3-2202-WW, were dose ranging studies and considered supportive towards the efficacy and safety of the 450 mg dosage. Study MNPK1117 was completed to compare the bioavailability and pharmacokinetics between Relistor® SC and (b) (4) tablets that were used in Phase 3 Study MNTX3201. Study MNOC1111 was completed in patients to compare the bioavailability and pharmacokinetics between the 450 mg oral formulation used in study MNTX3201 ((b) (4) and the to-be-marketed (TBM) formulation ((b) (4) and SC methylnaltrexone bromide, for comparability of PK, C_{max} and AUC values.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title: Study MNTX3201
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Subjects with Chronic, Non-Malignant Pain.

Study Overview:
Study MNTX3201 is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of an oral MNTX (b) (4) formulation versus placebo in the treatment of 804 adult patients with chronic nonmalignant pain who have OIC. Study MNTX3201 included a 14 day screening period and a 28 day double blind treatment period of daily dosing followed by a 56 day continuation study with as needed (PRN) dosing. This study was conducted at 156 sites in the United States. The first subject was prescreened on 01 September 2010 and the last patient completed his/her last visit on 08 November 2011.

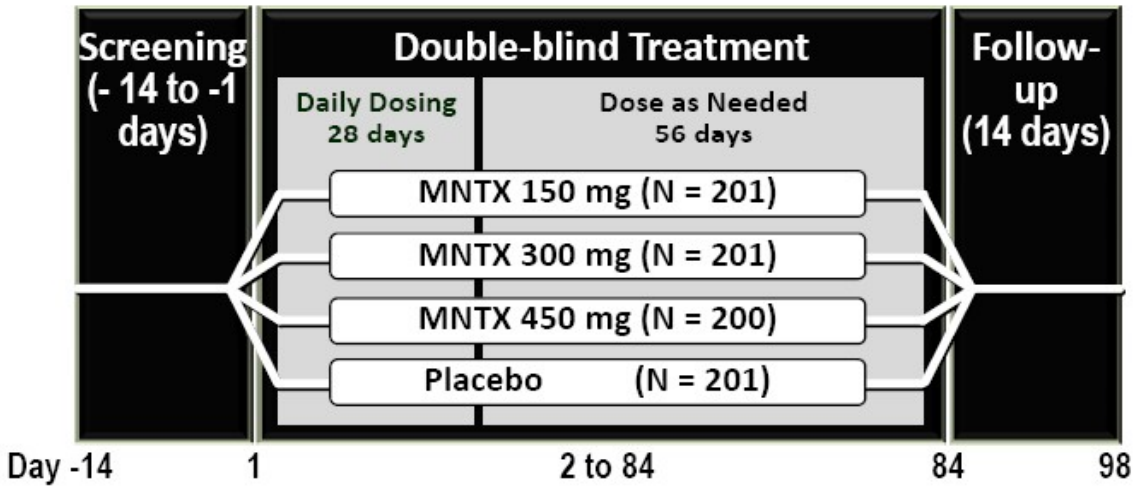
Reviewer Comments: The Division currently recommends a 12 week primary analysis period for phase 3 clinical trials in OIC. However, methylnaltrexone SQ injection was approved based on a primary analysis period 28 days in duration. As the oral formulation is relying, in part, on data from the subcutaneous drug, the length of this phase 3 study is acceptable to this reviewer.

Study Objectives:
Primary Objective:
To evaluate the safety and efficacy of oral methylnaltrexone bromide (MNTX) versus placebo in subjects with chronic nonmalignant pain who have OIC.

Secondary Objective:
To determine an oral MNTX dosing regimen in subjects with chronic non-malignant pain who have OIC.

Study Design: Eligible subjects entered a 14 day screening period (+/- 2 days) where objective evidence of constipation was assessed for enrollment. Subjects eligible for enrollment (Day 1) were randomly assigned to receive methylnaltrexone bromide tablets at 150 mg, 300 mg, or 450 mg QD (150 mg tablets) or placebo QD in a 1:1:1:1 allocation ratio. Subjects were instructed to take 3 tablets per day of oral methylnaltrexone bromide tablets, methylnaltrexone bromide tablets plus placebo, or placebo first thing in the morning on an empty stomach (prior to breakfast). Subjects took the study drug QD during the first 28 days; dosing was PRN during the remaining 56 days of the treatment period. Double blind status was maintained throughout the course of the study. (Figure 2)

Figure 2: MNTX3201 Study Design



Abbreviations: MNTX or MOA-728 = methylnaltrexone, PRN = as needed, QD = daily
Copied and electronically reproduced from Applicant's submission, Study MNTX3201 Clinical Study Report, Figure 2

5.3.2 Key Inclusion Criteria:

Screening visit:

1. Outpatient men and women who were ≥ 18 years of age and able to sign an ICF.
2. Documented history of chronic nonmalignant pain (originating from a nonmalignant source with conditions(s) underlying the chronic pain of ≥2 months' duration before the screening visit.
3. Stable medical status (e.g., general good health) for ≥ 30 days before the screening visit.
4. A calculated creatinine clearance (Cockcroft-Gault glomerular filtration rate) ≥ 30 mL/min
5. Taking oral, transdermal, intravenous, or SC opioids for chronic nonmalignant pain for ≥1 month.
6. Receiving a daily dose ≥ 50 mg of oral morphine equivalents per day for ≥ 14 days before the screening visit with no anticipated changes during the study.
7. No known history of chronic constipation prior to the initiation of opioid therapy.
8. A history of constipation due to opioid use for ≥ 30 days before the screening visit. History of constipation is defined as <3 RFBMs per week on average (over the last 4 consecutive weeks) and 1 or more of the following (based upon subject's reported history):
    a. Hard or lumpy stools
    b. Straining during bowel movements.

   c. A sensation of incomplete evacuation after bowel movements.
9. All men and women who were not surgically sterile or postmenopausal agreed and committed to the use of a medically acceptable method of birth control (e.g. Oral, implantable, or injectable contraceptives; spermicide in conjunction with a barrier such as a condom or diaphragm or intrauterine device or sexual abstinence for the duration of the study, including 30 days after the last dose of study drug.
10. Currently taking laxative therapy for ≥ 30 days and willing to discontinue all laxative therapy at the start of the screening period and use only study permitted rescue laxatives throughout the screening and double-blind treatment periods.
11. Willingness and ability to participate in all aspects of the study, including oral dosing compliance, completion of subjective evaluations, attending scheduled clinic visits, access to a telephone, and compliance with all protocol requirements as evidenced by written ICF.

Additional eligibility criteria were assessed at the Baseline visit after completion of the 13-day screening period, as follows:

1. Subjects continued to meet screening eligibility criteria.
2. Taking oral, transdermal, intravenous, or SC opioids for chronic nonmalignant pain and receiving a daily dose ≥ 50 mg of oral morphine equivalents per day during the screening period with no anticipated changes during the study.
3. Constipation due to opioid use during the screening period: Constipation is defined as <3 RFBMs per week on average (no laxative use within 24 hours prior to bowel movement) that were associated with 1 or more of the following (based upon subjects diary report):
   a. A BSS type 1 or 2 for ≥25% of the RFBMs.
   b. Straining during ≥ 25% of the RFBMs.
   c. A sensation of incomplete evaluation after ≥25% of the RFBMS
4. At least 1 bowel movement during the screening period.

5.3.3 Key Exclusion Criteria

Screening Visit:

1. Prior treatment with methylnaltrexone bromide tablets
2. Prior treatment with Relistor® SC \ within 30 days of screening
3. World Health Organization (WHO) performance status >2[10]
4. Women who were pregnant, breastfeeding, or planned to become pregnant during the study.
5. A history of mechanical bowel obstruction or mega colon

[10] Oken et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol (CCT)5:649-655, 1982

6. Fecal incontinence, rectal prolapse, fecal ostomy or other clinically significant GI disorders such as inflammatory bowel disease or clinically significant irritable bowel syndrome that would have made bowel movement assessment inaccurate.
7. Rectal bleeding within 60 days of signing ICF not associated with hemorrhoids or fissures.
8. Need for manual disimpaction or pelvic floor support techniques, including manual maneuvers, within 14 days before the screening visit.
9. Presence of rectal outlet obstruction or fecal impaction at screening visit.
10. A history of substance abuse (Diagnostic and statistical Manual of Mental Disorders, Fourth Edition, Text Revision) within 1 year before the screening visit.
11. Any unstable hepatic, renal, pulmonary, cardiovascular (including uncontrolled hypertension), ophthalmologic, neurologic, psychiatric, or any other medical condition that might have compromised the study or put the subject at greater risk during study participation.
12. A history or presence of symptomatic orthostatic hypotension.
13. At the investigator's discretion, other significant abnormalities on screening physical examination (including rectal examination, ECG, or laboratory tests.
14. Planned surgery during the study, including the follow-up period.
15. Known allergy or other contraindication to opioids, opioid derivatives, or opioid antagonists (e.g., codeine, naltrexone, or naloxone).
16. Use of investigational treatments within 30 days before the screening visit.
17. Current treatment with partial opioid agonists (e.g., buprenorphine) or combination agonists/antagonists.
18. Urine drug screen negative for the presence of opioids.

<u>During Baseline Visit:</u>

1. Noncompliance with subject diary completion (>2 days overall) during screening period.
2. Noncompliance with rescue laxative usage (subjects who did not have a bowel movement for 3 full consecutive days during the study were permitted rescue laxative oral bisacodyl tablets as a single dose [up to 3 tablets], used within a 24 hour period) during the screening period.

Premature discontinuation of treatment with study drug or withdrawal from participation in study activities by any subject was permitted at any time for any reason. Withdrawal was allowed for pregnancy, protocol non-compliance and if the investigator determined it was in the best interest of the subject. Reasons for discontinuation were recorded on the CRF and prematurely discontinued subjects were followed for safety observation for 14 days after the last dose of study drug or final visit. If subjects were discontinued due to a SAE or AE, they were followed until resolution of the SAE or 14 days, respectively.

Subjects withdrawn after dosing were not replaced.

5.3.4 Study Medication, Concomitant Medications

Treatment
Patients were randomly assigned 1:1:1:1 to 1 of 4 treatment groups via computer generated randomization schedule. Patients were instructed to take three tablets daily, prior to breakfast and food ingestion. Study drug was provided in blister cards containing a 7 day supply of 21 tablets (b) (4)). The investigator/designee was responsible for all blister cards/ kits, which were labeled according to regulations. Each dose of study drug contained 3 tablets and was provided as follows:

- Placebo group: 3 placebo tablets
- 150 mg methylnaltrexone bromide group: 2 placebo tablets plus one 150 mg methylnaltrexone bromide tablet
- 300 mg methylnaltrexone bromide group: 1 placebo tablet plus two 150 mg methylnaltrexone bromide tablets
- 450 mg methylnaltrexone bromide group: 3 150 mg MNTX tablets.

Rescue medication:
Subjects who did not report a bowel movement for 3 full, consecutive days during the screening or treatment period (QD and PRN dosing periods, Days 1 - 84), were allowed oral bisacodyl tablets to use as rescue medication. Oral bisacodyl tablets were provided by the sponsor. Bisacodyl tablets were to be taken as a single dose of 1, 2, or 3 tablets. As recommended on the bisacodyl bottle label, bisacodyl tablets were to be taken by mouth with a glass of water and swallowed whole. Bisacodyl tablets were to be taken ≥ 5 hours and no more than 8 hours following dosing with study drug during the 84-day treatment period.

Prohibited and concomitant medication and therapies:
All opioid and non-opioid medications taken within 30 days prior to enrollment were recorded in the CRF. Enrollment was defined as the date the subject signed the ICF.

Doses of opioid medication were converted to oral morphine equivalents using information from approved product labels or literature referenced in approved product labels. The average of daily morphine equivalents during a specific month was calculated as the sum of oral equivalents divided by the number of days in that specific month.

Use of the following medications and therapies were prohibited: enemas, except after failure of rescue with oral bisacodyl tablets; rectal suppositories (hemorrhoid therapies are permitted); lubiprostone or tegaserod; 5HT3 receptor antagonists; prokinetic agents; manual maneuvers; bulking agents; stool softeners; loperamide; and anticholinergic medications, except for inhaled anticholinergic medications.

Additional prohibited medications and therapies included: partial opioid agonists or combination opioid agonists/antagonists; changes to overall diet and exercise regimen; newly prescribed therapeutic iron supplements or calcium channel blockers; and any other treatment that was expected to cause either constipation or diarrhea.

Antidepressants (listed below) were prohibited during the study unless taken for ≥ 30 days before the baseline visit were expected to continue during the study if the subjects did not have a history of constipation associated their use:

- Selective serotonin reuptake inhibitors
- Serotonin and norepinephrine reuptake inhibitors
- Norepinephrine-dopamine reuptake inhibitors
- Norepinephrine-dopamine releasing agents
- Norepinephrine reuptake inhibitor
- Tricyclic antidepressants.

Patients were permitted to continue with a stable dose of iron supplements or calcium channel blocker if utilized for ≥ 45 days before the baseline visit and patient expected to continue use throughout the study duration.

Any change to a subject's diet was to be discussed with the study physician and recorded (i.e., addition of prune juice or Activia® yogurt).

Premature discontinuation of treatment with study drug or withdrawal from participation in study activities by any subject was permitted at any time for any reason. Withdrawal was allowed if the investigator determined it was in the best interest of the subject

5.3.5 Study Visits and Procedures

The schedule of events and study procedures for the prescreening, screening and double blind treatment periods in Study MNTX3201 is provided in Table 11.

Prescreening and Screening Period:
During the 14-day screening period, objective evidence of constipation was assessed and used as the basis for enrollment. Constipation was defined as < 3 RFBMs per week on average associated with 1 or more of the following (based upon subject's diary report):

- A Bristol Stool Form Scale (BSS) type 1 or 2 ≥25% of the RFBMs
- Straining during ≥ 25% of the RFMBs
- A sensation of incomplete evaluation after ≥25% of the RFBMs.

No laxative use within 24 hours prior to bowel movement was acceptable.

Double-Blind Treatment Period:
Subjects who remained eligible at the baseline visit were randomly assigned to receive MNTX 150, 300, 450 mg QD or placebo QD in a 1:1:1:1 allocation ratio. Subjects were instructed to swallow the tablets whole and never to chew, divide or crush and wait ≥30 minutes prior to food ingestion.

Subjects took the study drug QD during the initial 28 days and then PRN during the remaining study 56 days.

Follow-Up Period: Subjects who completed the 12-week (84) day treatment period were to return to the clinic for a follow-up visit at 14 days (+/- 2 days) after the last dose of study drug.

Table 11: MNTX3201 Schedule of Assessments and Procedures

Study Interval	Screening Period	Double-blind Treatment Period						Follow-up
		Daily (QD) Dosing			As Needed (PRN) Dosing			
Study Day	-14 to -1 (± 2 days)	Day 1	Day 14 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 84 (± 2 days)	Day 98 (± 2 days)
Visi	1	2 (Baseline)	3	4	5	6	7	8
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Subject Demographics	X							
Medical/Surgical History	X							
Pain History	X							
Constipation History	X							
Physical Exam [1]	X			X			X	
Vital Signs [2]	X	X (pre and 1hr post)	X	X	X	X	X	
Laboratory Tests [3]	X			X			X	
Urine drug screen (opioids)	X							
Pregnancy Test [4]	X	X		X			X	
Electrocardiogram	X			X				
Randomization		X						
Concomitant Medications	X	X	X	X	X	X	X	X
Study drug ingestion (3 tablets)		Daily			As Needed			
Adverse Events		X (pre and 1hr post)	X	X	X	X	X	X
WHO Performance Scale	X							
Objective Opioid Withdrawal Scale (OOWS)		X (pre and 1hr post)	X	X	X	X	X	
Subjective Opioid Withdrawal Scale (SOWS)		X (pre and 1hr post)	X	X	X	X	X	
Pain Intensity Scale		X	X	X	X	X	X	
Subject								
Bowel Movement Time	Daily							
Bristol Stool Form Scale	Daily							

Source: Table 6, MNTX CSR Report

Table 12: MNTX3201 Schedule of Assessments and Procedures - continued

Study Interval	Screening Period	Double-blind Treatment Period						Follow-up
		Daily (QD) Dosing			As Needed (PRN) Dosing			
Study Day	-14 to -1 (± 2 days)	Day 1	Day 14 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 84 (± 2 days)	Day 98 (± 2 days)
Vis	1	2 (Baseline)	3	4	5	6	7	8
Straining Scale	Daily							
Sense of Complete Evacuation Scale	Daily							
Rescue laxative use	Daily							
Recording of opioids	Daily							
Patient Reported Outcomes								
Patient Assessment of Constipation – Symptoms (PAC-SYM)		X	X	X			X	
Patient Assessment of Constipation – Quality of Life (PAC-QoL)		X	X	X			X	
European Quality of Life-5 Dimensions (EQ-5D)		X	X	X			X	
Work Productivity and Activity Impairment Questionnaire General Health V2.0		X	X	X	X	X	X	
Global Clinical Impression of Change				X			X	

Source: Table 6, MNTX CSR Report

[1] Rectal exam was mandatory at the screening visit to access the presence of rectal outlet obstruction or fecal impaction (exclusion #9). Subjects that had either a physical examination with a documented rectal examination or a GI work up that included a documented rectal examination within the past 30 days was not required to undergo a rectal examination at the screening visit.

[2] Height and weight measurements were performed at screening visit only.

[3] Creatinine clearance (Cockcroft-Gault Glomerular Filtration Rate) ≥ 30 mL/min, calculated from the screening labs (inclusion #4).
[4] Urine pregnancy test done at baseline, other pregnancy evaluations were serum pregnancy tests.
Copied and electronically reproduced from Applicant's submission, Study MNTX3201 Clinical Study Report, Table 6

5.3.6 Control Procedures

Randomization
A centralized randomization list was generated by an interactive voice response system (IVRS) and managed by (b) (4) The Trial Master File (TMF) was maintained at the sponsor site. (b) (4) provided the randomization list to the labeling and packaging facility. (b) (4) underwent corporate reorganization and is now (b) (4)

Placebo Control
This was a placebo-controlled trial. Matching placebo and MNTX tablets were round and white (some tablets may have had traces of yellow hue), and placebo tablets were identical in appearance and shape to MNTX tablets. Placebo tablets contained microcrystalline cellulose and magnesium stearate.

Blinding
The identities of MNTX and placebo tablets were blinded to subjects and to study personnel during the 84 day treatment phase. All patients, investigators, and study site personnel were unaware of the treatment assignments for the patients. In the event of a SAE that necessitated unblinding, the investigator was required to first contact the sponsor's medical monitor before being able to break the blind within the IVRS.

Compliance:
Compliance was monitored by study site personnel. At each study visit, the number of tablets in dispensed versus returned blister cards was compared and the dosing information reported by the subject on their paper diary and IVRS entries were compared. Discrepancies were reconciled with the subject during the office visit. Compliance and any unresolved discrepancies were documented in the source document and on the drug inventory record.

IVRS diary compliance was also enforced based upon the following criteria:

- The subject was not to be randomized to double blind treatment for Non-compliance or lack of IVRS diary submission for >2 days during the screening period.
- The subject was removed from the double blind treatment period for noncompliance and did not report IVRS diary information
    - for > 2 consecutive days or a total of >4 days during the double blind QD dosing period
    - For > 4 consecutive days or a total of 8 days during the double-blind PRN dosing period.

Data Management
The study was monitored by the sponsor in accordance with the ICH GCP guidelines. Additionally, an independent DSMB reviewed aggregate semi-blinded or unblinded safety data collected through completion of this study. The progress of the study and data quality was monitored via periodic on-site review of study procedures; frequent telephone communication between the investigator, clinical study manager, clinical monitor and medical monitor; and review of CRFs and clinical records. Electronic case report forms (eCRF) were used in this study and all changes inclusive of date and person performing corrections were documented, along with the reason for alteration. An IVRS was used by the subjects to record electronic diary entries. Electronically collected data and data extracted from the study-specific clinical database were provided in the form of SAS® datasets to the Biostatistics Department at Salix. The database was released when all data-management and quality control procedures were completed.

5.3.7 Outcome Measurements

Primary Efficacy Endpoint:
The primary efficacy endpoint was the average percentage of dosing days resulted in RFBMs within 4 hours of dosing during Weeks 1-4. A RFBM was defined as a bowel movement without laxative use within 24 hours prior to bowel movement. The weekly number of RFBMs was calculated as 7 x total RFBMs in a week/all nonmissing assessment days.

Secondary Efficacy Endpoints:
The key secondary efficacy endpoints were listed as:

- **Responder endpoint:** Proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as ≥ 3 RFBMs/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 out of the first 4 weeks of the treatment period.
- Change in weekly number of RFBMs from baseline over the entire first 4 weeks (28 days) of dosing.

Additional secondary endpoints:

- Proportion of subjects with RFBM within 4 hours of the first dose of study drug, fasting or non-fasting
- Time to the first RFBM after the first dose, censored at 24 hours or time of the second dose, whichever occurred first, fasting or non-fasting
- Percentage of doses resulting in RFBMs within 1, 2, 3, 4, 6, 8, and 24 hour(s).
- Weekly number of RFBMs.
- Proportion of subjects with a weekly RFBM rate ≥ 3 and an increase of ≥ 1 in the weekly RFBM rate from baseline for the specific week.

- Proportion of subjects responding (responder/non-responder) to study drug over the entire 12-week treatment period, where a responder is having ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks.
- Proportion of subjects responding (responder/non-responder) to study drug over the entire 12-week treatment period, where a responder is having ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks and including ≥ 3 of the last 4 weeks of treatment.
- Proportion of subjects achieving ≥ 3 RFBMs per week.
- Proportion of subjects with an increase of ≥ 1 in the weekly RFBM rate from baseline.

Patient- and Clinician – Reported Outcomes

The applicant included multiple exploratory patient and clinician reported outcome evaluations that are noted in Appendix C.

Reviewer Comments: As noted in previous comments by this reviewer, the primary efficacy endpoint in Study MNTX 3201 was the average percentage of dosing days which resulted in RFBMs within 4 hours of dosing during Weeks 1-4 . This was not an acceptable primary endpoint as it was not felt to be clinically meaningful. The current recommendation for drug trials for the indication of OIC is for submission of two placebo controlled, double-blind studies of at least 12 weeks in duration which use a 12-week responder definition incorporating improvement in stool frequency as measured by the number of complete spontaneous bowel movements per week (CSBM). An overall responder is defined as:

> *A patient is considered to be an overall responder if he/she is a weekly responder for at least 9 weeks out of 12 weeks of treatment and 3 of which are in the last 4 weeks (to show durability). A weekly responder should be defined as a patient who has ≥ 3 RFBM/week and an increase from baseline of ≥ 1 RFBM/week for that week.*

Relistor® SC was previously approved for OIC for patients with chronic non-cancer pain based on a 4-week responder endpoint of the percent of patients ***with ≥ 3 SBMs per week*** *for the entire study (Study 3356). The applicant's key secondary 4-week responder endpoint (1st key secondary endpoint) for Study MNTX3201 was similar to the primary endpoint used for Relistor® SQ, however, their endpoint required that patients would need to be a weekly responder, defined as* ***≥ 3 SBMs per week, for 3 out of 4 weeks with an increase of ≥ 1 RFBM/week over baseline*** *in the double blind portion of the study. This reviewer recognizes that the responder endpoints are not identical for Studies MNTX 3201 and 3356. However the secondary responder*

endpoint in study MNTX3201 is the most clinically relevant. In addition, the Applicant also assessed response over 12-weeks of treatment as secondary endpoints. , The totality of evidence will be used to comment upon the efficacy of results in Study MNTX3201 and their comparability to the Relistor® SC Study 3356.

5.3.8 Statistical Information

The reader is referred to the Statistical review completed by Dr. Parfionovas and Dr. Farr for more detailed information of the Applicant's statistical analysis.

Planned sample size was 750 subjects but was increased to 804, with approximately 200 subjects per treatment group.

The primary endpoint was analyzed for differences between subjects who ingested methylnaltrexone bromide tables and placebo using an analysis of covariance (ANCOVA) model with the randomized dose group as effects and the analysis center as a covariate. In the end, the last-observation-carried-forward (LOCF) was not was not utilized for the primary endpoint as the results were robust with and without the LOCF appoach. In addition, sensitivity analyses were performed to include the following:

- Non-parametric model
- PP population
- Multiple imputation to handle missing data (based upon daily data)
- Removal of the concomitant opioid use requirement (Inclusion criterion)

Efficacy analysis was completed on the intent-to-treat (ITT) population which included randomized subjects who received ≥ 1 dose of study drug. The Safety population included all randomized subjects who ingested at least 1 dose of study drug. The per-protocol population included ITT subjects without violations

The first key secondary endpoint (Responder endpoint) was analyzed for differences between subjects who ingested methylnaltrexone bromide tablets and placebo in the ITT population using logistic regression techniques adjusted for analysis center. Last-observation-carried forward (LOCF) data were also analyzed. For Weeks 1 - 4, the last non-missing 4 days with diary data was imputed for the week with < 4 diary days Sensitivity analyses included worst case (weeks with non-missing data on < 4 days were counted as nonresponse for those weeks) and multiple imputation to handle missing data (based on weekly data).

The second key secondary endpoint was also analyzed using ANCOVA with randomized dose group as effect and baseline value and analysis center as covariates. To determine the weekly average number of RFBMs, non-missing data were required for ≥ 4 days in a given week. Analysis was performed using LOCF and sensitivity analyses included observed case and multiple imputation methods.

There were multiplicity concerns regarding the comparison of 3 dosing arms to placebo. To control for the likelihood of type I error, the Sponsor addressed these concerns by the use of 2 approaches:

- Approach 1: Application of a truncated Hochberg gate-keeping procedure to adjust for multiple comparisons in the hierarchical analysis of primary and key secondary efficacy endpoints (as outlined in Section 9.7.1.6.1 of this report).
- Approach 2: Analysis of both the primary efficacy endpoint and responder endpoint as co-primary endpoints in a supplemental analysis by using the Hochberg multiplicity testing procedure (as outlined in Section 9.7.1.6.2 of this report).

Both approach 1 and 2 considered the importance of the responder endpoint (key secondary endpoint #1) to the labeling information that was communicated by the FDA at the 07 Mar 2012 and 04 Nov 2014 meetings.

Reviewer comments: As previously stated, the Division does not agree that the pre-specified primary endpoint is appropriate for labeling as it does not adequately define an overall responder for a chronic condition and is not readily interpretable. The Division conveyed to the applicant during a pre-NDA meeting in 2014 that in order for the results of study 3201 to support the approval of oral methylnaltrexone bromide, the results of pre-specified analyses supporting the proposed dose would first need to be statistically valid, allowing for evaluation of key secondary analyses of interest. Please refer to the Statistical Review for more details on this decision.

5.3.9 Protocol Amendments

The initial protocol for Study MNTX3201 was dated 16 June 2010 (received 19 August 2010) 4 subsequent protocol amendments between 18 August 2010 and 22 June 2011 were noted with data lock reported on 15 December 2011. The amendments are summarized below:

Amendment 1 (18 August 2010): The purpose of this amendment was to note administrative changes along with protocol changes to include:

- Clarification for procedures to administer the study drug
- Updated inclusion and exclusion criteria
- Clarifications regarding prohibited medications and therapies.
- Updated rescue medication procedures
- Revision and addition of study assessment and visit procedures

- Background information was updated
- Exploratory efficacy endpoints were added

Amendment 2 (08 October 2010): This amendment included clarification, revision and updating of the following; inclusion criteria, prohibited medications and therapies, rescue medications, instructions regarding prior and concomitant medications, study design procedures, study assessments and visit procedures, and interim analysis and data monitoring procedures were modified. Specific revisions included:

- Definition of constipation: <3 RFBM per week on average that were associated with 1 or more of the following:
  - Bristol Stool Form Scale type 1 or 2 for at least 25% of bowel movements
  - Straining during at least 25% of the bowel movements
  - A sensation of incomplete evacuation after at least 25% of the bowel movements.
- Definition of exclusion criteria: Non-compliance with rescue laxative usage used (subjects who do not have a bowel movement for three consecutive days during the study are permitted rescue laxative oral bisacodyl tablet as a single dose (up to 3 tablets), used within a 24-hour period) during the screening period.
- Prohibited medications: rectal suppositories
- Revision to study assessments:
  - Following the administration of double-blind study drug at the baseline visit, vital signs, AEs and a second OOWS and SOWS assessment will be completed approximately one hour post-dose. Subjects will be instructed to continue recording paper and IVRS diary information (study drug compliance).
  - For the timing of the study procedures and treatment of subjects and for a summary of efficacy and safety assessments (see section 9.10 and 13.1 of this protocol), please refer to the Schedule of Visits and Evaluations presented in Appendix 1.

Amendment 3 (05 November 2010): This amendment noted specific protocol revisions to include:

- Definition of constipation: <3 RFBM per week on average that were associated with 1 or more of the following:
  - Bristol Stool Form Scale type 1 or 2 for at least 25% of rescue free bowel movements
  - Straining during at least 25% of the rescue free bowel movements
  - A sensation of incomplete evacuation after at least 25% of the rescue free bowel movements.
- Definition of exclusion criteria:
  - Non-compliance with rescue laxative usage used (subjects who do not have a bowel movement for three consecutive days during the study are

permitted rescue laxative oral bisacodyl tablet as a single dose (up to 3 tablets, used within a 24-hour period) during the screening period.

- Prohibited medications: Rectal suppositories (except for use for hemorrhoid therapy).
- Revisions to study assessments: During baseline visit (Visit 2) the date and time of the subject's most recent meal must be recorded in the subject's source documents and CRFs. In addition, following the administration of double-blind study drug at the baseline visit, vital signs, AEs, and a second OOWS and SOWS assessment will be completed approximately one hour post-dose. Subjects will be instructed to continue recording paper and IVRS diary information (study drug compliance).

Amendment 4 (04 February 2011): This amendment included protocol revisions to include the following:

- Definition of constipation due to opioid use during the screening period was clarified to: Definition of constipation: <3 RFBM per week on average (no laxative use within 24 hours prior to bowel movement) that were associated with 1 or more of the following (based on subject's diary report):
  - Bristol Stool Form Scale type 1 or 2 for at least 25% of rescue free bowel movements
  - Straining during at least 25% of the rescue free bowel movements
  - A sensation of incomplete evacuation after at least 25% of the rescue free bowel movements. Revisions to study assessments and visit procedures: For the timing listing of study procedures and treatment of subjects and for a summary of efficacy and safety assessments (see section 9.10 and 13.1 of this protocol), please refer to the Schedule of Visits and Evaluations presented in Appendix 1.
- Text regarding the interpretation of screening ECG was modified.
- The following assessments were removed as attachments to the protocol, and were instead provided as separate documents: OOWS, Pain Intensity, BSS, Straining Scale, Sense of Complete Evacuation Scale, PAC-SYM, PAC-QoL, EQ-5D, WPAI:GH, and GCIC.
- Clarification was added to the sequential step-down testing procedure for evaluating primary and key secondary endpoints.

Amendment 5 (22 June 2011): The purpose of this amendment was to remove the planned interim analysis of efficacy data. An interim analysis of safety and efficacy data by an independent Data Safety Monitoring Board was planned with the intent to discontinue 1 or 2 of the MNTX dose groups based on inferior efficacy or safety considerations. Due to the rate of accrual of subjects, the planned enrollment would have completed before completion of an interim analysis. Because the interim analysis was no longer planned and the minimum α significance level for any dose level comparison with placebo was 0.0167, the sample size was adjusted from approximately

700 subjects to 750 subjects to guarantee adequate power. Additional protocol revisions included:

- Standard language for the investigator's protocol agreement and other administrative information was modified to reflect the change in study sponsorship from Progenics Pharmaceuticals, Inc. to Salix.
- Eudract number was removed and other modifications were made to reflect that MNTX3201 was not conducted outside of the United States.
- Prohibited medications and therapies were updated to allow administration of inhaled anticholinergic medications during the study.
- The one-way analysis of variance model was removed from the evaluation of demographic data. Comparison across groups was to be performed only when difference(s) were observed.
- Efficacy analyses were modified to reflect an α significance level for any dose group comparison with placebo of ≥ 0.0167, due to 3 comparisons with placebo.
- The co-primary efficacy endpoint of the proportion of subjects with RFBM within 4 hours of the first dose of study drug was removed, because it reflects short term efficacy and is not needed for the evaluation of chronic dosing or chronic disease state.
- Analysis set for the primary efficacy analysis was changed from a modified ITT analysis set to an ITT analysis set.
- Key secondary endpoints were modified. The time to first RFBM after the first dose only addresses the first day treatment effect. The replaced first key secondary efficacy endpoint, response to study drug during Weeks 1 to 4, is established for 4 weeks of treatment and is a more clinically meaningfully and stringent endpoint.
- Clarification was added to the primary and key secondary analyses for the description of the step-up and closed sequential procedures to maintain the overall family wise Type 1 error rate at 0.05 with 3 dose comparisons.
- Exploratory efficacy endpoints were reclassified as other secondary endpoints, and another secondary endpoint was added to evaluate response across all 12 weeks of treatment.
- Adjustments by analysis center were added to the analysis methods for the other secondary endpoints.
- Clarification was added about when the first dose of study medication could have been taken during the baseline visit. This change was made based on the timing of the baseline visit. Also the requirement for taking the first dose of study medication at the baseline visit on an empty stomach was removed.
- Clarification was added regarding the withdrawal of subjects for compliance violations.
- Tabulation of all AEs was removed from the analyses of AEs, as only TEAEs were to be tabulated.
- Clarification was added regarding the classification of events as SAEs, regardless of relationship to study drug, and the documentation of post treatment

SAEs that may have been reasonably related to study treatment or study participation.
• Details for reporting SAEs were added to clarify the SAE reporting process.

6 Review of Efficacy

Efficacy Summary

Clinical trial MNTX3201 provided reasonable evidence to support that methylnaltrexone bromide tablets at a dosage of 450 mg (3,150mg tablets) are effective for the treatment of opioid induced constipation in adults with chronic non-cancer pain (CNCP). A single phase 3 clinical trial (MNTX3201) was conducted to support this efficacy claim. The primary objective of the study was to evaluate the safety, efficacy and tolerability of methylnaltrexone tablets in patients with CNCP. The primary endpoint of this study was the average percentage of dosing days that resulted in a RFBM within 4 hours of dosing during the study length of 28 days, comparing methylnaltrexone bromide tablets and placebo. As noted, the Division communicated with the Applicant that this endpoint is not acceptable (Appendix B; pre-NDA meetings 7 March 2012 and 4 November 2014), and that support for the approval of oral methylnaltrexone bromide would require the results of the pre-specified analyses supporting the proposed dose to first be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product. In addition, the results of these key analyses of clinical endpoints considered suitable for purposes of labeling would need to be robust (e.g., analyses comparable to the analyses presented in subcutaneous methylnaltrexone product labeling for the indication of OIC in chronic pain.).

In the single Phase 3 Study MNTX3201, the first key secondary endpoint was the proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as ≥ 3 RFBMs/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 out of the first 4 weeks of the treatment period. The endpoint used for Relistor® SC approval was similar, but not identical, as it was defined as the proportion of subjects who recorded ≥ 3 RFBMs/week with study drug over Week 1 to 4, not 3 out of 4 weeks.

During Study MNTX3201, 803 patients were randomized 1:1:1:1 to receive 150 mg, 300 mg 450 mg methylnaltrexone bromide tablets or placebo. The proportion of responders, as defined above, during Weeks 1-4 was significantly higher in patients receiving 450 mg methylnaltrexone bromide tablets compared with placebo (54.5% vs. 40.8%, p = 0.0052, Table 23). Neither the 150 mg nor 300 mg dosages demonstrated statistically significant improvement for the Responder endpoint.

The Applicant did include a responder analysis assessing patients who recorded ≥ 3 RFBMs/week with study drug during weeks 1 through 4, so direct comparison with the

results of SQ program was possible over the 4 week primary analysis period. However, additional analyses of response over 12-weeks of treatment supported that MNTX 450 mg/day was effective. While the prn dosing after week 4 confounded interpretation of these results, the continued response was reassuring and support the efficacy of MNTX 450 mg/day. In summary, the totality of the evidence provided does support that oral methylnaltrexone bromide (450 mg) is effective in the treatment of OIC in adults with chronic, non-cancer pain.

6.1 Indication

The Applicant is proposing that oral methylnaltrexone receive an indication for the treatment of adults with opioid induced constipation (OIC) with chronic non-cancer pain.

6.1.1 Methods

This NDA submission is based on the development of an oral tablet dosage form as an alternative to the approved SC formulation. The Applicant provides PK/PD modeling data to allow extrapolation of efficacy results from clinical studies for the approved SC formulation to support the efficacy of the oral tablet dosage form (see Section 4.4 and the clinical pharmacology review by Dilara Jappar, PhD, for additional details). Thus, only a single phase 3 clinical trial (MNTX3201) was conducted to support the efficacy claim for oral methylnaltrexone tablets for the treatment of OIC in patients with chronic non-cancer pain.

MNTX3201 was a multicenter, randomized, double-blind, placebo-controlled U.S. based study which included 804 adult patients with OIC in the intention-to-treat population for efficacy analysis. Patient and clinician reported outcomes included daily self-assessment (collected using IVRS) of bowel movements, Bristol Stool Scale, Straining Scales, Sense of Complete Evaluation Scales and recording of study drug and rescue laxative use from the initiation of screening until study day 84 or early withdrawal.

The definition of study populations included in the efficacy and safety analyses for MNTX3201 are described in Table 13.

Table 13: Definition of Analysis Sets for MNTX3201

Analysis set	Definition
Intention-to-treat (ITT)	All randomized subjects who ingested ≥ 1 dose of study drug.
Safety	All randomized subjects who ingested ≥ 1 dose of study drug.
Per-protocol (PP) population	ITT subjects who did not have the following major violations: • No history of constipation due to opioid use or history of constipation due to opioid use for < 30 days before the screening visit. • Not taking oral, transdermal, intravenous, or SC opioids for chronic nonmalignant pain or receiving a daily dose < 50 mg of oral morphine equivalents per day for chronic nonmalignant pain during the screening period and throughout the study. • History of chronic constipation prior to the initiation of opioid therapy. • Administration of the wrong study drug.

Source: Reviewer's table, summarized from Applicant's Clinical Study Report for MNTX3201 (Section 9.7.1.2)

6.1.2 Demographics

The study population for MNTX3201 consisted of adults with OIC and chronic non-cancer related pain for at least 2 months in duration. Baseline demographic data from MNTX3201 are presented in Table 14.

Table 14: Demographic Characteristics (ITT) for Study MNTX3201

Variable	MNTX 150 mg N = 201	MNTX 300 mg N = 202[a]	MNTX 450 mg N = 200	Placebo N = 201
Age (years)				
Mean (SD)	50.9 (10.32)	51.6 (10.53)	51.4 (10.50)	52.6 (10.33)
Min, Max	18, 79	24, 82	23, 78	23, 78
Age group, n (%)				
18-40	34 (16.9)	22 (10.9)	26 (13)	22 (10.9)
41-64	152 (75.6)	161 (79.7)	155 (77.5)	157 (78.1)
≥ 65	15 (7.46)	19 (9.4)	19 (9.5)	22 (10.9)
Gender, n (%)				
Male	68 (33.8)	88 (43.8)	72 (36.0)	71 (35.3)
Female	133 (66.1)	114 (56.7)	128 (64.0)	130 (64.7)
Race, n (%)				
White	164 (81.6)	158 (78.2)	172 (86)	166 (78.7)
Black	30 (14.9)	38 (18.8)	25 (12.5)	27 (13.4)
Asian	--	--	--	1 (0.5)
American Indian or Alaska Native	3 (1.5)	2 (1.0)	--	3 (1.5)
Native Hawaiian or Pacific Islander	--	1 (0.5)	-	1 (0.5)
Other	4 (2.0)	--	3 (1.5)	3 (1.5)
Ethnicity, n (%)				
Hispanic or Latino	14 (7.0)	18 (8.9)	12 (6.0)	8 (3.9)
Non-Hispanic or Latino	187 (93.0)	184 (91.1)	188 (93.5)	193 (96.1)
Weight (kg)				
Mean (SD)	89.45 (24.780)	97.76 (24.508)	87.79 (23.098)	89.67 (24.156)
Median (Min, Max)	89.45 (37.8, 190.0)	87.30 (42.1,184.0)	84.10 (41.3,181.0)	87.50 (45.3, 158.8)

Source: Modified from Table 9 from CSR MNTX3201 and demographics dataset for MNTX3201 with IR response from sponsor, clarifying number of subjects from ages 18-40 years..
[a]One participant requested withdrawal prior to receiving study drug.

Reviewer Comments: The majority of patients were both white and female. Demographics were generally similar between treatment groups and the proportion of patients who were ≤ 40 years was slightly higher in the 150 mg group. However, this reviewer does not believe that this should have a substantial impact on results. This reviewer believes that the baseline demographic characteristics of patients across arms were sufficiently similar and correlative to the demographics of patients with non-cancer related OIC within the U.S and in Study 3356 from the Relistor® SC development program

Baseline opioid dose was defined during the screening period as an average of daily oral morphine equivalents within 30 days of the first dose of study drug. Morphine equivalents were calculated as the sum of total oral morphine equivalents during the screening period divided by the number of days during the screening period. The mean baseline opioid use was 224 mg in the methylnaltrexone bromide tablet group and 210

mg morphine equivalents per day in the placebo group. Medical history data was coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 13.0). The most commonly reported primary pain diagnosis was back pain. Baseline disease characteristics of the ITT population are summarized in Table 15.

Table 15: Baseline Disease Characteristics (ITT Population)

Characteristic Category or statistic	All MNTX	MNTX 150 mg	MNTX 300 mg	MNTX 450 mg	Placebo
N	602	201	201	200	201
Primary Pain Condition – n(%)					
Back pain	403 (66.9)	132 (65.7)	136 (67.7)	135 (67.5)	145(72.1)
Joint or extremity pain	40 (6.6)	13 (6.5)	16 (8.0)	11 (5.5)	10 (5.0)
Arthritis	54 (9.0)	20(10.0)	15 (7.5)	19 (19.5)	12 (6.0)
Neurologic or neuropathic pain	45 (7.5)	16 (8.0)	13 (6.5)	16 (8.0)	11 (5.5)
Fibromyalgia	34 (5.6)	15 (7.5)	8 (4.0)	11 (5.5)	12 (6.0)
Other	26 (4.3)	5 (2.5)	13 (6.5)	8 (4.0)	11 (5.5)
Opioid Morphine Equivalents (mg/day)					
N	601	200	201	200	201
Mean (SD)	223.58 (236.493)	199.97 (205.213)	252.59 (298.144)	218.02 (189.051)	209.68 (199.118)
Median (Min, Max)	151.0 (27,2289.3)	141.05 (30,1280.0)	177.50 (47.4,2289.3)	155.55 (27,1272.0)	132.00 (42.6,1007.3)
Average Number RFBMs per Week[a]					
Mean (SD)	1.40 (0.865)	1.46 (0.911)	1.35 (0.891)	1.37 (0.789)	1.49 (1.045)
Median (Min, Max)	1.50 (0,4.4)	1.50 (0,4.2)	1.40 (0,4.4)	1.4 (0,3.2)	1.40 (0,7.5)
Average Number of RFBMs per Week <3[a] – n (%)					
Yes	581 (96.5)	191 (95.0)	195 (97.0)	195 (97.5)	188 (93.5)
No	21 (3.5)	10 (5.0)	6 (3.0)	5 (2.5)	13 (6.5)

Source: Table 10 Clinical Study Report MNTX3201

[a] Subjects were using oral, transdermal, intravenous, or subcutaneous opioids for ≥ 1 month (daily dose ≥ 50 mg of morphine equivalents per day for ≥ 2 weeks) and had a history of constipation because of opioid use for ≥ 1 month.

Reviewer's Comments: Common primary pain diagnoses appeared at a similar rate across all arms of the study and were comparable in prevalence to patients included in both naloxegol oxalate and Relistor® SC phase 3 trials.

The applicant did not stratify based on baseline mean oral morphine equivalents (OME) or maximum morphine equivalents (mg/day) in the design of Study MNTX3201. This reviewer notes that the 300 mg arm had the highest baseline OME of the treatment arms. The OME for the 450mg treatment arm was 218.02 compared with 209.68 for the placebo arm. As the baseline OME for the 450mg treatment arm was comparable to that of the placebo arm, this reviewer finds this to be acceptable. In addition, the baseline OME was similar to that from study MNTX3356 (SC methylnaltrexone bromide for the indication of OIC in non-cancer related pain) reviewed under NDA 021964. Of

note, the baseline OME in the pivotal trials for oral naloxegol oxalate for the same indication was lower across all treatment arms (mean range of OME were 135.6 mg/day, 139.7 mg/day and 143.2 mg/day for placebo 12.5 mg and 25mg respectively). The clinical significance of this is unclear. However, the similar baseline OME across treatment arms is acceptable.

While the reported OME in Oral and SC methylnaltrexone bromide studies appear to reflect the baseline population for the Applicant, stratification would have ensured a more even distribution of OME across treatment arms. That being said, the baseline OME between the 450 mg group and placebo were similar and unlikely to significantly impact the results.

6.1.3 Subject Disposition

In Study MNTX3201 a total 1745 patients were prescreened and 804 subjects met inclusion/exclusion criteria. 803 subjects received ≥1 dose of study medication (Table 16). The most frequent explanations given for screening failure included subject request (QD period), protocol violation and lost to follow-up (PRN period).

Table 16: Analysis Populations by Treatment Groups Study MNTX3201

	MNTX 150 mg	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
Intent-to-Treat	201 (100%)	201 (99.5%)	200 (100 %)	201 (100 %)
No study drug ingested	0	1 (0.5%)	0	0
Safety	201 (100%)	201 (99.5%)	200 (100 %)	201 (100 %)
No study drug ingested	0	1 (0.5%)	0	0
Per-Protocol	173 (86.1%)	176 (87.6%)	188 (93.1%)	179 (89.5%)
No study drug ingested	0	1 (0.5%)	0	0
Wrong study drug administered	2 (1%)	0	1 (0.5%)	130 (64.7)
Noncompliance with rescue laxative during screening	7 (3.5%)	4 (2.0%)	11 (5.5%)	10 (5.0%)
No constipation at baseline	12 (6.0%)	7 (3.5%)	6 (3.0 %)	16 (8.0%)
Baseline opioid < 50 mg/day	6 (3.0%)	4 (2.0%)	3 (1.5%)	4 (2.0%)

Source: Table 8, MNTX3201 CSR
Note: Some subjects had more than 1 reason for exclusion from the per-protocol population

Reviewer comments: Of the 804 subjects who were randomized and enrolled at 117 investigational sites in the United States, 1 subject in the methylnaltrexone bromide 300mg arm did not receive study drug due to elective withdrawal prior to study initiation. That subject was not included in the analysis populations. The ITT and safety analysis populations were identical and included 803 patients who were randomized and

received at least a single dose of study drug. The per-protocol (PP) analysis population excluded patients with specific protocol violations. More patients were excluded from the per-protocol population for noncompliance with rescue laxatives during screening in the 450 mg and placebo arms, though the rates between these two groups were similar. The number of patients excluded due to baseline opioid use of < 50 mg/day was similar across all arms.

Approximately 90% of randomized patients in both the methylnaltrexone bromide and placebo groups completed the 4 week QD dosing period. Approximately 86% of patients initially randomized to Study MNTX3201 continued to participate in the PRN dosing period. Similarly, 83% of patients initially randomized to the placebo arm continued to participate in the PRN dosing period. The rate of early discontinuation during the 8 week PRN period was on average 12% in the MNTX treated patients and 14% in placebo treated patients (Table 17).

Table 17: Subject Disposition by Dosing Period (All subjects and PRN Subjects)

	All MNTX n(%)	MNTX 150 mg n(%)	MNTX 300 mg n(%)	MNTX 450 mg n(%)	Placebo n(%)
Subjects Randomized (N)	**603**	**201**	**202**	**200**	**201**
Intent-to-Treat	**602 (99.8)**	**201 (100.0)**	**201 (99.5)**	**200 (100.0)**	**201 (100.0)**
Completed 4-week QD Period	**543 (90.0)**	**184 (91.5)**	**184 (91.1)**	**175 (87.5)**	**180 (89.6)**
Discontinued QD Period	**60 (10.0)**	**17 (8.5)**	**18 (8.9)**	**25 (12.5)**	**21 (10.4)**
Primary reason					
Ineligibility	2 (0.3)	0	0	2 (1.0)	0
Protocol violation	5 (0.8)	3 (1.5)	2 (1.0)	0	7(3.5)
Adverse event	10 (1.7)	1 (0.5)	3 (1.5)	6 (3.0)	4 (2.0)
Subject request	22 (3.6)	8 (4.0)	8 (4.0)	6 (3.0)	6 (3.0)
Lost to follow-up	11 (1.8)	3 (1.5)	1 (0.5)	7 (3.5)	0
Insufficient response	9 (1.5)	2 (1.0)	3 (1.5)	4 (2.0)	3 (1.5)
Other	1 (0.2)	0	1 (0.5)	0	1 (0.5)
Treated in PRN Period	**521 (98.9)**	**174 (98.3)**	**178 (98.3)**	**169 (100.0)**	**165 (98.8)**
Completed PRN Period	**464 (88.0)**	**160 (90.4)**	**156 (86.2)**	**148 (87.6)**	**143 (85.6)**
Discontinued PRN Period	**63 (12.0)**	**17 (9.6)**	**25 (13.8)**	**21 (12.4)**	**24 (14.4)**
Primary reason					
Ineligibility	0	0	0	0	0
Protocol violation	19 (3.6)	3 (1.7)	6 (3.3)	10 (5.9)	4 (2.4)
Adverse event	7 (1.3)	1 (0.6)	6 (3.3)	0	4 (2.4)
Subject request	13 (2.5)	6 (3.4)	4 (2.2)	3 (1.8)	7 (4.2)
Lost to follow-up	18 (3.4)	7 (4.0)	5 (2.8)	6 (3.6)	8 (4.8)
Insufficient response	5 (0.9)	0	4 (2.2)	1 (0.6)	1 (0.6)
Other	1 (1.2)	0	0	1 (0.6)	0

Source: Table 7 MNTX3201 based upon Tables 14.1.1b and 14.1.1.1c
[a] Intent-to treat is defined as any randomized subject taking ≥1 dose of study medication
[b] A PRN subject is defined as a subject who had a PRN period visit or took PRN study drug after study day 28.

Reviewer Comments: The rate of discontinuation in Study MNTX3201 during weeks 1-4 was similar across treatment arms and should not impact results. The most common reason for early discontinuation was subject request (QD period) and insufficient response (PRN period), and the rates of discontinuation were comparable across treatment arms. Of all 33 subjects coded as discontinuing due to subject request, this medical officer's review of the AE data set demonstrated that 27 also had AEs, the highest (10) related to Gastrointestinal disorders (1:1:3:5 as related to 150 mg, 300 mg, 450 mg and placebo, respectively). It is possible that some of these patients should have been coded as discontinuing due to an AE; however, the rates were similar across treatment groups, so this is unlikely to impact results.

This reviewer compared the rate of dropout after 12 weeks in Study MNTX3201 to studies completed for the approval of naloxegol oxalate (MO review NDA 204760). The dropout rate after 12 weeks was similar for oral methylnaltrexone (17%-23% in all treatment and placebo arms) compared to oral naloxegol oxalate (a range of 17% to 25% in all treatment and placebo arms). At the to-be-marketed dose of 450 mg, 12.5% of subjects had discontinued study MNTX3201 at 4 weeks and 12.4 % during the 8 week PRN phase. During the QD and PRN periods, a total of46 subjects who discontinued study MNTX3201, which correlated to 23% of subjects who took 450 mg tablets. This rate is similar to that reported from Phase 3 studies for oral naloxegol oxalate over 12 weeks ((17.1% and 22.7% at the to be marketed dosage in for two different phase 3 studies.) .

This reviewer's evaluation of the MNTX3201 POP dataset differs somewhat from the information provided by the Applicant in Table 17 in the rates of discontinuation related to insufficient response to treatment. For the entire length of both QD and PRN periods, this reviewer noted that 7:8:5:7 subjects discontinued due to insufficient response to treatment in 150 mg, 300 mg, 450 mg and placebo arms, compared to 0:4:1:1 as noted in by the Applicant Table 17. This reviewer does not believe that these differences would change interpretation of efficacy results as they were noted across all dosage arms inclusive of the placebo arm.

Protocol Violations:

In Study MNTX3201, a total of 43 patients were reported with major protocol violations in during the QD period. Violations of inclusion and exclusion criteria were the most common in all study arms. Less major protocol violations were noted throughout the duration of the PRN arm, per the Applicant (Table 18).

Table 18: Study MNTX3201 Summary of the Incidence of Major Protocol Deviations by Category (Deviations Reported During the QD/PRN Phases) in Randomized Subjects

	MNTX 150 mg N=201	MNTX 300 mg N=202	MNTX 450 mg N=200	Placebo N=201
QD	201	201	200	201
Subjects Reporting a Deviation	9 (4.5%)	6 (3.0%)	12 (6.0%)	16 (8.0%)
01-Inclusion Criteria	1 (0.5%)	0 (0.0%)	4 (2.0%)	5 (2.5%)
02-Exclusion Criteria	6 (3.0%)	3 (1.5%)	4 (2.0%)	6 (3.0%)
03-Study Drug	2 (1.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)
04-Assessment Safety	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
06-Visit Window	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
07-Informed Consent	1 (0.5%)	1 (0.5%)	2 (1.0%)	1 (0.5%)
08-Other	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)
PRN				
Subjects Reporting a Deviation	7 (3.5%)	2 (1.0%)	4 (2.0%)	2 (1.0%)
02-Inclusion Criteria	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
03-Exclusion Criteria	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
04-Study Drug	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
05-Assessment Safety	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
07-Informed Consent	3 (1.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)
08-Other	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Table 14.1.1.1f provided by the Applicant on 19 November 2015

A total of 43 major protocol violations were reported during the QD period, the highest occurrence (16) in the placebo arm (Table 18). During the PRN period, protocol violations 7 were reported at the 450 mg dosage in comparison to 2 reported in the placebo arm..

Reviewer Comments: According to the data provided, protocol violations occurred more frequently during the QD period and most frequently in the placebo and 450 mg arms. Lack of constipation at baseline, noncompliance with rescue laxative during screening period, and too low baseline opioid equivalents were the three most commonly reported protocol violations and the incidences were similar across groups. There were no significant concerns in review of this data.

Protocol Violations in Laxative Use

Review of efficacy data for Study MNTX3201 noted discrepancies in laxative coding. The protocol for Study MNTX3201 clarifies that during days 0-28, Bisacodyl will be specifically used as “Rescue Laxative”. In review of the concomitant medication (CM) dataset for the entire duration of Study MNTX3201, laxative use was coded both as CMCAT (constipation medications, rescue laxative medications) and as CMCLAS (general concomitant medications). Table 19, describes the concomitant medication dataset variables and highlights the laxative use which was identified under the CMCAT variable of “General Concomitant Medication”.

Table 19: Statistical Concerns with Analysis of Study MNTX3201

Variable	Definition	Example	Concerns
CMCAT	Medication	Constipation Medications Rescue laxative medications	Only 4 broad categories were considered in this variable: • Constipation Medication • Rescue Laxative Medication • Opioid Medication • General Concomitant Medication
CMINDC	Indication for medication	Constipation	Typographical errors: i.e. constipation, constipation, OI-C
CMSTDT	Start date and time of medication		Time of medication was not specified
CMCLAS	Medication class		An additional 1160 incidents of laxative use were described under the category of General concomitant medication (CMLAS) in 419 patients that was not addressed in the analysis (as they were labeled "general concomitant medication" in CMCAT)

Source: Medical Officer summary of Variables CSR MNTX3201

However, in review of study MNTX 3201, it became clear that the Applicant utilized the category of CMAT for analysis of rescue laxative usage throughout Study MNTX3201, inclusive of the screening period, Days 0-28, Days 29-84 and the follow-up period. The number of subjects who used any laxatives during the time periods were provided in an IR dated 5 February 2015 are noted in Table 20.

Table 20: Percentage of Subjects using Laxatives during Study MNTX3201 (total subjects and %)

	MNTX 150 mg n (%)	**MNTX 300 mg n (%)**	**MNTX 450 mg n (%)**	**Placebo n (%)**
Screening	N=201	N=201	N=200	N=201
Rescue Laxative Medications	129 (64.2%)	133 (66.2%)	122 (61.0%)	136 (67.7%)
Other Laxative use	192 (95.5%)	191 (95.0%)	194 (97.0%)	195 (97.0%)
Total	198 (98.5%)	197 (98.0%)	197 (98.5%)	197 (98.0%)
QD dosing period (Days 0-28)	N=201	N=201	N=200	N=201
Rescue Laxative Medications	90 (44.8%)	95 (47.3%)	98 (49.0%)	100 (49.8%)
Other Laxative use	0 (0%)	1 (0.5%)	0	0
Total	90 (44.8%)	95 (47.3%)	98 (49.0%)	100 (49.8%)
PRN dosing period (Days 29-84)	N=167	N=181	N-169	N=167
Rescue Laxative Medications	80(45.2%)	72 (39.8%)	67 (39.6%)	76 (45.5%)
Other Laxative use	3 (1.7%)	1(0.6%)	5 (3.0%)	0
Total	76(45.5%)	73 (40.3%)	71 (42.0%)	76 (45.5%)
After day 84 (follow-up)	N=201	N=201	N=200	N=201
Rescue Laxative Medications	1(1.5%)	4(2.0%)	0(0%)	3(1.5%)
Other Laxative use	32(15.9%)	32 (15.9%)	27 (13.5%)	29(14.4%)
Total	33(16.4%)	35(17.4%)	27 (13.5%)	32(15.9%)

Source: IR response from Applicant 5 February 2016. Table 14.1.6.3.e

Reviewer Comments: Coding as "other laxative use" appeared to occur almost exclusively during the pre-screening period and follow-up period (after day 84), which should not impact the primary efficacy analysis. While it appears there were a few episodes of laxative use which were not coded as rescue laxative during the primary analysis period, these numbers were small and occurred in all study arms similarly. This reviewer does not believe this will impact study results.

This reviewer identified additional episodes of laxative use during Days 0-28 using CM dataset variables CMAT and CMCLAS as noted in Table 21.

Table 21: Episodes of Reported Laxative use by Concomitant Medication Dataset Variables

	MNTX			
	150 mg	**300 mg**	**450 mg**	**Placebo**
CMAT (Medication)				
Constipation Medications	8 (N=2)	2 (N=2)	4 (N=3)	7 (N=4)
Rescue Laxative Medications	300 (N=89)	282 (N=94)	264 (N=98)	335 (N=100
Total	308 (N=91)	284 (N=96)	268 (N=101)	342 (N=104)

Source: Reviewer's analysis of CM dataset Study MNTX3201
N=number of subjects

Reviewer comments: As noted, the protocol for Study MNTX3201 specified that during days 0-28, bisacodyl will be specifically used as "Rescue Laxative". The Applicant clarified that during this time period, other laxative use was also coded as rescue laxative, and patients were considered as nonresponders on days that such laxatives were used. However, during the screening and weeks 5-12, bisacodyl and other laxatives were less consistently identified as rescue medications and were also frequently identified as "Constipation Medication" or "Other". This is not expected to impact study results however, as the response definition included only the primary analysis period from days 0 – 28.
During the Day 0-28 time period, this reviewer did identify 3 subjects receiving methylnaltrexone bromide 450mg who used laxative medications besides bisacodyl which were not identified as rescue laxatives. Specifically one subject used an enema, another used a glycerol suppository and the third used sodium phosphate to aide in laxation. These three subjects were also identified as treatment failures. A few similar examples were identified in each treatment arm. Table 21 shows a comparison of subjects using laxative medications during days 0 – 28, as reported by the Applicant and as assessed by this reviewer. As shown, this reviewer identified a small number of patients who received laxatives and who weren't identified by the Applicant.

Comparison of "Total" subjects in Table 20 vs. Table 21 note changes in all dosage between the Applicant's data (Table 20) and this medical reviewer's data (Table 21).

Number of subjects who used any medication as a laxative (rescue or other) during days 0-28 in Study MNTX3201				
	150 mg	***300 mg***	***450 mg***	***Placebo***
Applicant's analysis (Table 20 " total")	*90*	*95*	*98*	*100*
Medical reviewer's analysis (Table 21 " total")	*91*	*96*	*101*	*104*

While it appears there were a small number of patients who took a laxative which was not coded as rescue laxative use, these numbers were small and similar in each study arm. This reviewer believes that while there were noted inconsistences in coding for laxative use during the double blinded phase of Study MNTX3201 between the applicant and this medical officer's analysis, all study arms were affected and the degree of inconsistency within Weeks 1-4 were not substantial enough to compromise the efficacy analyses of Study MNTX3201 during this period.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for Study MNTX3201 was the average percentage of dosing days resulting in RFBMs within 4 hours of ingestion of the study drug during Weeks 1 – 4. A RFBM was defined as a bowel movement without the aid of laxative use within 24 hours prior (Table 22). The Applicant performed sensitivity analyses using nonparametric methods, Per Protocol (PP) population results, multiple imputations to handle missing data.

Table 22: Percentage of Dosing Days that Resulted in RFBMs within 4 hours of Dosing during Weeks 1-4

Percentage of Dosing Days that Resulted in RFBMs within 4 hours of Dosing During Weeks 1-4	**Dose MNTX**			
	150 mg	**300 mg**	**450 mg**	**Placebo**
Intention-to-Treat Population (ITT)				
n	201	201	200	201
Mean percentage(SD)	21.05 (20.1116)	24.64 (21.311)	27.40 (23.453)	18.18 (16.995)
Median percentage (min, max)	14.81 (0.0,96.4)	21.43 (0.0,92.9)	23.54 (0.0,100)	14.29 (0.0,92.9)
LS mean	21.06	24.75	27.37	18.23
LS mean difference (vs. placebo)[a]	2.83	6.51	9.13	--
95% CI for difference (vs placebo) [a]	-1.21,6.86	2.47,10.55	5.09,13.18	--
Raw p-value (vs. placebo)	0.3076	0.0339	0.0043	--

Source: Table 13, MNTX3201 Clinical Study Report
[a] From ANCOVA model with treatment as effect and analysis region covariate

Reviewer's Comment: There was a statistically significant difference in the percentage of dosing days that resulted in RFBMs within 4 hours of dosing during weeks 1 – 4 for of 300 and 450 mg/day of methylnaltrexone bromide tablets compared to placebo, and the Applicant reports consistent results using a variety of sensitivity analyses. As previously noted, this primary endpoint was not found to be acceptable by the reviewing Division (refer to Reviewer's comments in Section 5.3.7 and (Appendix B, pre-NDA meeting 07 March 2012). While the Division does not find this primary endpoint as clinically meaningful in this patient population, the information will be used as part of the totality of evidence toward for NDA 208271 approval. The remainder of this review, will focus on the secondary endpoints that are more acceptable to the Division as clinically meaningful for this population (Appendix A, pre-NDA meetings on 07 March 2012 and 04 November 2014).

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant included two key secondary endpoints, the proportion of study drug responders and the change in weekly number of RFBMs. The applicant also assessed correlation between these two key secondary endpoints and the pre-specified primary study endpoint.

Proportion of Study Drug Responders:

The Applicant's first key secondary endpoint is a **responder endpoint**. A responder was defined as a subject who had ≥3 RFBMs/week with an increase of ≥1 RFBM/week over baseline for ≥ 3 out of the first 4 weeks of the treatment period.

Table 23 shows the results for the key secondary endpoint in the ITT population.

The proportion of study drug responders during Weeks 1 through 4 was 45.3% (150 mg), 51.7% (300 mg) and 54.55% (450 mg) in patients treated with oral methylnaltrexone compared with 40.8% in the placebo group. The primary analysis used a last observation carried forward (LOCF) approach. The weekly number of RFBMs was calculated as 7X total RFBMs in a week/all nonmissing assessment days in the week. The weekly number of RFBMs was set to missing for any week when the subjects completed <4 diary days. RFBM was defined as a bowel movement without laxative use within 24 hours prior to bowel movement. If a subject did not receive concomitant daily opioid treatments during a week, the subject was considered a non-responder for the week. Analysis was performed using LOCF and sensitivity analyses included observed case and multiple imputation (based on weekly data) methods.

Table 23: First Key Secondary Endpoint (Responder Endpoint) - Defined as ≥ 3 RFBM/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 out of the first 4 weeks of the treatment period. (ITT Population)

Proportion of Subjects Responding to Study Weeks 1-4	**Dose MNTX**			
	150 mg	**300 mg**	**450 mg**	**Placebo**
n	201	201	200	201
LOCF Approach				
Yes-n (%)	91 (45.3%)	104 (51.7%)	109 (54.5%)	82 (40.8%)
Percentage Difference (vs Placebo)	4.5%	10.9%	13.7%	
95% CI for Odds Ratio	0.82,1.84	1.03, 2.29	1.20, 2.66	
Raw p-value (vs. Placebo)	0.3076	0.0339	0.0043	
Worst Case Approach				
Yes-n (%)	86 (42.8%)	99 (49.3%)	103 (51.5%)	77 (38.3%)
Percentage Difference (vs Placebo)	4.5%	10.9%	13.2%	
95% CI for Odds Ratio	0.82, 1.84	1.04, 2.32	1.19, 2.65	
Raw p-value (vs. Placebo)	0.3185	0.0321	0.0052	

Source: 3201 CSR Table 14.2.2.1a/ Summary Clinical Efficacy MNTX3201 Table 3
Last observation carried forward (LOCF) approach: the last nonmissing 4 days with diary data was imputed for the week with <4 diary days.
Worst case approach: missing weeks were classified as nonresponse for that week.
.

Reviewer Comments: In analysis of efficacy for the key secondary endpoint (Responder endpoint) there was a statistically significant difference in response rates between the 450 mg treatment arm and placebo, with 54.5% of patients in the MNTX 450 mg arm responding, compared with 40.8% in the placebo arm (p = 0.0043). In the 300 mg group, 51/7% of patients were responders compared with 40.8% in the placebo arm (p = 0.0339). In the MNTX3201 CSR, the Applicant stated that statistical significance for this endpoint (the responder endpoint) utilized a hierarchical testing

procedure (Hochberg-Based Gatekeeping Procedure) which required p ≤ 0.0167 for all doses as they were significant in the primary efficacy endpoint. By these criteria, only the 450 mg dosing was interpreted to have statistical significance.

Change from Baseline in Weekly Number of RFBMs

The second key secondary endpoint was the change from baseline in weekly number of RFBMs over the entire first 4 weeks (28 days) of dosing (Table 24).

The greatest improvement from baseline in weekly number of RFBMs was noted in the 300mg and 450mg arms compared to placebo. (Appendix E).

Table 24: Second Key Secondary Efficacy Endpoint: Change in Weekly Number of RFBMs from Baseline over the First 4 Weeks of Dosing in Study 3201 (ITT Population)

Number of RFBMs	MNTX 150 mg	MNTX 300 mg	MNTX 450 mg	Placebo
Baseline				
n	201	201	200	201
Mean (Standard Deviation)	1.46 (0.911)	1.35 (0.891)	1.37 (0.789)	1.49 (1.045)
Median (Min, Max)	1.5 (0.0,4.2)	1.4 (0.0,4.4)	1.4 (0.0,3.2)	1.4 (0.0,7.5)
LOCF Approach[a]				
n	201	201	200	201
Mean (Standard Deviation)	1.98 (2.139)	2.43 (2.616)	2.44 (2.515)	1.87 1.052)
Median (Min, Max)	1.75 (-2.3,9.6)	2.08 (-2.2,12.6)	1.85 (-2.2,12.6)	1.56 (-2.4,9.3)
LS Mean[b]/LS Mean Difference (vs. Placebo)[b]	1.98/0.09	2.43/0.51	2.44/0.53	1.87
95% CI for LS Mean Difference (vs. Placebo)[b]	-0.36,0.55	0.06/0.973	0.07/0.98	
Raw p-value (vs. Placebo)[b]	0.9620	0.0237	0.0052	

Source: 3201 CSR Table 14.2.2.2.
[a] LOCF approach: the last nonmissing weekly number of RFBMs was applied for any missing week
[b] Based on ANCOVA model with treatment as effect and analysis region and baseline as covariates.

Reviewer's Comments: There were greater increases from baseline in weekly number of RFBMs in the MNTX 300mg/day and 450 mg/day group.

6.1.6 Other Endpoints -- Additional Secondary endpoints:

Additional exploratory secondary endpoints for Study MNTX3201 included:

- Proportion of subjects with RFBM within 4 hours of the first dose of study drug, fasting or non-fasting
- Time to the first RFBM after the first dose, censored at 24 hours or time of the second dose, whichever occurred first, fasting or non-fasting
- Percentage of doses resulting in RFBMs within 1, 2, 3, 4, 6, 8, and 24 hour(s).
- Weekly number of RFBMs.
- Proportion of subjects with a weekly RFBM rate ≥ 3 and an increase of ≥ 1 in the weekly RFBM rate from baseline for the specific week.
- Proportion of subjects responding (responder/non-responder) to study drug over the entire 12-week treatment period, where a responder is having ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks.
- Proportion of subjects responding (responder/non-responder) to study drug over the entire 12-week treatment period, where a responder is having ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks and including ≥ 3 of the last 4 weeks of treatment.
- Proportion of subjects achieving ≥ 3 RFBMs per week.
- Proportion of subjects with an increase of ≥ 1 in the weekly RFBM rate from baseline.

As previously stated, the Division does not find endpoints of the evaluation of the occurrence of a RFBM within 4 hours of study drug to be clinically relevant. While the *key* secondary endpoints were a significant focus in this NDA, the majority of the secondary endpoints are not reviewed in detail.

The responder endpoint used for the Phase 3 study for Relistor ® SC approval for its use in subjects with OIC in subjects with chronic non-cancer pain (CNMP) was the proportion of subjects achieving ≥ 3 RFBMs per week for 3 of the 4 week period, with an increase of ≥1 RFBM/week over baseline. This endpoint was not assessed as a secondary endpoint in MNTX3201, however, the applicant assessed the proportion of subjects achieving at least 3 RFBMs per week in each of the 4 weeks (weeks 1 – 4).

The Applicant stated that in Study MNTX3201, the proportion of subjects achieving ≥ 3 RFBMs per week were numerically greater in the MNTX 450 mg/day MNTX treatment group than in the placebo group at most weeks during the QD and PRN treatment periods. This data is shown in Table 25.

Table 25: Proportion (%) of Subjects Achieving at Least 3 RFBMs per Week (LOCF) during Weeks 1-4 of Study MNTX3201 (Exploratory Endpoint)

Subjects Achieving ≥3 RFBMs/Week	MNTX 150 mg N=201	MNTX 300 mg N=201	MNTX 450 mg N=200	Placebo N=201
Week 1				
Yes – n/N (%)	120/201 (59.7%)	125/201 (62.2%)	129/200 (64.5%)	113/201 (56.2%)
% Difference (vs. Placebo	3.5%	6.0%	8.3%	
95% CI for % Diff (vs. Placebo	(-6.2%, 13.1%)	(-3.6%, 15.6%)	(-1.3%, 17.8%)	
Odds Ratio (OM/Placebo) [1]	1.15	1.29	1.48	
95% CI for Odds Ratio [1]	(0.78,1.72)	(0.86,1.93)	(0.98,2.22)	
P-value (vs. Placebo) [1]	0.4800	0.2143	0.0615	
Week 2				
Yes – n/N (%)	118/201 (58.7%)	124/201 (61.7%)	126/200 (63.0%)	109/201 (54.2%)
% Difference (vs. Placebo	4.5%	7.5%	8.8%	
95% CI for % Diff (vs. Placebo	(-5.2%, 14.2%)	(-2.2%, 17.1%)	(-0.8%, 18.4%)	
Odds Ratio (OM/Placebo) [1]	1.21	1.37	1.46	
95% CI for Odds Ratio [1]	(0.82,1.80)	(0.92,2.04)	(0.98,2.18)	
P-value (vs. Placebo) [1]	0.3413	0.1247	0.0660	
Week 3				
Yes – n/N (%)	119/201 (59.2%)	126/201 (62.7%)	114/200 (57.0%)	118/201 (58.7%)
% Difference (vs. Placebo	0.5%	4.0%	-1.7%	
95% CI for % Diff (vs. Placebo	(-9.1%, 10.1%)	(-5.6%, 13.5%)	(-11.4%, 8.0%)	
Odds Ratio (OM/Placebo) [1]	1.03	1.18	0.97	
95% CI for Odds Ratio [1]	(0.69,1.54)	(0.79,1.77)	(0.65,1.45)	
P-value (vs. Placebo) [1]	0.8687	0.4112	0.8739	
Week 4				
Yes – n/N (%)	111/201 (55.2%)	118/201 (58.7%)	119/200 (59.5%)	108/201 (53.7%)
% Difference (vs. Placebo	1.5%	5.0%	5.8%	
95% CI for % Diff (vs. Placebo	(-8.2%, 11.2%)	(-4.7%, 14.7%)	(-3.9%, 15.5%)	
Odds Ratio (OM/Placebo) [1]	1.06	1.24	1.30	
95% CI for Odds Ratio [1]	(0.72,1.58)	(0.84,1.85)	(0.87,1.93)	
P-value (vs. Placebo) [1]	0.7587	0.2813	0.2004	

Source: Table 14.2.4.4a CSR Study MNTX3201

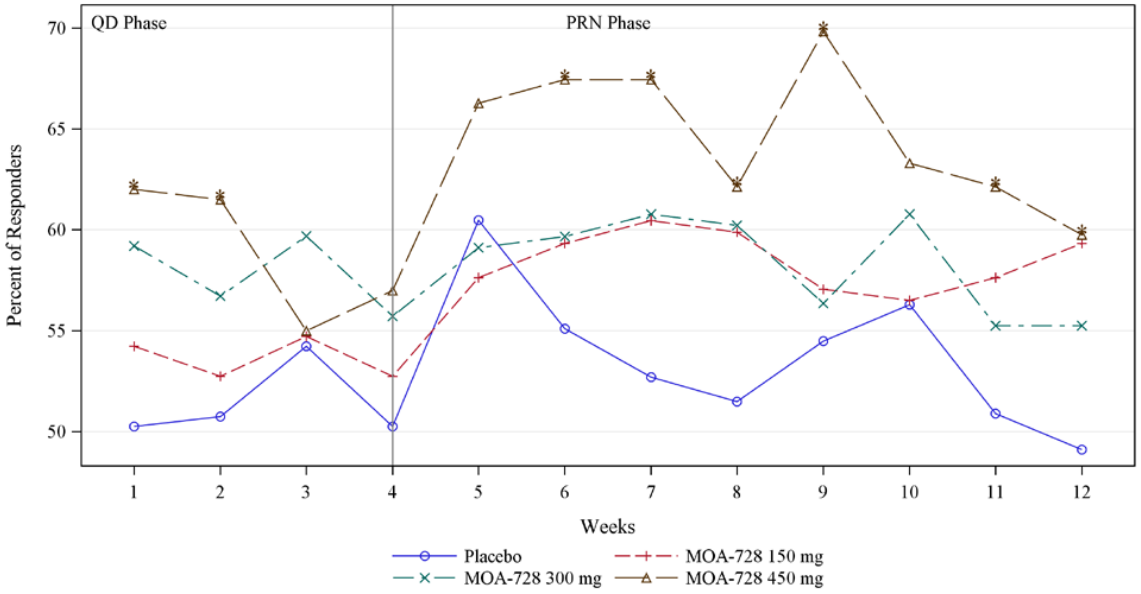
Only the key secondary endpoints (study drug responder and change in weekly RFBMs) were controlled for multiplicity, and the additional secondary endpoints are not considered for labeling.

Reviewer Comments: The data was reviewed. The percentage of patients achieving ≥ 3 RFBMs per week was numerically greater in the MNTX 450 mg/day compared with

placebo during weeks 1 and 2 however, the results during weeks 3 and 4 were similar between MNTX 450mg/day and placebo.

Weekly Responder:
A weekly responder was defined as the proportion of subjects with a weekly RFBM rate ≥ 3 and an increase of ≥ 1 in the weekly RFBM rate from baseline for the specific week. The sponsor also assessed the proportion of subjects responding to study drug over the entire 12-week treatment period, as is shown in Figure 3.

Figure 3: Proportion of subjects responding (responder/nonresponder) to study drug over the entire 12-week treatment period



Source: Figure 9 MNTX3201 CSR
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward; MNTX or MOA-728 = methylnaltrexone; PRN = as needed; QD = daily.

Reviewer Comments: The applicant's analysis appears to suggest a greater proportion of responders in the MNTX treatment arms over 12 weeks of treatment, with the 450 mg dose showing the highest response rate throughout. There did appear to be a decrease in response in the 450 mg group at Week 3 and again after 9 weeks of treatment. While the use of prn dosing after week 4 confounds interpretation of the data, it is reassuring that there appears to be continued response to MNTX 450 mg over 12 weeks of treatment.

Responder to Study Drug over Entire 12 Weeks of Treatment:

The Applicant assessed the proportion of responders over the 12-week treatment period, and an overall response was defined as ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks. A greater proportion of overall responders was reported in the 450 mg/day MNTX group versus placebo (42.0% vs 29.4%) as shown in Table 26.

Table 26: Overall Responders with Durability for the Last Month – Proportion (%) of Subjects Responding to Study Drug for ≥9 of 12 Weeks Including ≥ 3 of the Final 4 Weeks of Treatment (ITT Population)

Responders[a]	**MNTX 150 mg**	**MNTX 300 mg**	**MNTX 450 mg**	**MNTX 450 mg**
N	201	201	200	20
LOCF Approach[b]				
Yes, n (%)	76 (37.8)	71 (35.3)	84 (42.0)	59 (29.4.)
Percentage Difference (vs Placebo)	8.5	6.0	12.6	--
95% CI for % Difference (vs. Placebo)	(-0.7%, 17.7%)	(-3.2%, 15.1%)	(3.4%, 21.9%)	
P-value (vs Placebo)[c]	0.0616	0.2479	0.0063	--

Source: Table 21, CSR MNTX3201
Abbreviations: ITT = intent-to-treat; LOCF = last observation carried forward; MOA-728 = MNTX or methylnaltrexone; RFBM = rescue-free bowel movement
a Response with durability for the last month was defined as ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks and including ≥ 3 of the final 4 weeks of treatment. For Weeks 1 – 4, the weekly number of RFBMs was calculated as 7 × total RFBMs in a week/all nonmissing assessment days in the week. The weekly number of RFBMs was set to missing for any week when the subjects completed < 4 diary days. For Weeks 5 – 12, the weekly number of RFBMs was calculated as 7 × total RFBMs in a week/total number of dosing days in the week. RFBM was defined as a bowel movement without laxative use within 24 hours prior to bowel movement. If a subject did not receive concomitant daily opioid treatments during a week, the subject was considered to have no RFBMs for that week.
b LOCF approach: For Weeks 1 – 4, the last nonmissing 4 days with diary data was imputed for the week with < 4 diary days. For Weeks 5 – 12, the last nonmissing weekly number of RFBMs was applied to any missing weeks.
c Based on logistic regression model with treatment as effect and analysis region as a covariate.
d Worst case approach: missing weeks were classified as nonresponse for that week.

Reviewer comments: As noted in Table 26, the 450 mg treatment arm had a numerically higher number of responders over 12 weeks, compared to the placebo arm. While the use of PRN dosing after Week 4 can confound the interpretation of these results, this reviewer believes that the information is consistent with the trend of efficacy of response with MNTX 450 mg and with the experience of durability noted for Relistor® SC.

Overall Responder with Durability for the last month:

To further assess the durability of response, the Applicant assessed overall responders over the 12-week treatment period t including a response for the last month on study drug. Response and durability for the last month was thus defined as ≥ 3 RFBMs a week, with an increase of ≥ 1 RFBM for the specific week over baseline, for ≥ 75% of the weeks and including ≥ 3 of the last 4 weeks of treatment.

Table 27: Overall Responders-Proportion (%) of Subjects Responding to Study Drug for ≥9 of 12 Weeks of the treatment Period (ITT Population)

Responders[a]	**MNTX 150 mg**	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
N	201	201	200	201
LOCF Approach[b]				
Yes, n (%)	85 (42.3)	85 (42.3)	102 (51.0)	72 (35.8)
Percentage Difference (vs Placebo)	6.5	6.5	15.2	--
P-value (vs Placebo)[c]	0.1545	0.2166	0.0016	--

Source: Table 20 MNTX3201 Study report

Proportion of subjects with improvement in BSS with an increase of ≥ 1 in the weekly RFBM rate from baseline.

Reviewer Comments: (b) (4)

The results in Table 27 suggest greater response with MNTX 450 mg compared to placebo. (b) (4) *sponsor did not control for multiplicity during the entire length of study MNTX3201. However, as noted in commentary regarding Table 26, this reviewer believes that the information is consistent with the trend of efficacy and this reviewer does not agree that these results support that there is a clear durability of response with MNTX 450 mg and with the experience of durability noted for Relistor® SC. demonstrated trending of higher number of responders in both analyses over placebo, however, the interpretation of this response may confounded by the consistency use of the PRN phase* (b) (4)

Furthermore, these results are confounded, as the applicant used PRN dosing after week 4 of the study. (b) (4)

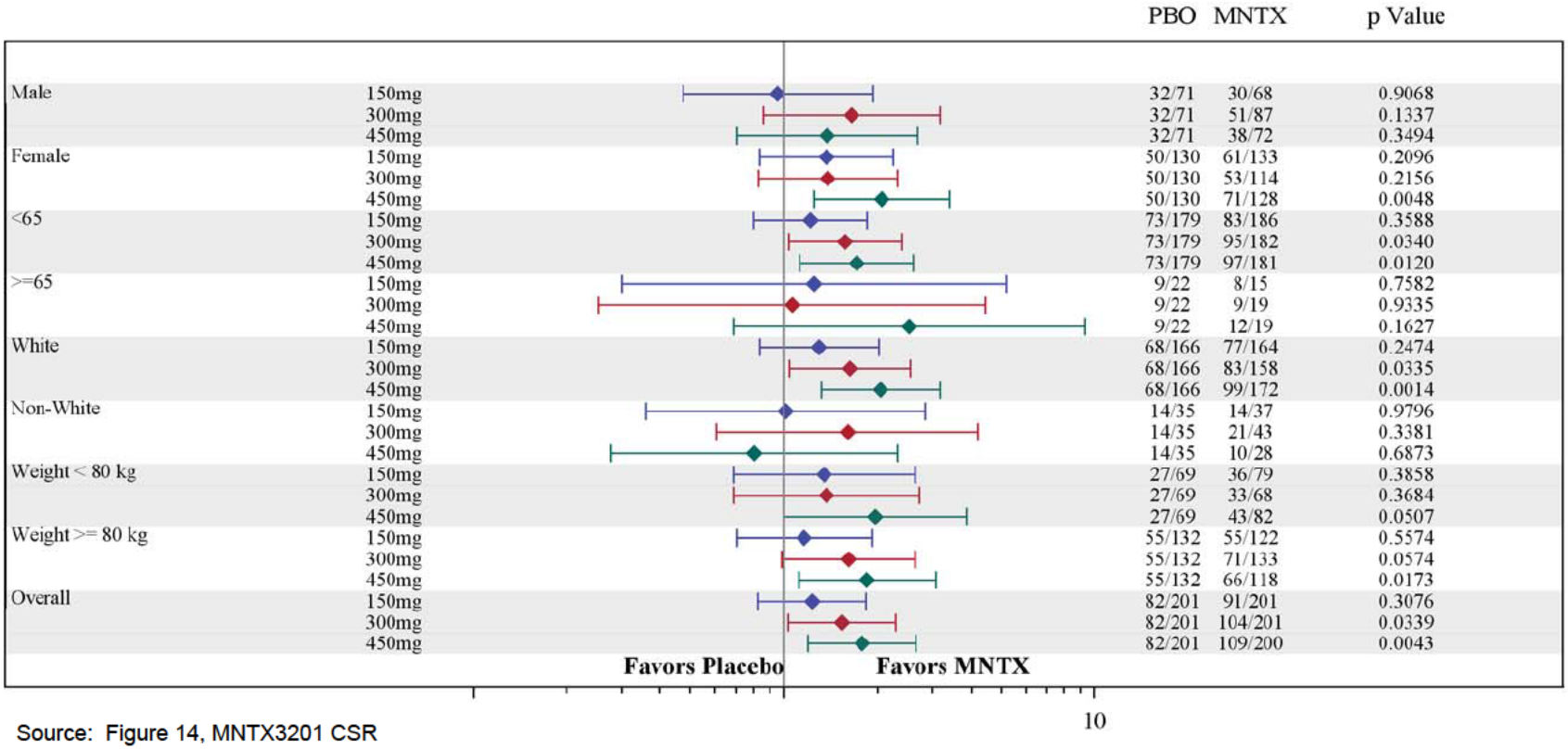
6.1.7 Subgroup Analyses

The primary endpoint and key secondary endpoint were analyzed for each of the subgroups listed below in study MNTX3201, and the results of the key secondary endpoint (responder endpoint) are presented in Figure 4. The Applicant stated these outcomes were consistent with those found in study SC MNTX 3356 but the number of subjects in study 3201 was too few to perform meaningful analyses of population subgroups.

- Gender
- Age
- Race
- Weight
- Baseline daily opioid dose
- Primary pain condition

Figure 4: Subgroup Analysis of Key Secondary Efficacy Endpoint #1: Proportion of Drug Responders (ITT Population)
MNTX 3201

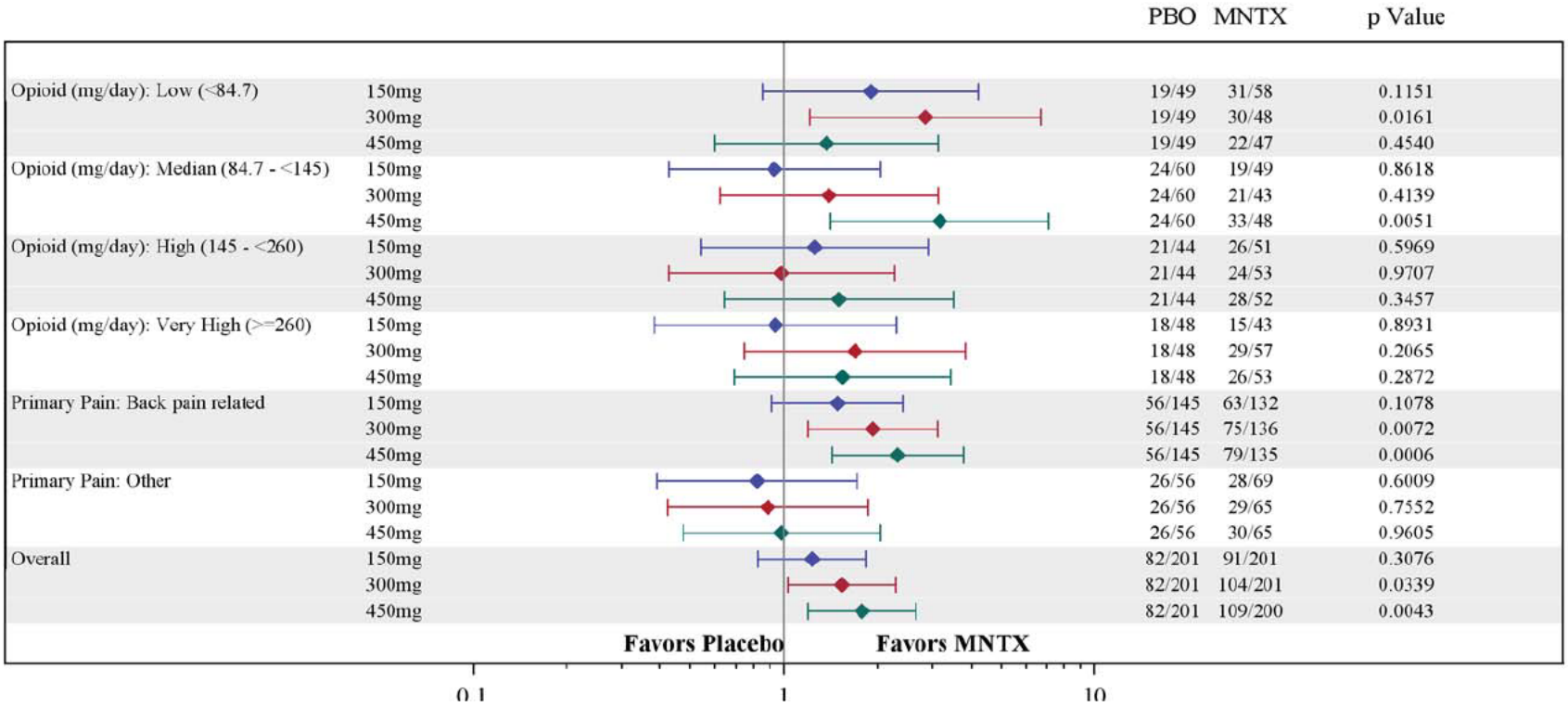
Subgroups by Demographic Characteristics



Source: Figure 14, MNTX3201 CSR

Figure 5: (continued): Subgroup Analysis of Key Secondary Efficacy Endpoint #1: Proportion of Drug Responders (ITT Population) MNTX 3201

Subgroups by Baseline Characteristics



Source: Figure 14, MNTX3201 CSR

Gender

Study MNTX3201 contained a total number of 505 female subjects and 229 male subjects. The applicant assessed the key secondary responder endpoint by gender as is shown in *Table 28*.

Table 28: Key Secondary Efficacy Endpoint 1 (Responder Endpoint): Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Gender Population: ITT

	MNTX 150 mg	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
Male	**(n=68)**	**(n=87)**	**(n=72)**	**(n=71)**
Yes -n(%)	30 (44.1%)	51 (58.6%)	38 (52.8%)	32 (41.1%)
% Diff. (vs. Placebo)	-1.0%	13.6%	7.7%	
Odds Ratio	0.96	1.65	1.38	
p-value (vs. Placebo)	0.9068	0.1337	0.3494	
Female	**(n=133)**	**(n=114)**	**(n=128)**	**(n=130)**
Yes -n(%)	61 (45.9%	53 (46.5%)	71 (55.5%)	50 (38.5%)
% Diff. (vs. Placebo)	7.4%	8.0%	17.0%	
Odds Ratio	1.37	1.39	2.07	
p-value (vs. Placebo)	0.2096	0.2156	0.0048	

Source: 14.2.21b MNTX3201 CSR. **A Responder was defined as having >=3 RFBMs/week and >= 1 RFBM/week increase from baseline, for at least 3 weeks of Weeks 1 - 4. Weekly #** of RFBMs was calculated as 7 x total RFBMs in a week/all non-missing assessment days in the week. Weekly # of RFBMs was set to missing for any week when a subject completed <4 diary days in a week. A RFBM was a bowel movement without laxative use within 24 hrs. prior to the bowel movement. If Subject didn't take any opioid dose during a week, subject was considered no change from baseline for the week.

Reviewer Comments: More women than men were enrolled. The subgroup analysis by gender indicates a higher response rate with MNTX 450 mg, compared to placebo, in both men and women, though women appeared to have a slightly higher response. The results failed to reach statistical significance for men at any dose, however, the number of sample sizes for male patients was small, impacting the ability to show statistical significance. These were post-hoc analyses and not controlled for multiplicity, but appear to show consistency across gender.

Age

The majority of subjects (78.5%) were between 40 and 65 years of age. The applicant completed a subgroup analysis using the Responder endpoint as shown in Table 29.

Table 29: Key Secondary Efficacy Endpoint 1 (Responder Endpoint) : Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Age Group Population: ITT

	MNTX 150 mg	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
<40	**(n=28)**	**(n=27)**	**(n=26)**	**(n=22)**
Yes -n(%)	13 (46.4%)	14 (51.9%)	16 (61.9%)	6(27.3%)
% Diff. (vs. Placebo)	19.2%	24.6%	34.3%	
Odds Ratio	2.74	2.83	9.20	
p-value (vs. Placebo)	0.1187	0.1026	0.0090	
40 -65	**(n=160)**	**(n=155)**	**(n=157)**	**(n=158)**
Yes -n(%)	72 (45.0%)	81 (52.3%)	83 (52.9%)	68 (43.0%)
% Diff. (vs. Placebo)	2.0%	9.2%	9.8%	
Odds Ratio	1.11	1.42	1.50	
p-value (vs. Placebo)	0.6466	0.1247	0.0739	
>65	**(n=15)**	**(n=19)**	**(n=19)**	**(n=22)**
Yes -n(%)	8 (53.3%)	9 (47.4%)	12 (63.2%)	9 (40.9%)
% Diff. (vs. Placebo)	12.4%	6.5%	22.2%	
Odds Ratio	1.25	1.06	2.52	
p-value (vs. Placebo)	0.7582	0.9335	0.1627	

Tables 14.2.2.1c Study MNTX3201 and information provided by the Applicant and IR response from 24 February 2016. **A Responder was defined as having >=3 RFBMs/week and >= 1 RFBM/week increase from baseline, for at least 3 weeks of Weeks 1 - 4. Weekly**

Reviewer Comments: Age grouping were initially divided into <65 years and > 65 years. In this reviewer's opinion, there was insufficient representation of patients >65 years to appropriately interpret the results, and the < 65 cohort is too broad to make clinical commentary. The applicant was asked to reanalyze the subgroup analysis by age using 3 age cohorts (<40, 40-65, and > 65 years). Review of this newly organized data showed higher response rates with MNTX 450 mg across age cohorts. While the number of patients > 65 and < 40 were small, the results appeared consistent to those seen in the 40 – 65 year age group.

Race

In study MNTX3201, 660 patients self-identified as white (82.2%), 120 patients were black (14.9%), 1 was Asian (0.1%), 8 were American Indian or Alaska Native (1%), 2 were Native Hawaiian or Pacific Islander (0.2%) and 10 self-identified as Other (1.2%). Results of the Applicant's subgroup analysis by race are shown in Table 30 below.

Table 30: Key Secondary Efficacy Endpoint 1 (Responder Endpoint) : Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Race: ITT

	MNTX 150 mg	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
White	**(n=164)**	**(n=158)**	**(n=172)**	**(n=166)**
Yes -n(%)	77 (47.0%)	83 (52.5%)	99(57.6%)	68 (41.0%)
% Diff. (vs. Placebo)	6.0%	11.6%	16.6%	
Odds Ratio	1.30	1.63	2,05	
p-value (vs. Placebo)	0.2474	0.0335	0.0014	
Non-White	**(n=37)**	**(n=43)**	**(n=28)**	**(n=35)**
Yes -n(%)	14 (37.8%)	21 (48.8%)	10 (35.7%)	14 (40.0%)
% Diff. (vs. Placebo)	-2.2%	8.8%	-4.3%	
Odds Ratio	1.01	1.60	0.80	
p-value (vs. Placebo)	0.9796	0.3381	0.6873	

Source: Tables 14.2.2.1c 14.2.2.1d, Study MNTX3201 and Information Request to Applicant. **A Responder was defined as having >=3 RFBMs/week and >= 1 RFBM/week increase from baseline, for at least 3 weeks of Weeks 1 - 4. Weekly**

Reviewer Comments: This reviewer notes that there were a smaller percentage of responders who were non-white and randomized to the 450 mg arm compared to placebo. The subjects who were non-white and randomized to the 150 mg arm also reported less responders than subjects randomized to placebo. As the numbers of subjects who were non-white are significantly lower than those who were white, a direct comparison of responder rate is difficult to interpret. This reviewer believes that there is insufficient information to interpret these differences of possible ethnic based differences in response to methylnaltrexone tablets.

Baseline Opioid Dose

Baseline opioid dose was assessed via morphine equivalents and divided into four categories: low (<84.7 mg/day), medium (84.7- <145 mg/day), high (145 - < 260 mg/day) and very high (>= 260 mg/day). The groups appeared to be similar in size and distribution as noted in Table 31.

Table 31: Key Secondary Efficacy Endpoint 1 (Responder Endpoint): Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Baseline Opioid morphine equivalent dose groups:

	MNTX 150 mg	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
<84.7 (LOW)	**(n=49)**	**(n=58)**	**(n=47)**	**(n=49)**
Yes -n(%)	31 (53.4%)	30 (62.5%)	22 (46.8%)	19 (38.8%)
% Diff. (vs. Placebo)	14.7%	23.7%	8.0%	
Odds Ratio	1.91	2.86	1.37	
p-value (vs. Placebo)	0.1151	0.0161	0.4540	
84.7 to ≤145 (MEDIUM)	**(n=49)**	**(n=43)**	**(n=48)**	**(n=60)**
Yes -n(%)	19 (38.8%)	21 (48.8%)	33 (68.8%)	24 (40.0%)
% Diff. (vs. Placebo)	-1.2%	8.8%	28.8%	
Odds Ratio	0.93	1.40	3.17	
p-value (vs. Placebo)	0.8618	0.4139	0.0051	
145 TO ≤ 260 (HIGH)	**(n=51)**	**(n=53)**	**(n=52)**	**(n=44)**
Yes -n(%)	26 (51.0%)	24 (45.3%)	28 (53.8%)	21 (47.7%)
% Diff. (vs. Placebo)	3.3%	-2.4%	6.1%	
Odds Ratio	1.26	0.98	1.5	
p-value (vs. Placebo)	0.5969	0.9707	0.3457	
≥260 (VERY HIGH)	**(n=43)**	**(n=57)**	**(n=53)**	**(n=48)**
Yes -n(%)	15 (34.9%)	29 (50.9%)	26 (49.1%)	18 (37.5%)
% Diff. (vs. Placebo)	-2.6%	13.4%	11.6%	
Odds Ratio	0.94	1.69	1.55	
p-value (vs. Placebo)	0.8931	0.2065	0.2872	

Source: Table 14.2.2.1f Study MNTX3201. **A Responder was defined as having >=3 RFBMs/week and >= 1 RFBM/week increase from baseline, for at least 3 weeks of Weeks 1 - 4. Weekly**

Reviewer Comment: Statistically significant efficacy was only observed in the Medium category of (84.7 to ≤145) Baseline opioid equivalence for the to-be-marketed 450 mg dose, however, the sample sizes are small when subdividing based on baseline opioid use, making inferences challenging. In addition, these were post-hoc analyses and not controlled for multiplicity, so statistical significance should not be claimed. Overall, this reviewer believes the data support that MNTX 450mg is effective across baseline opioid morphine equivalent dose groups.

Primary Pain Condition:

The applicant assessed the impact of patients' primary pain condition on their response as is shown in Table 32.

Table 32: Key Secondary Efficacy Endpoint 1 (Responder Endpoint) Proportion (%) of subjects responding to study drug during weeks 1 to 4 by Baseline primary pain condition using the Responder Endpoint

	MNTX 150 mg	MNTX 300 mg	MNTX 450 mg	Placebo
Back Pain	**(n=132)**	**(n=136)**	**(n=135)**	**(n=145)**
Yes -n(%)	63 (47.7%)	75 (55.1%)	79 (58.5%)	56 (38.6%)
% Diff. (vs. Placebo)	9.1%	16.5%	19.9%	
95% CI for % Difference (vs. Placebo)	(-2.5%, 20.7%)	(5.0%, 28.0%)	(8.4%, 31.4%)	
Odds Ratio	1.49	1.93	2.33	
p-value (vs. Placebo)	0.1078	0.0072	0.0006	
Other[a]	**(n=69)**	**(n=65)**	**(n=65)**	**(n=56)**
Yes -n(%)	28 (40.6%)	29 (44.6%)	30 (46.2%)	26 (46.4%)
% Diff. (vs. Placebo)	-5.8%	-1.8%	-0.3%	
95% CI for % Difference (vs. Placebo)	(-23.3%, 11.6%)	(-19.6%, 16.0%)	(-18.1%, 17.5%)	
Odds Ratio	0.82	0.89	0.98	
p-value (vs. Placebo)	0.6009	0.7552	0.9605	

Source: Table 14.2.2.1g MNTX3201 CSR
[a] "Other" includes cervical/neck pain, fibromyalgia, osteoarthritis, neuropathic pack pain. "Other" diagnoses such as well as reflux sympathetic dystrophy or Chiari malformation were also included but were reported by a single subject per study arm, at most. **A Responder was defined as having >=3 RFBMs/week and >= 1 RFBM/week increase from baseline, for at least 3 weeks of Weeks 1 - 4. Weekly**

Reviewer Comments: The subgroup analysis using baseline pain diagnosis appeared to suggest that MNTX 450 mg was less effective in patients with a primary diagnosis other than back pain. Review of these diagnoses in the demographic dataset provided by the Sponsor (POP.xpt) noted that the most common primary pain diagnosis (PPDIAG) in all groups was back pain. As the sample size was small for patients with a PPDIAG other than back pain, and the placebo response rate was higher in this group, conclusions difficult to make.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The oral methylnaltrexone doses chosen for the single phase 3 study (150mg, 300mg, and 450mg) were selected based on the induction of laxation results following single doses of 150mg, 300, 450, and 600mg in study 2201. Study 2201 was a 28 day, multicenter, randomized, double blind, placebo controlled, dose ranging, adaptive design study where a greater proportion of patients reported an RFBM within 4 hours of ingestion of 450mg methylnaltrexone compared with placebo. There was no increase in response seen with the 600mg dose.

Study MNTX 3201 supports that the 450 mg dose appears more effective than the 300 mg dose in both the Primary endpoint and the Responder endpoint, while the 300 mg

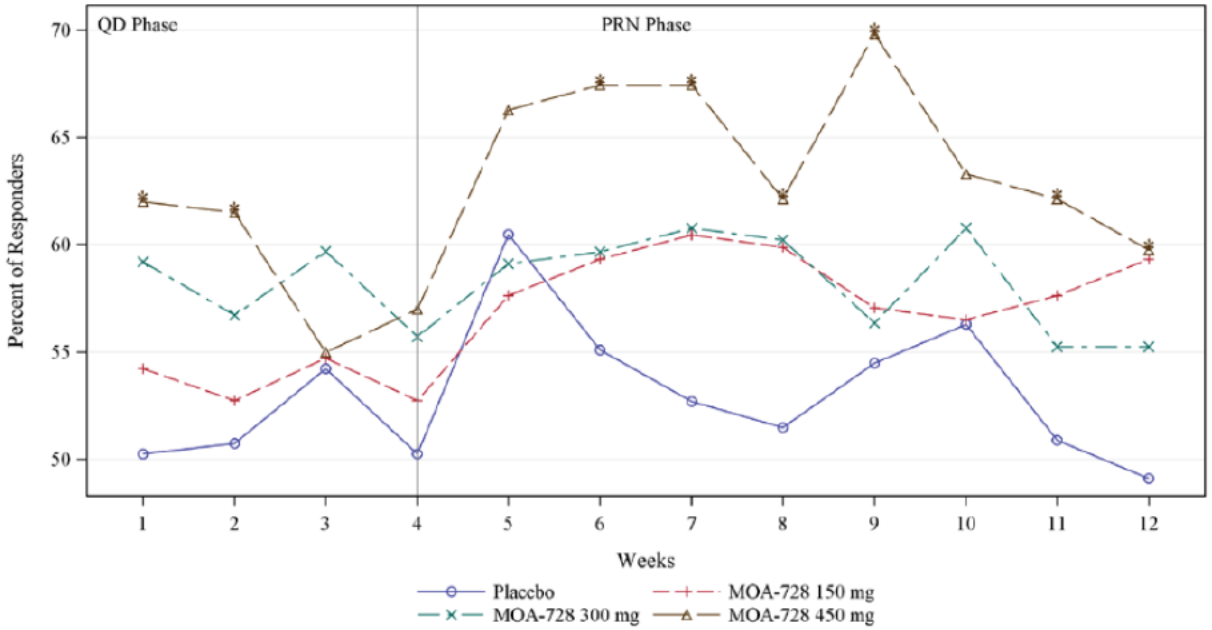
dose only demonstrated efficacy in the Primary endpoint and not the Responder endpoint.

Reviewer Comments: The Applicant is proposing marketing of the 450 mg once daily dose for most adult patients. In the oral development program, study 2201 demonstrated GI related AE at 600 mg dosing without additional observed efficacy, so the assessment of 150 mg, 300 mg, and 450 mg in the phase 3 Study was appropriate. Study MNTX3201 does demonstrate overall efficacy at the 450 mg dose, and this dose appears more effective than the 300 mg dose, when looking at a number of pre-specified endpoints and subgroup analyses. This reviewer concurs with this dose for most adult patients.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see Section 6.1.4 for a discussion of durability of treatment through 12 weeks. Table 27 notes the proportion (%) of responders to oral methylnaltrexone ≥9 of 12 Weeks of the treatment period. The Applicant also attempted to evaluate the durability of response, defined as ≥3 RFBMs a week, with an increase of ≥1 RFBM for the specific week for baseline for ≥75% of the weeks and including ≥3 of the final 4 weeks of treatment (Figure 6 and Table 33)

Figure 6: Proportion of Subjects with ≥ 3 Rescue-Free Bowel Movements per Week and an Increase of ≥1 Rescue-Free Bowel Movement from Baseline (ITT Population, LOCF Analysis)



Source: Figure 9, MNTX3201 Study Report

Table 33: Overall Responders with Durability for the Last Month- Proportion (%) of Subjects Responding to Study Drug for ≥9 of 12 weeks Inclusive of ≥3 of the Final 4 Weeks of Treatment (ITT Population)

Responders[a]	**MNTX 150 mg**	**MNTX 300 mg**	**MNTX 450 mg**	**Placebo**
N	201	201	200	201
LOCF Approach[b]				
Yes, n (%)	76 (37.8)	71 (35.3)	84 (42.0)	59 (29.4)
Percentage Difference (vs Placebo)	8.5	6.0	12.6	--
P-value (vs Placebo)[c]	0.0616	0.2479	0.0063	--
Worst Case Approach[d]				
Yes, n (%)	67 (33.3)	56 (27.9)	71 (35.5)	55 (26.9)
Percentage Difference (vs Placebo)	6.5	1.0	8.6	--
P-value (vs Placebo)c	0.1253	0.9792	0.0513	--

Source: Table 21 MNTX3201 Study Report

Reviewer Comments: *As previously stated, the applicant's analysis appears to suggest a greater proportion of responders in the MNTX treatment arms over 12 weeks of treatment, with the 450 mg dose showing the highest response rate throughout.* (b) (4)

While the results in

Table 33 suggest greater response with MNTX 450 mg compared to placebo, (b) (4) the sponsor did not control for multiplicity and, these results may be confounded, as the applicant used PRN dosing after week 4 of the study. However, given the totality of evidence throughout the entire duration of the study (Appendix D) this reviewer does believe the current results support an overall claim of durability of response in 9 of 12 weeks of treatment.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant also evaluated the protocol specified primary efficacy endpoint and the 1st key secondary efficacy endpoint (responder endpoint) as co-primary endpoints in an attempt to demonstrate correlation between these endpoints. These results are shown in Table 34 below.

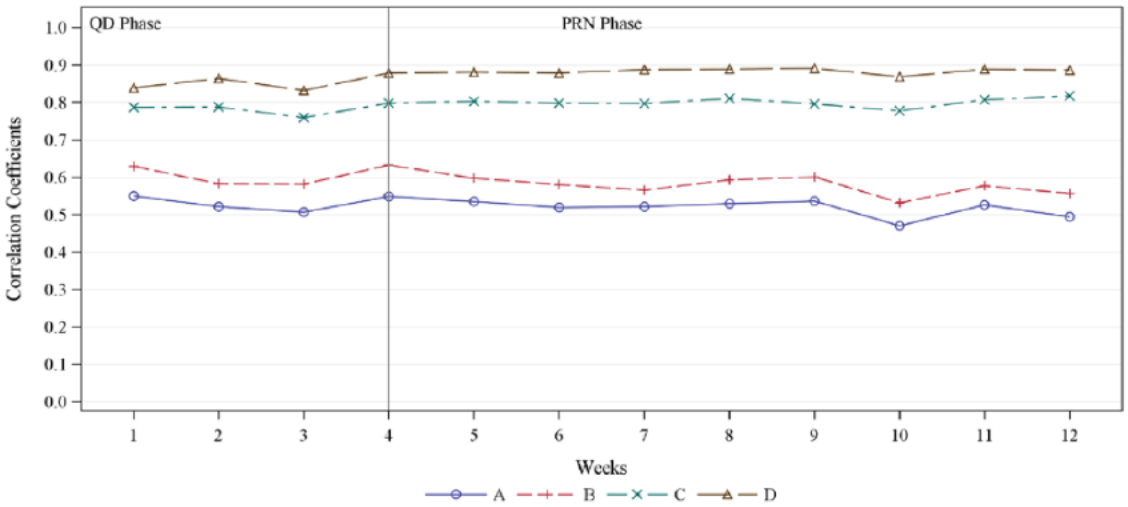
Table 34: Analysis of Coprimary Endpoints (ITT Population)

Daily Dose	Coprimary endpoints[a]	Raw p-value[b]	Adjusted p-value[c]	Decision rule[d]
150 mg	1	0.1692	0.3076	Not statistically significant
	2	0.3076		
300 mg	1	0.0016	0.0339	Not statistically significant
	2	0.0339		
450 mg	1	<0.0001	0.0043	450 mg dose is superior to placebo
	2	0.0043		

Source: Table 17 MNTX3201 Clinical Study Report
[a] 1=protocol specified primary endpoint and 2=responder endpoint (1st key secondary endpoint)
[b] Raw p-value is based on pairwise dose comparison with placebo
[c] Adjusted p-value is pi (refer to sections 9.7.1.6 and 9.7.1.6.2 of MNTX3201 Clinical Study Report)
[d] The maximum p-value to declare significance verses placebo was 0.0167 refer to section 9.7.1.6.2 of MNTX3201 Clinical Study Report)

In addition, Pairwise correlations were graphed between the primary and both key secondary endpoints (A and B in Figure 7) to demonstrate a correlation of efficacy between the primary endpoint, which was not accepted by the Division, and the Responder endpoint which was accepted by the Division.

Figure 7: Pairwise Correlations Among the Primary and Key Secondary Efficacy Endpoints During the QD and PRN Treatment Periods (ITT Population)



Source: Figure 14.2.6. Abbreviations: ITT = intent-to-treat; QD = once daily; PRN = as needed; RFBM = rescue-free bowel movement.
Notes: A = Average percentage of dosing days that resulted in RFBMs within 4 hours of dosing (primary endpoint) by week vs. responders - subjects who had ≥ 3 RFBMs/week, with an increase of ≥ 1 RFBM/week over baseline by week (key secondary endpoint 1).
B = Average percentage of dosing days that resulted in RFBMs within 4 hours of dosing (primary endpoint) by week vs. change from baseline in the weekly number of RFBMs (key secondary endpoint 2).
C = Average percentage of dosing days that resulted in RFBMs within 24 hours of dosing by week (additional secondary endpoint) vs. responders - subjects who had ≥ 3 RFBMs/week, with an increase of ≥ 1 RFBM/week over baseline, by week (key secondary endpoint 1).
D = Average percentage of dosing days that resulted in RFBMs within 24 hours of dosing by week (additional secondary endpoint) vs. change from baseline in the weekly number of RFBMs (key secondary endpoint 2).

Source: Figure 6, MNTX3201 CSR

Reviewer Comments: The Applicant attempted to demonstrate a correlation of the efficacy between the primary and the responder endpoints. (b) (4) *Review of the correlation of coefficients in Figure 7 does suggest correlation between the primary endpoint and the responder endpoint ("A") but also a higher correlation between improved RFBM within 24 hours of dosing and the Responder endpoint - subjects who had ≥ 3 RFBMS/week with an increase of ≥1 RFBM/week over baseline, by week ("C"). While both comparisons demonstrate positive correlation of coefficients, this reviewer finds "C" to represent a more meaningful correlation and also notes that this correlation is stronger remains 0.8 (in comparison to 0.5 in "A").*

This relationship does add to the totality of evidence that demonstrates the efficacy of methylnaltrexone bromide tablets in subjects with OIC due to CNCP.

7 Review of Safety

Safety Summary

Overall, the safety profile of methylnaltrexone bromide tablets was reasonably well characterized during the oral clinical development program. A total of 1122 subjects received at least 1 dose of methylnaltrexone bromide tablets during the oral clinical development program as of 13 June 2015, the submission for the NDA.

In the Phase 3 study MNTX3201, the rates of adverse events were similar in the ITT populations, with 127 (63.2%) of patients in the placebo arm having any treatment emergent adverse event (TEAE), compared to 118 (59.0%) in the 450 mg arm,

In the Oral Placebo-controlled OIC pool (Section 7.1), serious adverse events (SAEs) were reported in 25 (2.4%) of subjects receiving any dose of oral methylnaltrexone bromide, compared to 8 (2.3%)[11]of subjects who received placebo only. The only SAEs reported in ≥1% of patients were of gastrointestinal disorders (1.5%). Rates of AEs leading to clinical trial discontinuation in the Oral Placebo-controlled OIC pool were also similar between the placebo groups and 450 mg dosage groups at 20.3% and 19.7% respectively.[12] The most common AEs resulting in study discontinuation from the combined group at 450 mg were subjects who were lost to follow-up and protocol violations, while subject withdrawal and protocol violation were the most common reasons for discontinuation in the placebo cohort.

One death occurred in a male patient enrolled a Phase 2 study (2202) who received methylnaltrexone bromide 450 mg. This death was assessed by the investigator as related to atherosclerotic disease and not related to ingestion of study drug (refer to Section 7.3.1 for narrative).

The Applicant contends that the primary clinical studies completed for the approved SC methylnaltrexone bromide 12 mg QD injection are to be used as supportive information for long-term exposure (up to 48 weeks) and safety of methylnaltrexone bromide tablets for the indication of OIC in chronic non-cancer pain. Systemic exposure, as measured by AUC, is comparable between the 12 mg QD SC dose and the proposed oral methylnaltrexone bromide tablet dose of 450 mg QD (MNPK1117). In comparison, the C_{max} of an oral 450-mg dose was only 20% of that observed in comparison to the 12 mg SC methylnaltrexone bromide injection (MNPK1117). As such, this reviewer agrees that it is appropriate to consider the long-term safety data with Relistor® SC as supportive of the safety of oral methylnaltrexone bromide.

[11] Table 13, ISS
[12] Table 18, ISS

There appear to be an increased frequency of GI related TEAEs with increasing doses of methylnaltrexone bromide tablets in both the Oral Placebo-controlled OIC pool and the Phase 3 Study MNTX3201, particularly at the 300 mg and 450 mg dosages. Abdominal pain, nausea and vomiting were the most commonly reported of these GI complaints. The frequency of these GI related TEAEs were slightly less than the rates reported in Study MNTX3356 for Relistor® SC. Cross study comparison of AEs by Preferred Terms noted a higher incidence of abdominal pain and nausea for Relistor® SC in study MNTX3356 (21.3% and 9%, respectively) compared to oral tablets in Study MNTX3201 (13.5% and 3.5%, respectively) . The rates of diarrhea, vomiting and abdominal distension were comparable between dosage forms. Importantly, the tablet formulation used during the phase 3 study differed from the proposed to-be marketed formulation. The to-be-marketed formulation was studied only in a small number of PK/BE studies, including study MNPK1001 (healthy adults without OIC) and study MNOC1111 in patients with OIC and chronic non-cancer pain. Study MNOC1111 was a randomized, double blind, placebo controlled single dose, parallel group study in 128 patients who had demonstrated a response to Relistor® SC. This study showed a higher frequency of GI related TEAEs in subjects exposed to the to-be-marketed formulation compared with the formulation used in the Phase 3 study (12 AEs in 7 subjects compared to 4 AEs in 2 subjects). This was a small single dose study, so it is difficult to make safety conclusions based on these results; however, it does bring into question whether the to-be-marketed oral formulation would be expected to have better tolerability than the approved Relistor® SQ.

This reviewer believes that the safety profile of oral methylnaltrexone bromide characterized during the clinical development program is similar to that noted in the SC methylnaltrexone bromide development program.

7.1 Methods

This safety review is based primarily upon analysis of study MNTX3201, and evaluation of the integrated summary of clinical safety (ISS) datasets (Table 35). Study MNTX3201 is the only phase 3, double-blind, placebo-controlled study included in this application. The applicant seeks approval for the 450 mg dosing regimen, thus the AEs specific for the 450 mg and placebo treatment arms will be the focus of this safety review. Study MNTX3356 (Relistor® SC) was used by the Applicant for approval of OIC in non-cancer pain **(**Table 35). Safety results from this study were included by the Applicant for comparison to the oral studies. The Oral placebo-controlled pool includes only double-blind placebo controlled studies in patients with OIC and chronic non-cancer pain, whereas the Oral Methylnaltrexone bromide-only pool also includes subject receiving study drug from all OIC studies, including open label studies.

Table 35: Safety Populations and Definitions

Safety Population	Number of Subjects		Definition
	MNTX	Placebo	
Study MNTX3201	602	201	ITT population of patients who were enrolled in study MNTX3201
Oral placebo-controlled OIC pool	1057	344	Includes ITT population from the following studies: MNTX3201, 3200A3-200-WW, 3200A3-2201-US, 3200A3-2202-WW, MNOC1111
Oral methylnaltrexone bromide-only OIC pool	1122	N/A	Includes ITT population from the following studies: MNTX3201, 3200A3-200-WW, 3200A3-2201-US, 3200A3-2202-WW, 3200A3-1113-US MNOC1111,
SC methylnaltrexone double blind placebo pool	316	177	Includes double-blind period of Study 3356 and Study 2101 (subjects with NCP and OIC)

Source: Table 8, NDA 208271, ISS

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review focused on the safety data from study MNTX3201 (Table 36) and the intended marketed dose of 450 mg. Four additional studies in the OIC placebo-controlled trials using oral methylnaltrexone bromide are summarized in the integrated summary of safety (ISS) including MNOC1111, 3200A3-200-WW, 3200A3-2201-WW, 3200A3-2202 (Table 10 and Table 37). Safety data from study 3200A3-1113-US (Table 37) was also evaluated the ISS and in the Oral methylnaltrexone bromide-only pool data.

Table 36: Description of the Phase 3 Study Primarily Reviewed in Safety Review

Clinical Trial (Phase)	Trial Design/ # of Centers	Trial Population	Treatment Arms	Number of patients by treatment entered/completed	Gender M/F Median Age (Range)
MNTX 3201 Phase 3	Randomized, double-blind, parallel-group, placebo control, dose ranging study 56 centers in US	Adult patients using opioids for at least 30 days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD).	Oral MNTX: 150 mg PO QD 300 mg PO QD 450 mg PO QD Placebo	 201/184 202/184 200/175 201/180	 299/505 52 (18-82)

Source: MNTX3201 CSR

Table 37: Additional Studies used in Analysis for the Integrated Summary of Safety

Clinical Trial (dates)	Trial Design/ # of Centers	Trial Population	Treatment Arms	Number of patients by treatment entered/completed	Gender M/F Median Age (Range)
3200A3-1113-US 10/2008 to 1/2009	Part 1: Randomized, open-label, single-dose, two-period, four-sequence, crossover Part 2: Open-label, single dose, single-period, single sequence	Adult Patients with chronic non cancer-pain who have OIC	***Part 1:*** *450 mg IR* *300 mg (b) (4)/450 mg IR* *450 mg IR/ 300 mg (b) (4)* ***Part 2:*** *450 mg (b) (4)*	**19/14** **10/7** **11/8** **25/23**	38/27 51.0 (30-75)
MNOC 1111 8/2014 to 6/2015	Single dose, randomized, double-blind, placebo-controlled, parallel group study to evaluate the clinical efficacy and safety of oral methylnaltrexone tablets in subjects with chronic non-cancer pain and OIC who initially responded to subcutaneous methylnaltrexone bromide	Adult patients with chronic OIC for non-cancer pain responding to subcutaneous MNTX for at least 30 days.	450 mg QD (b) (4) tabs (37) 450 mg QD (b) (4) tabs (38) Placebo (37)	**37/37** **38/37** **37/37**	58/70 53.0 (21-85)
3200A3-200-WW 8/2006 to 2/2007	Phase 2, 28 day, multicenter, randomized, double blind, placebo controlled, dose ranging, adaptive design	Adult patients using opioids for at least 30 days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD).	10mg QD 50 mg QD 150 mg QD 300 mg QD 450 mg QD Placebo	31/26 36/33 33/32 45/41 47/35 44/38	97/139 51.0 (19-87)
3200A3-2201-US 12/2009 to 3/2010	Phase 2, 28 day, multicenter, randomized, double blind, placebo controlled, dose ranging, adaptive design	Adult patients using opioids for at least 30 days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD)	150 mg QD 300 mg QD 450 mg QD 600 mg QD Placebo	**7/6** **14/13** **35/27** **35/32** **33/28**	48/74 49.0 (19-78)
3200A3-2202-	28 day, multicenter, randomized, double	Adult patients using opioids for at least 30	:	**19/18**	51/88

WW 1/2008 to 6/2008	blind, placebo controlled, parallel–group dose ranging, study	days with chronic non-malignant pain with opioid induced bowel dysfunction (OIBD).	150 mg QD (19) 300 mg QD (20) 450 mg QD (30) 600 mg QD (30) Placebo (39)	**20/18** **30/25** **30/22** **29/29**	50.5 (26-77)

Sources: 3200A3-113-US CSR, 3200A3-200-WW CSR, 3200A3-2201-US CSR, 3200A3-2202-WW CSR, MNOC 1111 CSR

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were classified and coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (Version 13.0).

Treatment-emergent AEs (TEAEs) were defined as any event with a start date occurring on or after the first dose date of the study drug or, if pre-existing, worsening after the first dose date of the study drug. Drug related TEAEs were defined as occurring within 14 days of ingestion of the study drug. They were grouped by body system/organ class (SOC), preferred term (PT) and intensity. If a subject reported the same AE more than once, then that subject was counted only once for the summary of that AE, using the most severe intensity.

AEs were collected from patient observations, physical exam findings, laboratory values and EKG changes. All AEs, SAEs, TEAEs leading to premature withdrawal from the study, including deaths, were placed in separate listings.

TEAEs of special interest for assessment included TEAEs for Major Adverse Cardiac Events (MACE), bowel perforation and opioid withdrawal. Patients who experienced specific events relevant to cardiac safety were also evaluated for concurrent or prior TEAEs that may reflect possible symptoms of opioid withdrawal. Patients that met DSM-V criteria for opioid withdrawal exhibited a cluster of symptoms with greater than 3 of the following symptoms within minutes to several days after administration of study drug: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, or insomnia. This analysis was performed with and without the inclusion of GI symptoms as they are associated with the use of PAMORA.

AE preferred terms were summarized by numbers and percentages of subjects and were sorted by MedDRA SOC. AE variables are described in Table 38.

Table 38: Summary of Adverse Event Variables

AE Variable	Description
Overall Summary of AEs	Summary of AE outcomes including at least 1 AE, TEAE, related TEAE, severe TEAE, SAE, related SAE, TEAE leading to permanent discontinuation of study drug, or death.
Pre-treatment AEs	Any AE with onset dates before the start of treatment (double-blind medication for placebo-controlled studies and active treatment for open-label).
AEs assessed in the OOWS and SOWS questionnaires	AEs measured during the OOWS and SOWS assessments [a]
TEAEs	Any AE with an onset on or after the date of first dose of study medication and prior to 14 days after the date of last dose of study medication were classified as treatment-emergent.
TEAE by Intensity	Mild, Moderate, Severe, Life-threatening
Related TEAEs	AEs judged by the Investigator to be Possibly, Probably or Definitely related to the study drug
SAEs	As defined by CFR Part 312.32(a) [b]
TEAEs Resulting in Permanent Discontinuation of Study Drug	TEAEs resulting in permanent discontinuation of study drug.
Deaths	An event that resulted in the death of the subject.

Source: NDA 208271 ISS
Abbreviations: AE= adverse event; SAE=serious adverse event; TEAE=Treatment emergent adverse event
[a] Integrated Summary of Safety Section 2.3.6.3
[b] Integrated Summary of Safety Section 2.3.8.7

AE intensity was classified by investigators into 4 categories, mild, moderate, severe, and life threatening. If a subject had multiple occurrences of the same SOC or preferred term, then only the most severe event was summarized in tables. Missing severity assessments were considered as severe.

The Applicant's categorization of adverse events was assessed by comparing the reported terms to the preferred terms (PT) used by investigators and subjects in both Phase 2 and Phase 3 studies. Some splitting of terms related to AEs of hypertension and abdominal pain occurred as noted below (Table 39). This reviewer completed separate analyses to assess the potential impact of splitting of terms and these are noted throughout Section 7.

Table 39: AEDECOD Terms Re-assigned by Medical Officer

AETERM	AEDECOD Assigned	AEDECOD Re-assigned
Intermittent elevated systolic BP	Blood pressure systolic increased	Hypertension
Elevated blood pressure	Blood pressure increased	Hypertension
Increase in blood pressure, Increased blood pressure	Blood pressure increased	Hypertension
Elevated asymptomatic systolic blood pressure	Blood pressure systolic increased	Hypertension
Decreased blood pressure, Worsening decreased blood pressure	Blood pressure decreased	Hypotension
Elevated pulse rate, Elevated Pulse, Elevated pulse (intermittent)	Heart Rate increased	Tachycardia
Tenderness in left lower quadrant of abdomen, Left lower severe abdominal pain, Left lower quadrant tenderness, Cramp in lower abdomen Mid and lower abdominal burning pain	Abdominal pain lower	Abdominal pain
Stomach cramp(s), Stomach cramping, Stomach pain, Stomach ache, Right upper quadrant pain, Intermittent stomach cramps, Stomach pain, Tender left upper quadrant, Epigastric pain, Left upper abdominal pain, Stomach cramping - intermittent	Abdominal pain upper	Abdominal pain

Source: Medical Officer analysis of AE.xpt dataset from NDA 208271

Reviewer Comments: *The oral methylnaltrexone bromide-only OIC pool safety dataset was reviewed and the Applicant was asked to re-evaluate AE reports from Study MNTX3356 (Relistor® SC) so that comparison could be made with AE incidence from tablets. These results are shown in Section 7.2.2, Table 46.*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant completed a single randomized, double-blind, placebo controlled, Phase 3 study to support the safety and efficacy of oral MNTX tablets in the treatment of OIC for non-cancer pain. The Integrated Summary of Safety also included AEs from additional placebo controlled Phase 2 studies a single phase 1 study using oral formulation of with (b) (4) and (b) (4) (to the marketed) tablets of 150 mg MNTX Table 40).

Table 40: Treatment Groups from Oral Methylnaltrexone bromide-only OIC pool

Treatment Group	Contributing Studies
Oral MNTX 150 mg	MNTX3201, 3200A3-200, 3200A3-2201, 3200A3-2202
Oral MNTX 300 mg	MNTX3201, 3200A3-200, 3200A3-2201, 3200A3-2202, 3200A3-1113-US
Oral MNTX 450 mg	MNTX3201, 3200A3-200, 3200A3-2201, 3200A3-2202, MNOC1111, 3200A3-1113-US
Oral MNTX 600 mg	3200A3-2201, 3200A3-2202
Placebo	MNTX3201, MNOC1111, 3200A3-200, 3200A3-2201, 3200A3-2202,

Source: Table 12, ISS

Reviewer Comments: The pooling of data in the Applicant's integrated summary of safety is acceptable to this reviewer for evaluation of the to-be-marketed dosing, as the patients included in these studies are believed to be clinically similar. However it should be noted that the duration of each study is not identical. The double blind placebo-controlled duration of the majority of studies in the oral methylnaltrexone bromide-only OIC pool is 4 weeks in duration, except for study MNOC1111. Based upon the duration of exposure in the clinical development program of oral methylnaltrexone bromide tablets, there is insufficient data to evaluate long term safety of greater than a year duration, as the applicant did not complete a long term safety trial with oral formulation. However, the Applicant is relying on the long-term safety data of Relistor ® SC to support the long-term safety of the oral formulation. This is acceptable, as the AUCs between formulations are similar, and the Cmax of the oral tablet is less than that of Relistor ® SC.

7.2 Adequacy of Safety Assessments

The safety of oral methylnaltrexone bromide was assessed throughout the clinical development program via monitoring of AEs, echocardiogram, physical examination findings, vital sign measurements, clinical laboratory assessments, urine and serum pregnancy tests for women. The Objective Opioid Withdrawal Scale (OOWS), Subjective Opioid Withdrawal Scale (SOWS), and continued re-evaluation of concomitant medications were also completed throughout the study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the Oral placebo-controlled pool, 1057 subjects received oral methylnaltrexone bromide tablets and 344 subjects received placebo (Table 41). 715 subjects received at least 1 month of treatment with methylnaltrexone bromide tablets, 476 subjects received at least 2 months of treatment with methylnaltrexone bromide tablets, and 92 subjects received at least 3 months of treatment with methylnaltrexone bromide tablets. Three hundred eighty-five patients received oral methylnaltrexone bromide at the

450mg dose which is intended for marketing, 28 of whom received at least 3 months of dosing.

Table 41: Extent of Exposure: Oral Placebo-Controlled OIC Pool

Parameter	MNTX < 300 mg (N=327)	MNTX 300 mg (N=280)	MNTX 450 mg (N=385)	MNTX > 450 mg (N=65)	All MNTX (N=1057)	Placebo (N=344)
Duration of Drug Exposure (days)						
Mean (SD)	54.6 (28.8)	57.9 (28.5)	43.6 (33.9)	27.0 (6.3)	49.8 (31.0)	47.9 (31.4)
Median (min, max)	55.0 (1, 94)	79.5 (1, 91)	30.0 (1, 99)	28.0 (1, 36)	34.0 (1, 99)	31.0 (1, 91)
Duration of Drug Exposure by Category, n(%)						
≤1 day	5 (1.5)	4 (1.4)	82 (21.3)	1 (1.5)	92 (8.7)	37 (10.8)
>1 day - 7 days	6 (1.8)	6 (2.1)	9 (2.3)	1 (1.5)	22 (2.1)	7 (2.0)
>7 day - 14 days	8 (2.4)	10 (3.6)	14 (3.6)	2 (3.1)	34 (3.2)	13 (3.8)
>14 day - 28 days	61 (18.7)	48 (17.1)	53 (13.8)	32 (49.2)	194 (18.4)	75 (21.8)
>28 days - 56 days	84 (25.7)	56 (20.0)	70 (18.2)	29 (44.6)	239 (22.6)	65 (18.9)
>56 days - 84 days	134 (41.0)	121 (43.2)	129 (33.5)	0	384 (36.3)	128 (37.2)
>84 days	29 (8.9)	35 (12.5)	28 (7.3)	0	92 (8.7)	19 (5.5)

Source: Table 19, ISS NDA 208271

By comparison a total of 1122 subjects were exposed to methylnaltrexone bromide treatment for up to 99 days in the oral methylnaltrexone bromide-only OIC pool (Table 42) The mean (SD) duration of exposure was 47.0 (32.1) days, and the mean daily dose in the all methylnaltrexone bromide group was 302.1 (153.4) mg.

Table 42: Extent of Exposure: Oral MNTX-only OIC Pool

	MNTX < 300 mg (N=327)	MNTX 300 mg (N=300)	MNTX 450 mg (N=449)	MNTX > 450 mg (N =65)	All MNTX (N=1222)
Duration of Drug Exposure (days)					
Mean	54.6	54.1	37.6	27.0	47.0
Median (Min, Max)	55.0 (1,94)	69.0 (1-91)	29.0 (1,99)	28.0 (1,36)	31.0 (1,99)
Duration of Drug Exposure in Time Intervals – n(%)					
<= 1 day	5(1.5)	24(8.0)	127(28.3)	1(1.5)	119(10.6)
>1 day-7 days	6(1.8)	6(2.0)	28(6.2)	1(1.5)	60(5.3)
>7 days -14 days	8(2.4)	10(3.3)	14(3.1)	2(3.1)	34(3.0)
>14 days - 28 days	61(18.7)	48(16.0)	53(11.8)	32(49.2)	194(17.3)
>28 days - 56 days	84(134)	56(18.7)	70(15.6)	29(44.6)	239(21.3)
> 56 days - 84days	134(41)	121(40.3)	129(28.7)	0	384(34.2)
>84 days	29(8.9)	35(11.7)	28(6.2)	0	92(8.2)

Source: Table 9.3.1 ISS NDA 208271
Note: Mean daily dose is calculated as sum(each dose x each dose frequency x each dosing period)/total treatment period.
Note: Duration of drug exposure is calculated within each study as follows: [date of last dose of study medication in study – date of first dose of study medication in study +1 day], excluding any time off study medication (i.e., designed placebo run-in periods and wash-out periods).
Note: Duration of study exposure is calculated within each study as follows: [date of end of study – date of first dose of study medication in study +1 day].
Note: For a subject who received multiple treatments, exposure durations are summarized in each treatment group Respectively

The durations of drug exposure in study MNTX3201 (Table 43) were similar across dosage arms and longer compared to the Oral Placebo-controlled OIC pool and Oral methylnaltrexone bromide only pool (Table 41 and Table 42), with a mean of 69.1 days of exposure compared to 43.6 days (Oral Placebo-controlled OIC) and 37.6 days (Oral MNTX-only).

Table 43: Study Drug Exposure MNTX3201

	Placebo	MNTX 150 mg	MNTX 300 mg	MNTX 450 mg	All MNTX
Subjects Randomized (N)	**201**	**201**	**201**	**200**	**602**
Exposure (days) – Entire Treatment Period[a]					
n	201	201	201	200	602
Mean (SD)	67.4 (25.80)	71.5 (24.08)	70.0 (24.52)	69.1 (26.29)	70.2 (24.95)
Median (Min, Max)	83.0 (3, 91)	83.0 (1, 94)	83.0 (1, 91)	83.0 (1, 99)	83.0 (1, 99)
Exposure (days) – 4-Week QD Dosing Period[a]					
n	201	201	201	200	602
Mean (SD)	26.3 (4.86)	26.4 (5.45)	26.2 (5.64)	25.6 (6.49)	26.1 (5.88)
Median (Min, Max)	28.0 (3, 28)	28.0 (1, 28)	28.0 (1, 28)	28.0 (1, 28)	28.0 (1, 28)
Exposure (days) – 8-Week PRN Period[a]					
n	165	174	178	169	521
Mean (SD)	49.2 (13.21)	51.1 (11.21)	48.3 (15.17)	50.6 (11.39)	50.0 (12.79)
Median (Min, Max)	55.0 (1, 63)	55.0 (1, 61)	55.0 (1, 63)	55.0 (2, 71)	55.0 (1, 71)

Source: Table 14.1.5.1 MNTX3201 CSR
[a] Exposure duration = date of last dose – date of first dose + 1 for each period

Reviewer Comments: The applicant's safety database for oral methylnaltrexone bromide does not fulfill the ICH E1A recommendations for duration of premarketing exposure for drugs that are to be used on a chronic basis. (Reference: ICH E1A Guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions": http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf).

However, as methylnaltrexone bromide tablets contain the same active ingredient as the marketed Relistor® SC, and bioavailability of the two products was found to be similar, the Applicant contends that the safety data from the SC methylnaltrexone bromide program can be used to support the safety of oral methylnaltrexone bromide, particularly related to provide additional information on long-term exposure (up to 48 weeks) and are supportive of long-term safety of oral MNTX in this indication. This is acceptable to this reviewer.

The Applicant has also provided post marketing safety reports regarding the adverse events reported with SC methylnaltrexone bromide events), but spontaneous postmarketing reports can be challenging to interpret. To date, postmarketing reports with Relistor® have not led to any safety labeling changes (i.e. new AEs, W&P, or contraindications). Please see Section 8 for additional information.

7.2.2 Explorations for Dose Response

The Applicant explored 4 oral methylnaltrexone doses compared with a placebo arm in the phase 2 Study A200A3-2201 using a randomized, double-blind, parallel-group study with an adaptive design: 150, 300, 450, and 600 mg once QD in subjects diagnosed with chronic OIC. The Applicant offered that two doses, 450 mg and 600 mg demonstrated efficacy based on the endpoint of RFBM within 4 hours of oral methylnaltrexone ingestion (p=0.002 and p=0.005). Safety and limited efficacy data were also collected from phase 2 trials A200A3-2202 and A200A3-200.

AEs for all oral placebo-controlled OIC studies were summarized in Table 44. A single related SAE was reported in the >450 mg cohort. This cohort had the largest percentage of severe TEAEs and TEAEs leading to permanent discontinuation of the study drug. Based upon these results, the Applicant selected 150 mg, 300 mg and 450 mg doses for the phase 3 MNTX3201 study.

Table 44: Overview of Adverse Events: Oral Placebo-Controlled OIC Pool

Parameter	MNTX < 300 mg (N=327) n (%)	MNTX 300 mg (N=280) n (%)	MNTX 450 mg (N=385) n (%)	MNTX > 450 mg (N =65) n (%)	All MNTX (N=1057) n (%)	Placebo (N=344) n (%)
Number (%) of Subjects with						
TEAEs	168 (51.4)	159 (56.8)	194 (50.4)	34 (52.3)	555 (52.5)	183 (53.2)
Related TEAEs	49 (15.0)	65 (23.2)	88 (22.9)	9 (13.8)	211 (20.0)	68 (19.8)
Severe TEAEs	23 (7.0)	20 (7.1)	29 (7.5)	8 (12.3)	80 (7.6)	23 (6.7)
Deaths	0	0	1 (0.3)	0	1 (< 0.1)	0
SAEs	6 (1.8)	6 (2.1)	8 (2.1)	5 (7.7)	25 (2.4)	8 (2.3)
Related SAEs	0	0	0	1 (1.5)	1 (< 0.1)	0
TEAEs leading to permanent discontinuation of study drug	4 (1.2)	10 (3.6)	12 (3.1)	3 (4.6)	29 (2.7)	11 (3.2)

Source: Table 22 Integrated Safety Summary (ISS)
Note: The number of MNTX subjects who discontinued due to an AE is different in the disposition table (ST8.1; 28 subjects) and the AE tables (ST8.5.1.1 and ST8.5.2.2; 29 subjects). Subject 2201-008-0321 discontinued due to lack of efficacy, with an ongoing TEAE of increased constipation which was also considered a TEAE leading to discontinuation. For the disposition table this subject was only counted once with the primary cause of discontinuation, which was attributed to lack of efficacy.
Abbreviations: AE = adverse event; MNTX = methylnaltrexone; OIC = opioid-induced constipation; SAE = serious adverse event; and TEAE = treatment-emergent AE.

Reviewer Comments: Pooled oral AE data demonstrate similar rates of overall AEs across dose groups. The proportion of severe TEAEs and SAEs were higher in those patients who received 600 mg compared to 450 mg (severe TEAE 12.3% to 7.5%; SAEs 7.7% to 2.1%). The Applicant choose 450 mg as the highest dose to move forward in the phase 3 study MNTX3201, and based upon the data provided, this appears acceptable. The numbers of TEAEs reported were similar across dosages of methylnaltrexone tablets. However, there were a higher percentage of related TEAEs (23.2% and 22.9%) at 300 mg and 450 mg respectively. The <300 mg dosages demonstrated the least AEs, and the least efficacy (Section 6). The percentage of severe TEAEs was highest at the >450 mg dosage, which is the probable cause of discontinuation of this dosage during the oral development program.

AE data for Relistor® SC from Study SC MNTX 3356 was used for comparison to AE data from Study MNTX3201 (Table 45). A summary of AEs that occurred in ≥ 2% of subjects and more frequently in the MNTX treatment group than the placebo group for these two studies is included in Table 45 below.

Table 45: Adverse reactions that occurred in ≥2% of subjects and more frequently in the MNTX Treatment Group Than the Placebo Group in SC MNTX 3356 and in Oral MNTX Study 3201

	SC MNTX Study 3356		Oral MNTX Study 3201			
Preferred term	SC MNTX 12 mg QD 4 wks N = 150 N(%)	SC Placebo 4 wks N = 162 N(%)	Oral MNTX 450 mg QD – 4 wks N = 200 N(%)	Oral placebo 4 wks N =201 N(%)	Oral MNTX 450 mg QD – 12 wks N = 200 N(%)	Oral Placebo 12 wks N = 200 N(%)
Abdominal Pain	31(20.7)	10(6.2)	18(9.0)	12(6.0)	21(10.5)	17(8.5)
Nausea	13(8.7)	10(6.2)	9(4.5)	11(5.5)	12(6.0)	18(9.0)
Diarrhea	9(6.0)	6(3.7)	9(4.5)	4(2.0)	16(8.0)	7(3.5)
Hyperhidrosis	9(6.0)	2(1.2)	5(2.5)	2(1.0)	6(3.0)	9(2.0)
Headache	6(4.0)	4(2.5)	8(4.0)	4(2.0)	9(4.5)	8(4.0)
Hot Flush	4(2.7)	3(1.9)	2(1.0)	2(1.0)	2(1.0)	4(2.0)
Abdominal Distention	1(0.7)	1(0.6)	7(3.5)	4(2.0)	7(3.5)	6(3.0)
Vomiting	1(0.7)	8(4.9)	6(3.0)	3(1.5)	7(3.5)	9(4.5)
Rhinorrhea	2(2.3)	2(1.2)	4(2.0)	1(0.5)	3(1.5)	3(1.5)
Anxiety	3(2.0)	3(1.9)	3(1.5)	1(0.5)	7(3.5)	3(1.5)
Blood creatine phosphokinase increased	0	0	2(1.0)	0	4(2.0)	1(0.5)

Source: Table 25 MNTX3201 Clinical Study Report
SC MNTX Study 3365 – double blind, placebo controlled period – 4 weeks
Oral MNTX Study 3201 – double-blind, placebo controlled periods – 12 weeks total, including 4 weeks QD plus 8 weeks PRN dosing

In a response to an IR on 15 December 2015, the Applicant provided an additional table amended for recoded **(Table 39)** terms of the AE dataset from Study SC MNTX3356 over 4 weeks duration for recoded GI terms and vascular concerns to as noted in Table 46. This recoded analysis is compared to the AE analysis provided by the Applicant in the MNTX3201 Clinical Study report (Table 45)

Table 46: Comparison of the Applicant's Recoded AEs (Study MNTX3356) and Medical Officer's Recoded [redacted] (b) (4) in 4 Week Double-Blind Portions of Studies MNTX and MNTX3201

	SC MNTX 3356		***Oral MNTX3201***			
Adverse reaction	***SC MNTX 12 mg QD N=150***	***Placebo N=162***	***150 mg MNTX N=201***	***300 mg MNTX N=201***	***450 mg MNTX N=200***	***Placebo N=201***
Abdominal Pain	**32 (21.3%)**	**11 (6.8%)**	**14 (6.9%)**	**19 (9.5%)**	**27 (13.5%)**	**19 (9.5%)**
Diarrhea	**9 (6.0%)**	**6 (3.7%)**	**4 (2.0%)**	**8 (4.0%)**	**10 (5.0%)**	4 (2.0%)
Flatulence	7 (4.2%)[a]	6 (3.4%)[a]	**10 (5.0%)**	**5 (2.5%)**	**10 (5.0%)**	9 (4.5%)
Nausea	14 (9.0%)	9 (6.0%)	6 (3.0 %)	12 (6.0%)	9 (4.5%)	12 (6.0%)
Headache	**6 (4.0%)**	**4(2.5%)**	**1 (0.5%)**	**5 (2.5%)**	**8 (4.0%)**	5 (2.5%)
Abdominal Distention	1(0.7%)	1(0.6%)	**4 (2.0%)**	**2 (1.0%)**	**7 (3.5%)**	4 (2.0%)
Hyperhidrosis	9 (6.0%)	2 (1.2%)	2 (1.0%)	5 (2.5%)	5 (2.5%)	2 (1.0%)
Muscle spasms	[a]	[a]	**0**	**0**	**4 (2.0%)**	1 (0.5%)
Rhinorrhoea	**2 (2.3%)**	**2 (1.2%)**	**3 (1.5%)**	**3 (1.5%)**	**4 (2.0%)**	1 (0.5%)
Anxiety	**3 (2.0%)**	**3 (1.9%)**	**5 (2.5%)**	**6 (3.0 %)**	**3 (1.5%)**	**1 (0.5%)**
Chills	**1 (1%)**	**0**	**0**	**1 (0.5%)**	**3 (1.5%)**	**0**
Hot Flush	4 (3%)	3 (2%)	0	0	1 (0.5%)	1 (0.5%)
Tremor	1 (1%)	0	4 (2.0%)	2 (1.0%)	1 (0.5%)	0
Blood creatine phosphokinase increased	0	0	2(1.0%)	0	2(1.0%)	0

Sources: Medical officer's re-calculation of AEs during 4 week treatment period using recoded dataset provided by Applicant on 12-15 in response to IR.
sIND Medical Officer Review (1 April 2012) for sNDA 021964
[a] This data was derived from Table 73, sNDA 021964 submission on 1 April 2012 which included Relistor® SC studies 2101,3356 and 3358 with MNTX 12 mg QD (N=168) and Placebo (N=177). Muscle spasms were not recorded in Table 73

*Reviewer Comments: This reviewer compared the "recoded" AE tabulations from Study MNTX3201 for 4 and 12 weeks to which the Applicant provided for the MNTX3356 trial for Relistor® SC, focusing specifically on the 4 week double-blind, placebo-controlled study duration. No recoding was provided for Hot Flush or Tremor in the oral MNTX3201 study as they were <0.5% initially and the Division did not request recoding of related terms (**Table 39**). Similarly, AE frequency for Study MNTX 3356 was not available in the current label and not provided by the Applicant for the following: flatulence, abdominal distention, muscle spasms. Complaints of abdominal pain, diarrhea, chills and muscle spasm appeared to be more frequent in the 450 mg oral dosage and generally comparable in comparison to the SC dosing. There appears to be a dose related increase in abdominal pain with oral methylnaltrexone. This is also evident when looking at the full 12 week dosing (last 8 weeks were prn dosing). After recoding AEDECOD for Study MNTX3201, complaints of abdominal pain at 4 weeks increased from 9% to 13.5 % using the [redacted] (b) (4) formulation used in Study MNTX 3201. The incidence of hypertension appeared comparable to SC methylnaltrexone bromide at 450 mg during the 4 week study.*

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Table 11 outlined clinical testing and safety monitoring for study MNTX3201 and including assessment for AEs, serious AEs and deaths, as well as the following specific safety related testing:

- Clinical laboratory testing was conducted as specified in individual study protocols and included:
  - Hematology: WBC with differential, hemoglobin, hematocrit, platelet count, red blood cell count, MCV, MCH, MCHC
  - Serum Chemistry: AST, ALT, alkaline phosphatase, lactate dehydrogenase, bicarbonate, chloride, glucose, uric acid, blood urea nitrogen, total bilirubin, triacylglycerol lipase, total cholesterol, creatine kinase, phosphorus, total protein.
  - Urine analysis: specific gravity, protein, ketones, occult blood, calcium oxalate crystals, erythrocytes, hyaline casts, leukocytes
  - Serum/urine pregnancy testing in female patients of childbearing potential
- Vital signs were generally collected at each study visit
- Physical examination were conducted at periodic visits beginning at pre-screening and through the follow-up visit
- Electrocardiogram was conducted at periodic visits beginning at prescreening and through the follow-up visit
- Subjective opiate withdrawal scale

Reviewer Comments: The assessments appear appropriate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Methylnaltrexone bromide is excreted primarily as the unchanged drug in both urine and feces. Previous PK and PD evaluation of SC methylnaltrexone demonstrated active renal secretion of methylnaltrexone and suggested by renal clearance that is approximately 4-5 fold higher than creatinine clearance.

The Applicant completed study MNPK1004 a single dose PK and safety analysis of 18 subjects with hepatic impairment and 6 healthy controls. They concluded that there was increased systemic exposure in subjects with hepatic impairment consistent with Child-Pugh classes B and C, but no significant safety signals were identified. The Applicant recommends a lower dosage of 150 mg QD oral methylnaltrexone in those subjects fulfilling diagnostic criteria for Child-Pugh classes B and C, but not for Child-Pugh class A. (MNPK1004 CSR). For additional information, see the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Drugs in the peripherally acting mu opioid receptor antagonist (PAMORA) class have been associated with CV adverse events, bowel perforation and opioid withdrawal.

- Cardiovascular (CV) adverse events
    - Cardiac safety was monitored in the oral studies through collection and monitoring of AEs, analysis of ECG and laboratory data.

    - As noted in Section 2.4, the major safety signal associated with the PAMORA class is a potential for increased cardiovascular adverse events. This risk was identified in a 12 month controlled trial of alvimopan, to support an indication for OIC in patients with chronic pain. In this study, there was a numerical imbalance in myocardial infarctions (7 alvimopan vs. 0 placebo; randomized 2:1), noted in months 1 – 4 of exposure Cardiac safety was monitored in the oral studies through collection and monitoring of AEs, analysis of ECG and laboratory data.

    - The FDA Anesthetic and Analgesic Drug Products Advisory Committee (AC) in convened in 11 June 2014 (Section 9.3) with subsequent approval of two PAMORA (SC methylnaltrexone and naloxegol) with a PMR to conduct post-marketing observational studies for MACE assessment. Those PMR have not been completed.

    Reviewer Comments: The Applicant's assessment for CV adverse events was solely based on investigator reported AEs without adjudication. Given the concerns for MACE with PAMORA, adjudication of results would have been preferred and if this study were initiated currently, adjudication would be expected. However, this study was completed prior to the discussion within the Division and Agency regarding PAMORA and risk for MACE across the class.

- Bowel Perforation

    - After initial approval of SC methylnaltrexone for use in OIC in cancer patients who are receiving palliative care, Corken-Mackey et al[13] searched the Adverse Event Reporting System (AERS) database from the approval date of 24 April 2008 to 13 October 2009 to identify instances of GI perforation related temporally to methylnaltrexone usage. 7 of a possible 6500 projected patients were identified. Because of the possible causal relationship, labeling

[13] Corken Mackey A, Green L, Greene P, Avigan M. Methylnaltrexone and Gastrointestinal perforation. J Pain Sym Man 2010;40:1-3

for SC methylnaltrexone indicates GI perforation as a possible risk and bowel perforation is an submission specific AE of concern. Other PAMORA (naloxone, alvimopan) have not reported GI Perforation as a known safety signal.

- The potential for oral methylnaltrexone bromide to be associated with bowel perforation was monitored in the oral studies through routine collection and monitoring of AEs.

  Reviewer Comments: As noted for cardiac events, The Applicant's assessment for CV related adverse events was based investigator reported AEs without adjudication. As AEs of bowel perforation would be expected to lead to hospitalization, this reviewer believes it is unlikely that there were cases of bowel perforation which were not captured during the oral methylnaltrexone bromide clinical development program.

- Opioid Withdrawal.
  - Opioid withdrawal symptoms have been reported with SC methylnaltrexone and naloxegol and labeling for both PAMORA reflects this known risk. The most recent labeling for SC methylnaltrexone (September 2014) states:

    "Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with [methylnaltrexone]. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Take into account the overall risk-benefit profile when using [methylnaltrexone]. in such patients. Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients."

  - The potential for methylnaltrexone bromide tablets to affect opioid withdrawal symptoms or impact analgesia was evaluated by the following:
    - Analysis of investigator- and subject recorded opioid withdrawal questionnaires (OOWS and SOWS) administered at baseline, Day 1 (post dose), Day 14, Day 28, Day 42, Day 56, and Day 84.
    - Review of subject pain scores and opioid use throughout the trials. Scores were evaluated with and without abdominal cramping as it was considered a concomitant AE with oral methylnaltrexone bromide use
    - Assessments of potential opioid withdrawal symptoms recorded as AEs during treatment
  - Analysis of subjects who met DSM-V criteria for opioid withdrawal. Baseline differences in both OOWS and SOWS with or without cramping during the QD period were minimal and not interpreted by the Applicant to be clinically meaningful.

- In response to an information request from DAAAP (dated 30 October 2015), the Applicant provided narrative accounts of 5 patients who were determined to have experienced opioid withdrawal using DSM-V criteria. 4 of the 5 subjects continued with the test drug for at least 82 days while one discontinued enrollment after 1 day.

Reviewer Comments: The Applicant's approach to address AEs related to opioid withdrawal appears reasonable, although review of AE dataset noted only one subject (MNTX3201-080-17 where the AETERM was "Opioid Withdrawal", in comparison to the five identified by DAAAP. Overall, the review by DAAAP interpreted the information provided as an overall similar risk to OWS with methylnaltrexone bromide tablets as with use of Relistor® SC. Please refer to review by Dr. Elizabeth Kilgore, DAAAP for full consult evaluation.

7.3 Major Safety Results

7.3.1 Deaths

No subject died during the phase 3 study MNTX3201.

One death occurred during the oral methylnaltrexone bromide clinical development program in study 3200A3-2202-WW (Subject 2202-016-0684). The subject was a 56 year old male with a medical history of cervical and lumbar degenerative disc disease, chronic obstructive pulmonary disease and heavy smoking with concomitant medications of approximately 71.4 morphine equivalents, milk of magnesia and Amitiza. Screening ECG was interpreted as non-clinically significant bradycardia and a nonspecific interventricular conduction delay. After reported cessation of smoking he was enrolled in trial 2201 at a dosage of 450 mg MNTX. The patient died suddenly during his third week on study protocol and coroner's reported cause of death as related to atherosclerotic cardiovascular disease.

Reviewer Comments: This reviewer agrees with the investigators assessment that the single death reported in Study 3200A3-2202-WW may not be related to the study drug, however as no autopsy or further investigation was completed a full interpretation is difficult to make. As previously stated, there is a concern for MACE associated with this class of agents which will be further evaluated in a postmarketing observational study, should the product be approved.

7.3.2 Nonfatal Serious Adverse Events

AEs were classified as serious or non-serious and were defined in accordance with 21 Code of Federal Regulations (CFR) Part 312.32(a) as outlined in Table 47

Table 47: Serious Adverse Event Criteria

SAE Criteria	Definition
Death	An event that resulted in the death of the subject
Life-threatening	An event that placed the subject, in review of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death
Hospitalization	An event that resulted in an admission to the hospital for any length of time
Prolongation of Hospitalization	An event that occurred while the subject was hospitalized and prolonged the subject's hospital stay
Persistent or Significant Disability/Incapacity	An event that resulted in a condition that substantially interfered with the activities of daily living of a study subject. Disability was not intended to include the transient interruptions of daily activities or experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma
Congenital Anomaly/Birth Defect	An anomaly detected at or after birth, or any anomaly that resulted in fetal loss
Important Medical Event	Events that may not have resulted in death, been life-threatening, or required hospitalization may have been considered SAEs when, based upon appropriate medical judgment, they may have jeopardized the subject and required medical or surgical intervention to prevent one of the outcomes listed in the definition.

Abbreviation: SAE = serious adverse event.
Source Table 14; NDA 208271 ISS

During days 0-28 of study MNTX3201 there were 9 SAEs reported in 4 subjects on placebo, 6 SAEs reported in 3 subjects taking 150 mg tablets, 6 SAEs reported in 4 subjects taking 300 mg tablets, and 2 SAEs reported in subjects taking 450 mg tablets (Table 48). During the full 12 week study duration of Study MNTX3201, no SAEs were interpreted as related or possibly related to study drug by the investigators. One episode of "Drug Withdrawal Syndrome" was reported were in a patient (Subject number: 1020009) receiving 150 mg tablets was interpreted as related to withdrawal from Xanax and not study drug.

Table 48: Summary of SAEs for Study MNTX3201 for full 12 week duration

Treatment Group	Subject Number	Date of Onset/End Date	Study Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
Placebo	001-028	(b) (6)	59	Noncardiac chest pain	No	Moderate	Resolved
			59	Dyspnea	No	Moderate	Resolved
Placebo	024-007		+2	Faecaloma	Unlikely related	Severe	Resolved
Placebo	030-009		44	Spinal fusion surgery	No	Severe	Resolved
Placebo	054-023		2	Noncardiac chest pain	Unlikely related	Moderate	Resolved

Table 28 MNTX3201 CSR

Summary of SAEs for Study MNTX3201 for full 12 week duration - continued

Treatment Group	Subject Number	Date of Onset/End Date	Study Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
		(b) (6)	2	Hypersensitivity	Unlikely related	Moderate	Resolved
			2	Dyspnea	Unlikely related	Moderate	Resolved
Placebo	079-003		+5	Osteomyelitis	No	Severe	Resolved
Placebo	099-007		26	Enterocolitis infectious	No	Severe	Resolved
Placebo	119-015		19	Atrial flutter	No	Severe	Resolved
Placebo	127-003		1	Influenza	No	Severe	Resolved
			1	Diabetes mellitus inadequate control	No	Severe	Resolved
			+5	Diabetic ketoacidosis	No	Severe	Resolved
MOA-728 150 mg/day	069-025		50	Dyspnea	Unlikely related	Severe	Resolved
MOA-728 150 mg/day	102-009		59	Hyperkalemia	No	Moderate	Resolved
			+3	Drug withdrawal syndrome[b]	No	Moderate	Resolved
			+3	Depression	No	Moderate	Resolved
MOA-728 150 mg/day	125-006		+7	Overdose[c]	No	Moderate	Resolved
MOA-728 150 mg/day	134-015		17	Skin ulcer	No	Moderate	Resolved
			+1	Urinary tract infection	No	Moderate	Resolved
			+1	Suicidal ideation	No	Severe	Resolved
MOA-728 150 mg/day	143-029		63	Knee arthroplasty	No	Moderate	Resolved
MOA-728 300 mg/day	002-015		2	Chest pain	No	Moderate	Resolved
			2	Suicidal ideation	No	Mild	Resolved
MOA-728 300 mg/day	006-009		+2	Pulmonary embolism	No	Severe	Resolved
MOA-728 300 mg/day	035-008		+1	Pneumonia	No	Moderate	Resolved
			+1	Pleurisy	No	Moderate	Resolved
MOA-728 300 mg/day	039-026		43	Lumbar spinal stenosis	No	Moderate	Resolved
MOA-728 300 mg/day	077-016		+9	Renal failure acute	Unlikely related	Severe	Resolved

Table 28 MNTX3201 CSR

Summary of SAEs for Study MNTX3201 - continued

Treatment Group	Subject Number	Date of Onset/End Date	Study Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
		(b) (6)	+36	Chest pain	No	Moderate	Resolved
MOA-728 300 mg/day	127-004		56	Gastroenteritis	No	Moderate	Resolved
			56	Dehydration	No	Moderate	Resolved
MOA-728 450 mg/day	069-029		41	Bronchitis	No	Severe	Resolved
MOA-728 450 mg/day	127-006		+8	Myositis ossificans	No	Severe	Resolved
MOA-728 450 mg/day	131-017		19	Impaired gastric emptying	No	Severe	Resolved
MOA-728 450 mg/day	143-045		78	Cellulitis	No	Moderate	Resolved

Table 28 MNTX3201 CSR

Abbreviations: MOA-728 = MNTX or methylnaltrexone; SAE = serious adverse event.

a If the date was before the first dose date, then it was calculated as the event date minus the first dose date, and displayed as "–XX." If the date was on/after the first dose date but on/before the last dose date, then it was calculated as the event date minus the first dose date + 1 and is displayed as "XX." If the date was after the last dose date, then it was calculated as the event date – last dose date and was displayed as "+XX."

b Subject 102-009 had a SAE of drug withdrawal syndrome due to Xanax withdrawal.

c Subject 125-006 experienced oversedation with pain medications.

Note: Adverse events were coded using MedDRA Version 13.0. Serious adverse events are sorted by treatment group.

Note: Subject 062-044 had SAEs prior to the first dose of study drug. Subjects 125-005 and 066-004 had SAEs after Day +14.

Reviewer Comments: The reported SAEs during study MNTX3201 were reviewed. The numbers were small, similar across treatment arms, and not assessed as related to treatment. In this reviewer's opinion and based upon the information provided, no definitive conclusions can be made, but in the available narratives and information no definitive safety signal was seen. Specifically:

- *3201-125-006:*
  - *This subject was a 57 year old woman with a primary diagnosis of temporomandibular joint pain, bradycardia, ankle fracture, depression, anxiety, insomnia, panic attack, abdominal distension, abdominal pain (x2), constipation, rectal hemorrhage, knee arthroplasty (x3), osteoarthritis, sleep apnea syndrome, gastroesophageal reflux disease, dyspepsia (x2), anemia, epistaxis, edema peripheral, dysphagia, fatigue, diverticulitis, heart rate irregular, osteoporosis, and colonic polyp.. Concomitant medications reported were escitalopram, venlafaxine, clonazepam, gabapentin, zolpidem, botulinum toxin type A, and trazodone.*

- *On Study day 60 the subject was transported to hospital due to weakness and was assessed as over sedated related to her routine medications. She improved with dosage modifications and the investigator did not feel that the study drug was related to these events and its provision was continued.*

- *3201-002-015*
  - *This subject was a 35-year-old African American female with a primary pain diagnosis of cellulitis lymphedema, a medical history with the following conditions that were ongoing at study entry: constipation, asthma, gastroesophageal reflux disease, hypertension, and iron deficiency anemia. It was noted that the subject had no smoking, alcohol, or drug abuse history. Four months prior, she had a history of DVT and was placed on Coumadin.*

  - *One day after initiation of study drug, the subject complained of chest pain and upon hospital evaluation was found to be anemic. The subject denied diaphoresis, cough, fever, chills, sputum production, pedal edema, or calf pain. The investigator determined that the chest pain was musculoskeletal in nature and the shortness of breath was related to worsening of iron deficiency anemia. The subject was discharged after blood transfusion.*

- *3201-077-016*
  - *This subject was a 68-year-old white female with a primary pain diagnosis of back pain that required opioids and following conditions that were ongoing at study entry: rhinitis seasonal, osteoarthritis, type 2 diabetes mellitus, menopausal symptoms, obesity, drug hypersensitivity (x2), actinic keratosis, diabetic neuropathy, gastroesophageal reflux disease, depression, constipation, hyperlipidemia, hypertonic bladder, chronic obstructive pulmonary disease (COPD), sleep apnea syndrome, edema peripheral, and cardiac murmur. In addition, the subject continued to smoke 1 pack of cigarettes per day with more than a 100-pack-year history.*

  - *Eight days after completion of trial MNTX3201 (for 34 days) the subject was admitted to hospital for acute renal failure, most likely acute tubular necrosis due to severe dehydration. Discharge medications included vitamin D, insulin lispro, simvastatin, thiamine, clopidogrel, insulin glargine, multivitamin, oxycodone, pregabalin, furosemide, and sevelamer. Upon discharge, the subject's metformin, lisinopril, solifenacin, and oxybutynin were discontinued. One month later she was admitted for complaints of chest pain, possibly related to COPD, inadequate diabetic control and acute-on-chronic renal failure. A diagnosis of atypical chest pain was given upon discharge one day later.*

7.3.3 Dropouts and/or Discontinuations

In the Oral Placebo-controlled OIC pool, 18.3% of subjects treated with methylnaltrexone tablets discontinued early compared to 20.3 % of subjects on placebo. Of those subjects taking 450 mg tablets, 19.7 % discontinued early, a higher percentage than the <300 mg (16.2%), 300 mg (18.6%), and >450 mg arms (18.5%). A similar percentage of patients discontinued due to AEs in the MNTX and placebo arms, as noted in Table 49, however the rate was slightly higher for patients who received > 450 mg MNTX.

Table 49: Disposition of Subjects: Oral Placebo-controlled OIC Pool

Parameter	MNTX < 300 mg (N=327) n (%)	MNTX 300 mg (N=280) n (%)	MNTX 450 mg (N=385) n (%)	MNTX > 450 mg (N =65) n (%)	All MNTX (N=1057) n (%)	Placebo (N=344) n (%)
Subjects Treated	327 (100)	280 (100)	385 (100)	65 (100)	1057 (100)	344 (100)
Subjects Who Completed Study	274 (83.8)	228 (81.4)	309 (80.3)	53 (81.5)	864 (81.7)	274 (79.7)
Subjects Discontinued Early	53 (16.2)	52 (18.6)	76 (19.7)	12 (18.5)	193 (18.3)	70 (20.3)
Primary Reason for Early Discontinuation, n (%)						
Withdrawal by subject	16 (4.9)	12 (4.3)	16 (4.2)	3 (4.6)	47 (4.4)	17 (4.9)
Lost to follow-up	14 (4.3)	7 (2.5)	19 (4.9)	3 (4.6)	43 (4.1)	12 (3.5)
Protocol v olation	9 (2.8)	12 (4.3)	18 (4.7)	2 (3.1)	41 (3.9)	21 (6.1)
AE	4 (1.2)	10 (3.6)	11 (2.9)	3 (4.6)	28 (2.6)	11 (3.2)
Lack of efficacy	7 (2.1)	8 (2.9)	6 (1.6)	0	21 (2.0)	7 (2.0)
Other	3 (0.9)	3 (1.1)	4 (1.0)	1 (1.5)	11 (1.0)	2 (0.6)
Ineligible	0	0	2 (0.5)	0	2 (0.2)	0

Reference: ST8.1 and SL8.1. (ISS Table 18)
Abbreviations: AE = adverse event; MNTX = methylnaltrexone; and OIC = opioid-induced constipation.
Note: The number of MNTX subjects who discontinued due to an AE is different in the disposition table versus ST8.5.2.2 (TEAEs leading to permanent discontinuation; N=29). Subject 2201-008-0321 discontinued due to lack of efficacy, with an ongoing TEAE of increased constipation which was also considered a TEAE leading to discontinuation. For the disposition table this subject was only counted once with the primary cause of discontinuation attributed to lack of efficacy.

In Study MNTX3201, more subjects discontinued the QD period taking 450 mg methylnaltrexone bromide tablets (12.5%) compared to those taking 150 mg (8.5%), 300 mg (8.9%) and placebo (10.0%), though the rates for discontinuation due to adverse events was similar across treatment arms, as noted in Table 50.

Table 50: Study MNTX3201 Subject Disposition by Dosing Period (All Subjects and PRN Subjects)

Parameter	MNTX 150 mg n (%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	Placebo n (%)
Subjects Randomized	201	202	200	201
Intent-to-Treat[a]	201 (100.0)	201 (99.5)	200 (100.0)	201 (100.0)
Completed 4-week QD Period	184 (91.5)	184 (91.1)	175 (87.5)	180 (89.6)
Discontinued QD Period	17 (8.5)	18 (8.9)	25 (12.5)	60 (10.0)
Primary Reason				
Ineligibility	0	0	2 (1.0)	0
Protocol violation	3 (1.5)	2 (1.0)	0	7 (3.5)
Adverse Event	1 (0.5)	3 (1.5)	6 (3.0)	4 (2.0)
Subject request	8 (4.0)	8 (4.0)	6 (3.0)	6 (3.0)
Lost to follow-up	3 (1.5)	1 (0.5)	7 (3.5)	0
Insufficient Response	2 (1.0)	3 (1.5)	4 (2.0)	3 (1.5)
Other	0	1 (0.5)	0	1 (0.5)
Treated in PRN Period	174 (98.3)	178 (98.3)	169 (100.0)	165 (98.8)
Completed PRN Period	160 (90.4)	156 (86.2)	148 (87.6)	143 (85.6)
Discontinued PRN Period	17 (9.6)	25 (13.8)	21 (12.4)	24 (14.4)
Primary Reason				
Ineligibility	0	0	0	0
Protocol violation	3 (1.7)	6 (3.3)	10 (5.9)	4 (2.4)
Adverse Event	1 (0.6)	6 (3.3)	0	4 (2.4)
Subject request	6 (3.4)	4 (2.2)	3 (1.8)	7 (4.2)
Lost to follow-up	7 (4.0)	5 (2.8)	6 (3.6)	8 (4.8)
Insufficient Response	0	4 (2.2)	1 (0.6)	1 (0.6)
Other	0	0	1 (0.6)	0

Source: MNTX3201 CSR Table 7
[a] Intent-to-treat is defined as any randomized subject taking ≥1 dose of study medication
[b] A PRN subject is defined as a subject who had a PRN period visit or took PRN study drug after study day 28

A summary of the specific treatment emergent AEs leading to study discontinuation in Study MNTX3201 is presented in Table 51. Most AEs resulting in discontinuation were moderate in severity, with the highest numbers in both the placebo and 300 mg MNTX dosage group. At 450 mg, the most common AEs resulting in study discontinuation were GI related, inclusive of abdominal pain, constipation, and vomiting.

Table 51: Treatment-Emergent Adverse Events Leading to Study Discontinuation During 12 weeks of study (Randomized Subjects Population)

Preferred Term	Study Day[a]	Occurrence Information	Related to Drug?	Intensity
Placebo				
Urticaria	45	PRN	Probably related	Moderate
Vomiting	2	QD	Probably related	Moderate
Nausea	33	PRN	Probably related	Moderate
Diarrhea	+2	Day 27, QD phase, 2+ days after last dose	No	Severe
Pain in extremity	1	QD	Unlikely related	Mild
Cellulitis	+3	Day 82, PRN phase +3 days after last dose	No	Severe
Enterocolitis infectious[b]	26	QD	No	Severe
Abdominal distension	2	QD	Possibly related	Moderate
Diabetes mellitus inadequate control[b]	1	QD	No	Severe
150 mg MNTX				
Dyspnea	+1	Day 1, QD phase, +1 day after last dose	Probably related	Moderate
Nausea	53	PRN	Probably related	Severe
300 mg MNTX				
Pulmonary embolism[b]	+2	Day 68; PRN phase, +2 days after last dose	No	Severe
Diarrhea	+1	Day 61, PRN phase, +1 day after last dose	Probably related	Severe
Abdominal pain	3	QD	Possibly related	Severe
Diarrhea	3	QD	Probably related	Moderate
Pneumonia[b]	+1	Day 58, PRN phase, +1 day after last dose	No	Moderate
Renal failure acute[b]	+9	Day 43, PRN phase, +9 days after last dose	Unlikely related	Severe
ALT and AST increased	27	Day 27, QD phase (AE.xpt stated started and ended Day 45)	Probably related	Moderate
Syncope	+3	Day 45; PRN phase, +3 days after last dose	No	Moderate
Abdominal Pain upper	+1	Day 2, QD phase; +1 day after last dose	Definitely related	Severe
450 mg MNTX				
Vertigo	14	QD	No	Moderate
Abdominal pain	1	QD	Probably related	Moderate
Constipation	18	QD	Unlikely related	Moderate
Dyspnea	+1	Day 2; QD phase, +2 days after last dose	Possibly related	Mild
Hyperhidrosis	1	QD	Probably related	Mild

Vomiting	1	QD	Definitely related	Moderate
Diarrhea	16	QD	Definitely related	Moderate

Source: Table 29, MNTX3201 CSR with modification from Reviewer's analysis of AE.xpt
Abbreviations: AE = adverse event; MOA-728 = MNTX or methylnaltrexone.
a If the date was before the first dose date, then it was calculated as the event date minus the first dose date, and displayed as "−XX." If the date was on/after the first dose date but on/before the last dose date, then it was calculated as the event date minus the first dose date + 1 and is displayed as "XX." If the date was after the last dose date, then it was calculated as the event date − last dose date and was displayed as "+XX."
b Event was also considered to be a SAE.
Note: Adverse events were coded using MedDRA Version 13.0. Serious adverse events are sorted by treatment group

Reviewer Comments: The reasons for early discontinuation at 450 mg in both the phase 3 study MNTX3201 Oral Placebo-controlled OIC pool included subject ineligibility, protocol violations, AEs and subject request. During the 450 mg QD phase of study MNTX3201 more subjects were lost to follow-up, reported an adverse event or noted an insufficient response to study drug than in other arms of the study. In comparison, subject request was noted most frequently in the 150 mg and 300 mg arms.

Overall, 10 subjects reported TEAEs after at least 1 to 9 days after their last dose of study, as noted in Table 50. The number of subjects in Table 51 who discontinued any portion of the study due to TEAEs is not identical to those reported in Table 50. To clarify these discrepancies, each subject's TEAE was reviewed from the original AE data file for confirmation of dosage, explanation for discontinuation of trial and timing during the trial. Each subject was marked as "+" in the Study Day column. By this re-analysis, the numbers by dosage of subjects who discontinued Study MNTX3201 due to TEAEs are the following:

Comparison of Data from Table 50 for Discontinuation due to TEAE with Reviewer Analysis of the AE.xpt Dataset that correlated with Table 51

Study ARM	***QD***	***QD (Table 50)***	***PRN***	***PRN (Table 50)***
Placebo	*6*	*4*	*2*	*4*
150 mg	*1*	*1*	*1*	*1*
300 mg	*4*	*3*	*5*	*6*
450 mg	*7*	*6*	*0*	*0*

While this reviewer notes the inconsistencies, I do not feel that they change the overall interpretation of these reports. In this reviewer's opinion, though some subjects complained of more than one systemic complaint, those who reported TEAEs leading to discontinuation were most likely related to GI complaints. This is consistent with what has been reported throughout the methylnaltrexone bromide oral clinical development program.

There did not appear to be a clinically significant pattern of either Preferred Term (PT) or intensity across the treatment arms to relate causality for discontinuation. This may be related to and confounded by complicated by the underlying medical conditions of the participating patients.

7.3.4 Significant Adverse Events

Significant adverse events are discussed throughout the review.

Of note, Study MNOC1111 was a single-dose, randomized, double-blind, placebo controlled study to compare the PK and tolerability of the (b) (4) formulation used in Study MNTX 3201 with the TBM formulation. This study revealed an overall increase in AEs of the TBM formulation compared with the formulation used in MNTX3201. Specifically, for GI complaints, 7 subjects who used the TBM formulation complained of 12 GI related AE in comparison to 2 individuals (4 events) who used the Phase 3 study formulation and a single subject in the placebo arm who complained of 1 GI related AE. The most common AEs are noted in Table 52.

Table 52: Medical Officer Review of the Most Commonly Reported AEs in Study MNOC1111

	(b) (4) (used in MNTX3201)	(b) (4) (To-be-marketed)	Placebo
Abdominal pain + Abdominal pain upper	2	3	0
Dizziness	2		
Headache	1	3	3
Increased heart rate	2	2	2
Muscular weakness		1	
Musculoskeletal discomfort		3	
Nausea	1	4	
Vomiting	1	3	

Source: Reviewer's analysis of AE dataset, Study MNOC1111

Reviewer Comments: There were a higher number of GI related AEs in patients receiving the TBM formulation in Study MNOC1111, however, as this was a small, single dose study, definitive conclusions cannot be made. Specific formulation changes would not be expected to change the GI related safety profile given the similarity of PK between the two formulations, and lack of specific concerns based upon the composition of the TBM formulation (Section 4.1; Table 5). However, if additional studies are needed prior to approval of methylnaltrexone bromide tablets, this reviewer recommends that such studies should use the to-be-marketed formulation for a better assessment of the true incidence of GI related AEs in comparison to the Relistor ® SC formulation.

7.3.5 Submission Specific Primary Safety Concerns

As described in Section 7.2.6, submission specific primary safety concerns included AEs related Cardiovascular disorders with specific attention to MACE, gastrointestinal disorders and opioid withdrawal symptoms and were addressed in the protocol for study MNTX3201, the single Phase 3 study for methylnaltrexone bromide tablets.

- Cardiovascular Disorders: In the Oral Placebo-controlled OIC pool, 4 patients receiving 450 mg methylnaltrexone bromide tablets reported cardiovascular AEs reported as first degree AV block, sinus tachycardia, supraventricular tachycardia and trigeminal PVC's on PE and only 3 of those subjects were enrolled in Study MNTX3201. The Oral Placebo-controlled OIC pool also noted 8 subjects receiving 300 mg tablets (all from Study MNTX3201) and 4 subjects receiving placebo (2 from MNTX3201) as noted in Table 53. There were no sudden deaths reported in study MNTX3201.

Table 53: Cardiovascular Disorder AEs reported in the Oral Placebo-controlled OIC Pool (Recoded by Medical Officer)

AETERM	MNTX <300 mg	MNTX >300 mg	MNTX 300 mg	MNTX 450 mg	Placebo
ATRIAL FIBRILATION	1	0	0	0	0
ATRIAL FLUTTER	0	0	0	0	1
BIGIMINAL RHYTHM	0	0	1	0	0
BI-LATERAL CARDIAC ENLARGEMENT	2	0	0	0	0
BRADYCARDIA	0	0	1	0	0
CARDIAC DYSRHYTHMIA	1	0	0	0	0
CHEST PAIN (CARDIAC RELATED)	0	0	1	0	0
FIRST DEGREE AV BLOCK	0	0	0	1	0
LEFT ATRIAL DILATION	0	0	1	0	0
LEFT POSTERIOR FASCICULAR BLOCK	0	0	1	0	0
PALPATATIONS	0	0	1	0	0
PALPITATIONS	2	0	0	0	0
PREMATURE VENTRICULAR CONTRACTION	0	0	1	0	0
RIGHT BUNDLE BRANCH BLOCK	0	0	1	0	0
SINUS TACHYCARDIA	0	1	0	1	0
SUPRAVENTRICULAR TACHYCARDIA	0	0	0	1	0
TACHYCARDIA	0	0	0	0	3
TACHYCARDIA AT 110 BPM	0	0	0	0	1
TACHYCARDIA-ORTHOSTATIC	0	0	0	0	1
TRIGEMINAL P C'S ON PE	0	0	0	1	0
WORSENING BI-LATERAL CARDIAC ENLARGEMENT	1	0	0	0	0

Source: Reviewer recoded AE set from NDA 20871

- Bowel Perforation: No subjects reported bowel perforation in during the oral methylnaltrexone bromide development program.

- Opioid Withdrawal Syndrome: Adverse reactions (Table 45) potentially indicating symptoms of withdrawal (abdominal pain, diarrhea and hyperhidrosis) were compared for tablets (Study MNTX3201) and SC (Study MNTX 3356). In addition, Objective Opioid Withdrawal Scales (OOWS) and Subjective Opioid Withdrawal Scales (SOWS) were used for evaluation for OWS. In an IR Response dated 30 October 2015 reported 5 subjects in Study MNTX3201 with probable symptoms of Opioid Withdrawal Syndrome (OWS) based upon combination of reported AE consistent with DSM-V criteria. Narratives are noted below:

    - **Subject 099-011 (Randomized to 150 mg)**: This subject is a 62-year old white female with a primary pain diagnosis of Osteoarthritis on an oral dose of OxyContin of 80 mg at study entry. Medical History included the following medical conditions that were ongoing at study entry: arthritis generalized, (fused neck), two broken vertebrae, bilateral knee arthritis, opioid induced constipation, restless leg syndrome, seasonal allergies, insomnia, panic attacks, hypertension, dyspnea on exertion, diastolic heart murmur, hypoactive bowel sounds in all 4 quadrants, trace pedal edema, kyphosis, and skin lesions age related. The subject also had a past history of bilateral knee replacement, acid reflux, stomach ulcers, and partial hysterectomy. Concomitant medications at the onset of the adverse events included Restoril, OxyContin, requip, senna, xanax, vistaril, benadryl, ipratropium, chantix, and lisinopril. The subject received her first dose of study drug on 6 April 2011 and last dose on 28 June 2011. The total duration of exposure to study drug was 84 days. AEs were reported as below:

        - *Arthralgia* (7 April 2011; interpreted as severe and NOT related to study drug, with stop date unknown)
        - *Food poisoning* (29 April 2011; interpreted as severe and NOT related to study drug with resolution 1 May 2011)
        - *Vomiting* (14 May 11: interpreted as severe and NOT related to study drug with resolution 15 May 2011)
        - *Hyperhidrosis* (14 May 11; interpreted as severe and NOT related to study drug, without resolution on 15 May 2011)
        - *Nausea* (14 May 11; interpreted as severe and NOT related to study drug, with resolution on 15 May 2011)
        - *Diarrhea* (14 May 11; interpreted as severe and NOT related to study drug, with resolution on 15 May 2011)

    - **Subject 009-003 (Randomized to 300 mg)**: This subject is a 46-year old white male with a primary pain diagnosis of back pain. Medical history included the following medical conditions that were ongoing at study entry: hearing difficulty bilateral ears, rhinosinusitis, hypertension, obstructive sleep apnea, obesity, migraines, opioid induced constipation, headaches,

numbness bilateral lower extremities, numbness bilateral upper extremities, spinal degenerative disc disease, muscle spasms back, failed back syndrome, depression, anxiety, insomnia, attention-deficit hyperactivity disorder, cervical spondylitic myelopathic, right rotator cuff impingement syndrome, left knee ligament sprain, left iliotibial band syndrome, bilateral carpal tunnel syndrome, chronic obstructive pulmonary disease, tobacco abuse, and erectile dysfunction. The subject also had a past history of left knee joint effusion, baker cyst left knee, discectomy L5-S1, Laminectomy L3-S1, nasal deviated septum repair, ganglion cyst right wrist, nasal deviated septum, and ganglioncystectomy. Concomitant medications at the onset of the adverse events included Ritalin, ibuprofen, requip, senna, Excedrin migraine, hydrochlorothiazide, dulcolax, Colace, activia yogurt, oxycontin, oxycodone, avelox, potassium chloride, Cialis, soma, wellbutrin, and amoxicillin. At study entry, The subject was taking: oral oxycontin (160 mg daily) and oral oxycodone (120 mg daily). The subject received his first dose of study drug on 14 October 2010 and last dose on 03 January 2011.

- *Acute Sinusitis* (1 October 2010; interpreted as moderate and not related to study drug, with resolution 7 November 2011)
- *Dizziness* (14 October 2010; interpreted as mild and possibly related to study drug with resolution 14 October 2010)
- *Anxiety (*14 October 2010; interpreted as mild and possibly related to study drug with resolution 14 October 2010)
- *Hyperhidrosis* (interpreted as mild and probably related to study drug, without resolution on 14 October 2010)
- *Nausea (*14 October 2010; interpreted as mild and possibly related to study drug with resolution 16 October 2010)
- *Drug Dependence (*14 October 2010; interpreted as mild and possibly related to study drug with resolution 28 October 2010)

- **Subject 148-004 (Randomized to 300 mg):** This subject is a 63-year old white male with a primary pain diagnosis of low back pain and neck pain. Medical history included the following medical conditions that were ongoing at study entry: facial rash, musculoskeletal lower back pain, constipation, joint pain, anxiety, diabetes type 2, asthma, lumbar and cervical disc bulges, neck pain, and insomnia. The subject also had a past history of sinus infection. Concomitant medications at the onset of the adverse events included meloxicam, dilaudid, baclofen, amoxicillin, gabapentin, ambien, dulcolax, metformin, Qvar, and proair HFA. The subject received his first dose of study drug on 10 February 2010 and last dose on 02 May 2011.The total duration of exposure to study drug was 82 days. Upon study entry, the subject was taking: oral dilaudid (32 mg daily). AEs were reported as the following:

- *Upper abdominal pain* (10 February 2011; interpreted as mild and unlikely related to study drug, with resolution 15 February 2011)
- *Upper abdominal pain* (11 March 2011; interpreted as mild and possibly related to study drug, with resolution 12 February 2011)
- *Diarrhea* (11 March 2011; interpreted as mild and possibly related to study drug, with resolution 12 February 2011)
- *Muscle spasms* (11 March 2011; interpreted as mild and possibly related to study drug, with resolution 12 February 2011)
- *Hyperhidrosis* (11 March 2011; interpreted as mild and possibly related to study drug, with resolution 12 February 2011)

- **Subject 094-007 (Randomized to 450 mg)**: This subject was a 41-year old white male with a primary pain diagnosis of back pain. Upon study entry, his daily dose of oral morphine was 90 mg) Medical history included the following medical conditions that were ongoing at study entry: hypercholesterolemia, opioid induced constipation, chronic back pain, and elevated creatine kinase. The subject also had a past history of lumbar spine surgery and radiculopathy and spinal cord stimulator trial. Concomitant medications at the onset of the adverse events included Zetia, niacin, aspirin, Benefiber, and morphine. The subject received his first dose of study drug on 11 February 2011 with complaints of multiple AEs reported on 11 February 2011.

  - *Lower abdominal pain* (interpreted as mild and probably related to study drug, with resolution 12 February 2011)
  - *Dizziness* (interpreted as mild and probably related to study drug with resolution 12 February 2011)
  - *Tremor* (interpreted as mild and probably related to study drug with resolution 12 February 2011)
  - *Hyperhidrosis* (interpreted as mild and NOT related to study drug, without resolution on 12 February 2011)
  - *Nausea* (interpreted as mild and possibly related to study drug, with resolution on 14 February 2011)

- **Subject 001-011 (Randomized to 450 mg)**: This subject is a 63-year old white female with a primary pain diagnosis of back pain. Medical history included the following medical conditions upon entry: hypercholesterolemia, asthma, fibromyalgia, migraine headaches, seasonal allergies, constipation induced nausea, hypoglycemia, muscle spasms, insomniac, muscle stiffness, hypothyroid, bunion, allergies to penicillin, allergies to sulfas, irritable left ventricle, non-anginal chest discomfort, external hemorrhoid, internal hemorrhoid, gastro esophageal reflux disease, opioid induced constipation, post-menopausal, generalized pain, and back pain. The subject also had a past history of hysterectomy. Concomitant medications at the onset of the adverse events included salicylic acid derivatives, Benadryl, Amerge, Flexeril,

Toprol, synthroid, Voltaren 1% gel, Flector patch, omeprazole, dulcolax, Proventil, and Percocet. The subject received her first dose of study drug on 06 October 2010 and last dose on 26 December 2010. The total duration of exposure to study drug was 82 days. Upon study entry the subject was taking oral Percocet (50 mg daily). The following AEs were reported:

- *Upper abdominal pain* (3 November 2010; interpreted as moderate and definitely related to study drug, with resolution 1 December 2010)
- *Nausea* (3 November 2010; interpreted as moderate and definitely related to study drug, with resolution 1 December 2010)
- *Feeling cold* (3 November 2010; interpreted as moderate and definitely related to study drug, with resolution 1 December 2010)
- *Hyperhidrosis* (interpreted as mild and NOT related to study drug, without resolution on 12 February 2011)
- *Restlessness* (3 November 2010; interpreted as moderate and definitely related to study drug, with resolution 1 December 2010)
- *Upper respiratory infection* (21 November 2010; interpreted as moderate and definitely related to study drug, with resolution 5 December 2010)

*Reviewer Comments: There were no identifiable concerns based upon review of this data. The cardiovascular AEs were small in number and similar across treatment arms. There were no AEs of bowel perforation reported during the oral clinical development program. While the recoded AEs (*Table 46 *) noted higher percentage of abdominal pain for 450 mg tablets during weeks 1-4 of Study MNTX 3201 (13.5% to 21.3% SC in Study MNTX 3356), there did not appear to have higher concerns for other AEs related to OWS. This reviewer does believe that there is some overall inter-rater variability that may affect coding and consideration for OWS, but this may be difficult to determine given the complex patient population. Overall, this reviewer concurs with the review from DAAAP, that the oral methylnaltrexone bromide development program did not specifically utilize a study design that most accurately assess OWS. However, in review of the data presented in this NDA, the risk for OWS with usage of methylnaltrexone bromide tablets appears no different than identified for Relistor® SC.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events In study

TEAEs reported during the single Phase 3 study (MNTX3201) were similar in frequency across all treatment arms (range of 58.2% to 59.7%) and the placebo group (63%) as noted in Table 54 and Table 55. TEAEs reported by intensity were also similar across treatment arms in this study, though a lower number of subjects reported TEAEs in the 150 mg cohort as compared with placebo, 300 mg and 450 mg cohorts. Fewer subjects in the 150 mg cohort (2) discontinued enrollment in MNTX3201 as compared with the placebo (9), 300 mg (9) and 450 mg (7) arms.

Table 54: Summary of Adverse Events (Safety Population) of Study MNTX3201

	Placebo n (%)	MNTX 150 mg n (%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	A l MNTX n (%)
Subjects Randomized (N)	**201**	**201**	**201**	**200**	**602**
Subjects with any TEAE	127 (63.2)	117 (58.2)	120 (59.7)	118 (59.0)	355 (59.0)
TEAE Intensity[a]					
Severe	18 (9.0)	17 (8.5)	16 (8.0)	17 (8.5)	50 (8.3)
Moderate	51 (25.4)	52 (25.9)	61 (30.3)	58 (29.0)	171 (28.4)
Mild	58 (28.9)	48 (23.9)	43 (21.4)	43 (21.5)	134 (22.3)
Subjects Reporting TEAEs Related to Study Drug	46 (22.9)	34 (16.9)	49 (24.4)	50 (25.0)	133 (22.1)
Subjects with Treatment-Emergent SAEs	8 (4.0)	5 (2.5)	6 (3.0)	4 (2.0)	15 (2.5)
QD	4 (2.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (0.5%)
PRN	4 (2.4%)	5 (2.9%)	5 (2.8%)	3 (1.8%)	13 (2.5%)
Subjects with Treatment-Emergent SAEs Related to Study Drug	0	0	0	0	0
Subjects Discontinued Study Due to TEAE	9 (4.5)	2 (1.0)	9 (4.5)	7 (3.5)	18 (3.0)
QD	6 (3.0%)	1 (0.5%)	4 (2.0%))	7 (3.5%)	12 (2.0%)
PRN	3 (1.8%)	1 (0.6%)	5 (2.8%)	0	6 (1.2%)
Deaths	0	0	0	0	0

Source: Table 23, MNTX3201 CSR and Table 14.3.1.1a and 14.3.1.1b
Abbreviations: MNTX or MOA-728 = methylnaltrexone; SAE = serious adverse event; TEAE = treatment emergent adverse event.
a If a subject experienced more than one AE, the subject was counted only once for the maximum intensity.

Reviewer Comments: Most Treatment-Emergent SAEs occurred during the PRN phase while the TEAEs related to study discontinuation more frequently occurred during the QD phase of Study MNTX3201 with the highest number of discontinuation in both the Placebo and 450 mg study arms. This reviewer does note that the number of Treatment-emergent SAEs for 150 mg methylnaltrexone bromide tablets for both the QD and PRN phases do not add to the Applicant's total number (5), but is increased to 6. However, this single disparity in the presented SAEs does not appear significant enough to change the interpretation of the data.

Of the 1447 AEs reported in study MNTX3201, the most frequently reported treatment-emergent AEs were in the classes of GI disorders (417 total), Infections and infestations (227 total), and musculoskeletal and connective tissue disorders (128 total). Overall, Cardiac disorders (17 total) and Vascular disorders (25 total) were less frequent.

Table 55: Treatment-Emergent Adverse Events in Subjects Treated with MNTX or Placebo (Safety Population) in Study MNTX3201 over 4 weeks

System Organ Class Preferred Term	Placebo n (%)	MNTX 150 mg n (%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	All MNTX n (%)
Subjects Randomized (N)	**201**	**201**	**201**	**20**	**602**
Any system organ class	37 (18.4%)	29 (14.4%)	28 (18.9%)	43(21.5%)	110 (18.3%)
Gastrointestinal disorders	24 (11.9%)	23 (11.4%)	27 (13.4%)	35 (17.5%)	85 (14.1%)
Abdominal discomfort	2 (1.0%)	1 (0.5%)	01.0%	0	1(0.2%)
Abdominal distension	3 (1.5%)	3 (1.5%)	2 (1.0%)	6 (3.0%)	1 (0.2%)
Abdominal pain	8 (4.0%)	7 (3.5%)	11 (5.5%)	16 (8.0%)	34 (5.6%)
Abdominal pain lower	0	0	0	1 (0.5%)	1 (0.2%)
Abdominal pain upper	5 (2.5%)	3 (1.5%)	4 (2.0%)	2 (1.0%)	9 (1.5%)
Diarrhea	1 (0.5%)	0	5 (2.5%)	8 (4.0%)	1 (0.2%)
Flatulence	6 (3.0%)	9 (4.5%)	5 (2.5%)	9 (4.5%)	23 (3.8%)
Nausea	5 (2.5%)	3 (1.5%)	9 (4.5%)	9 (4.5%)	21 (3.5%)
Vomiting	2 (1.0%)	0	1 (0.5%)	4 (2.0%)	5 (0.8%)
Cardiac Disorders					
Palpitations	0	0	1 (0.5%)	0	1 (0.2%)
Nervous system disorders	4 (2.0%)	5 (2.5%)	7 (3.5%)	9 (4.5%)	21 (3.5%)
Dizziness	2 (1.0%)	1 (0.5%)	1 (0.5%)	3 (1.5%)	5 (0.8%)
Dysgeusia	0	0	0	2 (1.0%)	2 (0.3%)
Headache	1 (0.5%)	1 (0.5%)	4 (2.05)	3 (1.5%)	8 (1.3%)
Migraine	1 (0.5%)	0	0	0	0
Paresthesia	0	0	1 (0.5%)	0	1 (0.2%)
Tremor	0	3 (1.5%)	1 (0.5%)	1 (0.5%)	5 (0.8%)
Vascular headache	0	0	0	1 (0.5%)	1 (0.2%)
Vascular disorders	2 (1.0%)	0	0	3 (1.5%)	3 (0.5%)
Flushing	0	0	0	1 (0.5%)	1 (0.2%)
Hot flush	2 (1.0%)	0	0	1 (0.5%)	1 (0.2%)
Hypertension	0	0	0	1 (0.5%)	1 (0.2%)

Source: Modified from Table 14.3.1.7a, Study MNTX3201 CSR
Abbreviations: MNTX or MOA-728 = methylnaltrexone.
Notes: Adverse events were coded using MedDRA Version 13.0. A subject reporting more than one adverse event for a particular MedDRA preferred term or system organ class was counted only once for that MedDRA preferred term or system organ class.

Reviewer Comments: In review of the distribution of most common AEs reported in the ISS, this reviewer noted a similar pattern and distribution as described for Study MNTX3201 with the highest number associated with Gastrointestinal disorders, in dose related increases. During the QD period, both placebo and 150 mg arms reported 11.9% and 11.4% TEAEs GI related TEAEs, with 300 mg (13.4%) and 450 mg (17.5%) slightly increased.

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinically significant abnormalities, and changes over time were reviewed for clinical chemistry, hematology, and urinalysis parameters in the phase 3 study MNTX3201 (Table 56 and Table 57).

Table 56: Clinical Chemistry Parameters: Clinically Relevant Shifts from Baseline To the End of Treatment in ≥5% of Subjects in MNTX3201 Study Patients

Laboratory Shift from Baseline	Placebo n (%)	MNTX 150 mg n (%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	All MNTX n (%)
Randomized Subjects (N)[a]	**201**	**201**	**201**	**200**	**602**
BUN (mmol/L)					
Normal-Low	7 (3 7)	10 (5 2)	5 (2 6)	13 (7 0)	28 (4 9)
Uric acid (umol/L)					
Normal-High	6 (3 1)	9 (4 7)	11 (5 8)	10 (5 4)	30 (5 3)
Glucose (mmol/L)					
Normal-High	16 (8 5)	9 (4 7)	7(3 7)	6 (3 2)	22 (3 9)
Chloride (mmol/L)					
Normal-High	4 (2 1)	3 (1 6)	8 (4 2)	12 (6 5)	23 (4 0)
Bicarbonate (mmol/L)					
Normal-High	19 (9 9)	18 (9 4)	12 (6 3)	18 (9 7)	48 (8 4)
Lactate dehydrogenase (U/L)					
Normal-High	11 (5 8)	9 (4 7)	12 (6 3)	5 (2 7)	26 (4 6)
Alkaline Phosphatase (U/L)					
Normal-High	10 (5 2)	11 (5 7)	10 (5 2)	10 (5 4)	31 (5 4)
AST (U/L)					
Normal-High	10 (5 2)	12 (6 3)	13 (6 8)	12 (6 5)	37 (6 5)
ALT (U/L)					
Normal-High	11 (5 8)	12 (6 3)	14 (7 3)	13 (7 0)	39 (6 9)
Total bilirubin (umol/L)					
Normal-Low	25 (13 1)	25 (13 0)	21 (11 0)	16 (8 6)	62 (10 9)
Triacylglycerol lipase (U/L)					
Normal-High	11 (5 8)	8 (4 2)	8 (4 2)	11 (5 9)	27 (4 7)
Total cholesterol (mmol/L)					
Normal-High	14 (7 3)	15 (7 8)	18 (9 4)	21 (11 3)	54 (9 5)
Creatine kinase (U/L)					
Normal-High	8 (4 2)	9 (4 7)	11 (5 8)	6 (3 2)	26 (4 6)
Phosphorus (mmol/L)					
Normal-High	9 (4 8)	15 (7 8)	13 (6 8)	7 (3 8)	35 (6 2)
Protein (g/L)					
Normal-High	7 (3 7)	14 (7 3)	9 (4 7)	7 (3 8)	30 (5 3)

Source: Table 33 MNTX3201 CSR

Table 57: TEAEs Associated with Abnormal Laboratory Results in 1% of MNTX3201 Study Patients

	MNTX 150 mg N(%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	All MNTX n (%)	Placebo n (%)
N	201	201	200	602	201
Blood creatinine phosphokinase increased	2(1.0)			4(2.0)	1(0.5)
ALT increased	0	3(1.5)	1(0.5)	4(0.7)	3(1.5)
AST increased	0	2(1.0)	1(0.5)	3(0.5)	3(1.5)
Blood alkaline phosphatase increased	0	0	1(0.5)	1(0.2)	3(1.5)

Source: Table 35 MNTX3201 CSR

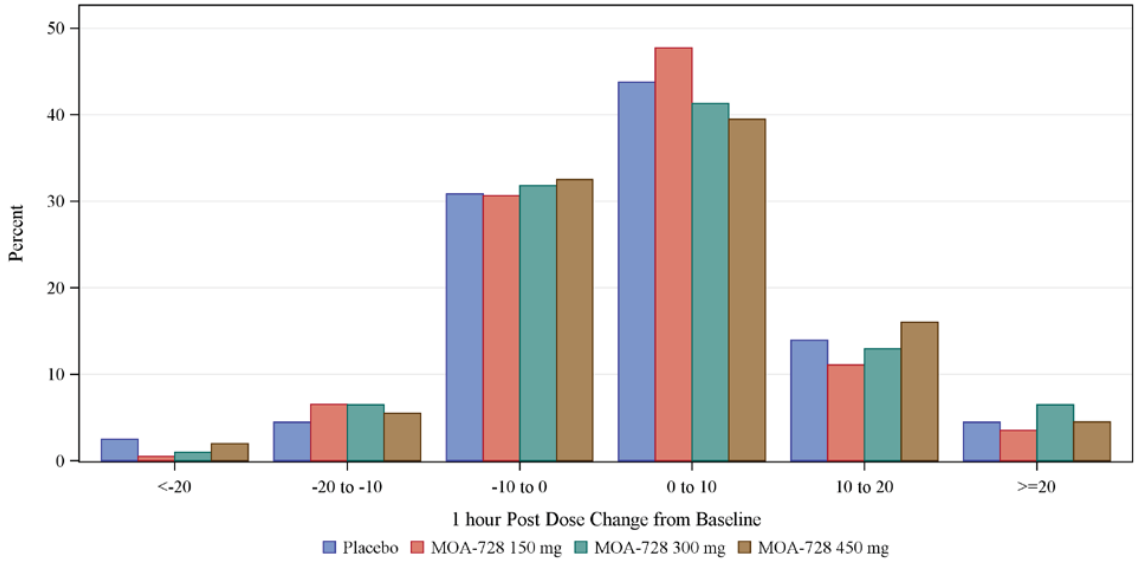
Reviewer Comments: No clinically relevant pattern of changes was observed and no apparent treatment related trends in serum chemistry or hematology over time.

7.4.3 Vital Signs

In re-analysis of AEs associated with the oral methylnaltrexone bromide-only OIC pool during the double blind portion of trial MNTX3201, no significant changes were identified that would indicate an increased risk for hypertension, hypotension, or heart rate with methylnaltrexone bromide tablets.

In the MNTX3201 protocol, the Applicant evaluated subject blood pressure 1 hour after ingestion of study drug and did not identify clinically significant changes in systolic blood pressure or heart rate between treatment arms (Figure 8)

Figure 8: Categorical Changes in Hemodynamic Parameters at 1 Hour following the First Dose of Study Drug by Treatment Group (Safety Population)



Source: Figure 16 MNTX3201 CSR

Reviewer Comments: There were no significant concerns related to vital sign changes in subjects during the oral methylnaltrexone clinical development program.

7.4.4 Electrocardiograms (ECGs)

The Applicant evaluated subject electrocardiograms at baseline and on Day 28. There were no clinically or statistically significant changes in heart rate, QRS duration, QT interval, RR interval, PR interval.

Reviewer Comments: There was no apparent increase in ECG abnormalities noted, and these findings methylnaltrexone bromide tablets appear consistent with what had been seen with SC MNTX.

7.4.5 Special Safety Studies/Clinical Trials

As noted in Section 7.2.5, MNPK1004 was completed to address dosing for patients with renal insufficiency.

7.4.6 Immunogenicity

No specific studies have been performed to determine the immunogenicity of methylnaltrexone bromide, as methylnaltrexone bromide is not a therapeutic protein product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted in Table 58 the Oral placebo-controlled OIC pool, all treatment and placebo arms reported AEs in greater than 50% of enrolled subjects. The highest rate of TEAEs were reported at 300 mg (56.8%), and the rate of related adverse event rates (TEAE) was higher at the 300 mg (23.2%) and 450 mg (22.9%) dosage compared to placebo (19.8%). The highest percentage of severe TAEs and SAEs were reported was in the > 450 mg subject cohort (12.3% and 7.7%, respectively). However, 300 mg and 450 mg dosing of appeared to have similar incidences of related TEAEs, Severe TEAEs, SAEs, and TEAEs leading to permanent discontinuation of the study drug. See also Table 44, in Section 7.2.2.

Table 58: Dose Dependency for Adverse Events in Oral Placebo-Controlled OIC pool

Parameter	MNTX < 300 mg (N=327) n (%)	MNTX 300 mg (N=280) n (%)	MNTX 450 mg (N=385) n (%)	MNTX > 450 mg (N =65) n (%)	All MNTX (N=1057) n (%)	Placebo (N=344) n (%)
Number (%) of Subjects with						
≥1 AE	182 (55.7%)	167 (59.6%)	206 (53.5%)	37 (56.9%)	592 (56.0%)	190 (55.2%)
≥1 TEAE	168 (53.2%)	159 (56.8%)	194 (50.4%)	34 (52.3%)	555 (52.2%)	183 (53.2%)
≥1 related TEAE	49 (15.0%)	65 (23.2%)	88 (22.9%)	9 (13.8%)	211 (20.0%)	68 (19.8%)
TEAE intensity						
Life Threatening	0	0	0	1 (0.3%)	1 (<0.1%)	0
Severe	23 (7.0%)	20 (7.1%)	29 (7.5%)	8 (12.3%)	80 (7.6%)	23 (6.7%)
Moderate	71 (21.7%)	78 (27.9%)	88 (22.9%)	14 (21.5%)	251 (23.7%)	77 (22.4%)
Mild	74 (22.6%)	61 (21.8%)	76 (19.7%)	12 (18.5%)	223 (21.1%)	83 (24.1%)
≥ 1 Treatment-Emergent SAE	6 (1.8%)	6 (2.1%)	8 (2.1%)	5 (7.7%)	25 (2.4%)	8 (2.3%)
≥1 Related Treatment-Emergent SAE	0	0	0	1 (1.5%)	1 (<0.1%)	0
≥1 Treatment-Emergent AE leading to permanent Discontinuation of Study Drug	4 (1.2%)	10 (3.6%)	12 (3.1%)	3 (4.6%)	29 (2.7%)	11 (3.2%)
≥ 1 Related Treatment AE leading to Permanent discontinuation of Study Drug	3 (0.9%)	6 (2.1%)	8 (2.1%)	2 (3.1%)	19 (1.8%)	5 (1.5%)
≥ 1 least treatment-Emergent AE resulting in Death	0	0	1 (0.3%)	0	1 (<0.1%)	0

Source: Table ST 8.5.1.1 NDA 208271 Summary of Clinical Safety

These rates of AEs were similar to what was reported in Study MNTX3201 (Table 59).

Table 59: Summary of Adverse Events – Study MNTX3201

	Placebo n (%)	MNTX 150 mg n (%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	All MNTX n (%)
Subjects Randomized (N)	**201**	**201**	**201**	**200**	**602**
Subjects with any TEAE	127 (63.2%)	117 (58.2%)	120 (59.7%)	118 (59.0%)	355 (59.0%)
TEAE Intensity[a]					
Severe	18 (9.0%)	17 (8.5%)	16 (8.0%)	17 (8.5%)	50 (8.3%)
Moderate	51 (25.4%)	52 (25.9%)	61 (30.3%)	58 (29.0%)	171 (28.4%)
Mild	58 (28.9%)	48 (23.9%)	43 (21. %4)	43 (21.5%)	134 (22.3%)
Subjects Reporting TEAEs Related to Study Drug	46 (22.9%)	34 (16.9%)	49 (24.4%)	50 (25.0%)	133 (22.1%)
Subjects with Treatment-Emergent SAEs	8 (4.0%)	5 (2.5%)	6 (3.0%)	4 (2.0%)	15 (2.5%)
Subjects with Treatment-Emergent SAEs Related to Study Drug	0	0	0	0	0
Subjects Discontinued Study Due to TEAE	9 (4.5%)	2 (1.0%)	9 (4.5%)	7 (3.5%)	18 (3.0%)
Deaths	0	0	0	0	0

Source: Table 14.3.1.1c. CSR MNTX3201
Abbreviations: MNTX or MOA-728 = methylnaltrexone; SAE = serious adverse event; TEAE = treatment emergent adverse event.

The most commonly reported TEAEs in the Oral Placebo-Controlled OIC pool was within the organ class of Gastrointestinal Disorders, and subjects ingesting 450 mg oral methylnaltrexone bromide noted the most frequent complaints (18.2% in comparison to 12.2% for placebo) as noted in Table 60.

Table 60: Related Treatment-Emergent Adverse Events by system Organ Class and Preferred Term: Oral Placebo-Controlled OIC Pool (3200A3-200-WW, 3200A3-2201-US, 3200A3-2202-WW, MNTX3201, MNOC1111)

System Organ Class MedDRA Preferred Term	MNTX <300 mg N=301 N(%)	MNTX 300 mg N=245 N(%)	MNTX 450 mg N=353 N(%)	MNTX >450 mg N=62 N(%)	All MNTX N=961 N(%)	Placebo N=304 N(%)
Any System Organ Class	49 (15.0%)	65 (23.2%)	88 (22.9%)	9 (13.8%)	211 (20.0%)	68 (19.8%)
Gastrointestinal disorders	36(11.0%)	41(14.6%)	70(18.2%)	4(6.2%)	151(14.3%)	42(12.2%)
Abdominal discomfort	2 (0.6%)	0	1 (0.3%)	0	3 (0.3%)	2 (0.6%)
Abdominal distension	6 (1.8%)	3 (1.1%)	9 (2.3%)	0	18(1.7%)	6 (1.7%)
Abdominal pain	12 (3.7%)	12 (4.3%)	26 (6.8%)	3 (4.6%)	53 (5.0%)	12 (3.5%)
Abdominal pain lower	1 (0.3%)	0	1 (0.3%)	0	0	2 (0.2%)
Abdominal pain upper	3 (0.9%)	7 (2.5%)	10 (2.6%)	0	20 (1.9%)	7 (2.0%)
Diarrhea	2 (0.6%)	9 (3.2%)	16 (4.2%)	2 (3.1%)	29 (2.7%)	3 (0.9%)
Flatulence	10 (3.1%)	10 (3.1%)	11 (3.9%)	0	35 (3.3%)	9 (2.6%)
Nausea	9 (2.8%)	13 (4.6%)	13 (3.4%)	2 (3.1%)	37 (3.5%)	12 (3.5%)
Vomiting	1 (0.3%) 1	1 (0.4%)	8 (2.1%)	1 (1.5%)	11 (1.0%)	2 (0.6%)

Source: The reviewer modified information from Table 8.5.3.2 NDA 208271 Summary of Clinical Safety

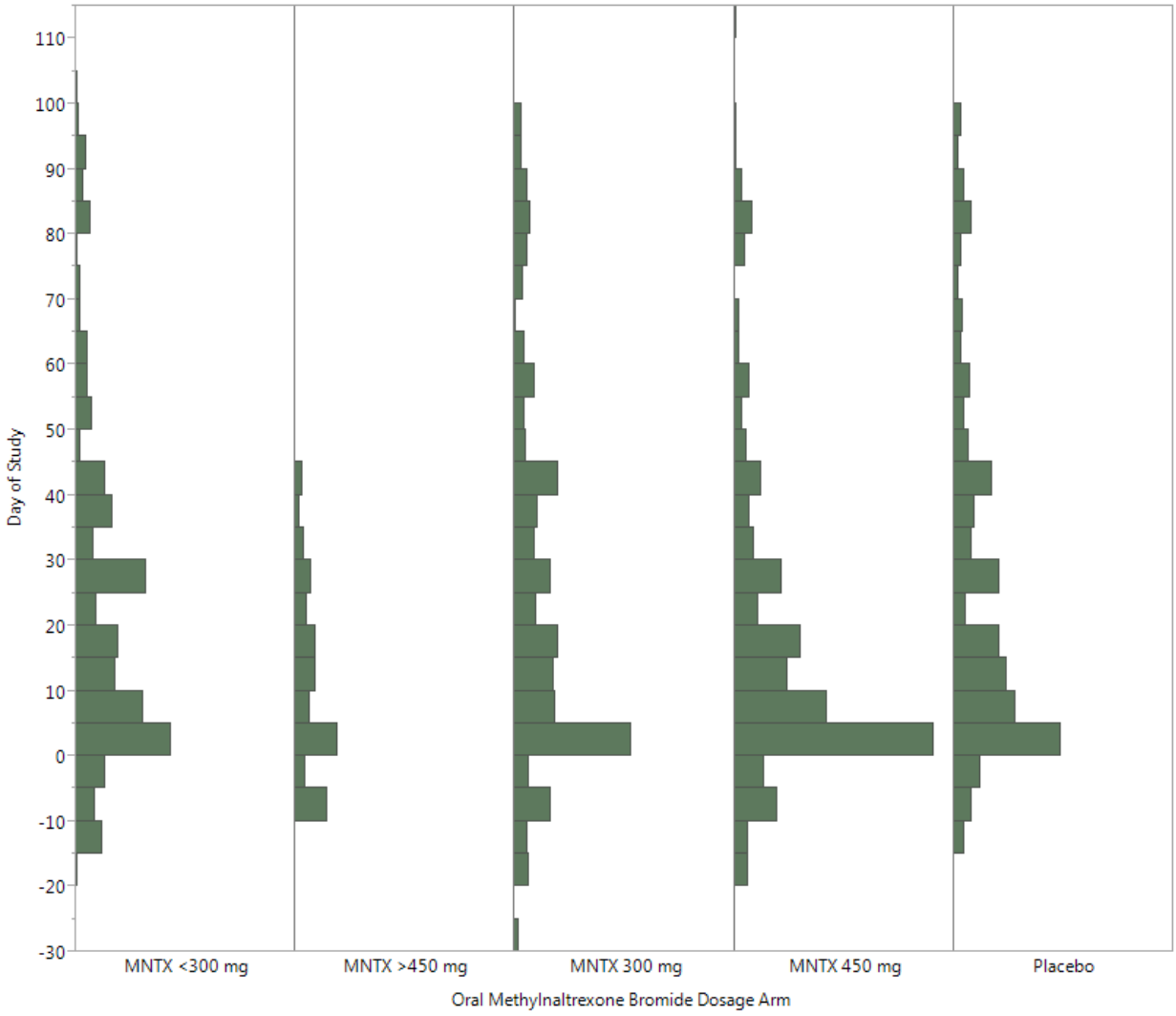
Reviewer Comments: In general, while the numbers of TEAEs and intensities of the TEAEs appeared similar in number in both the Oral Placebo-controlled pool and Study MNTX3201, there appeared to be a slightly higher level of AEs, overall in Study MNTX3201. This may be related to the fact that some of the studies in the Oral Placebo-controlled pool were of shorter duration. In general, the percentage of study drug related GI AEs appeared to increase with dosage.

7.5.2 Time Dependency for Adverse Events

`

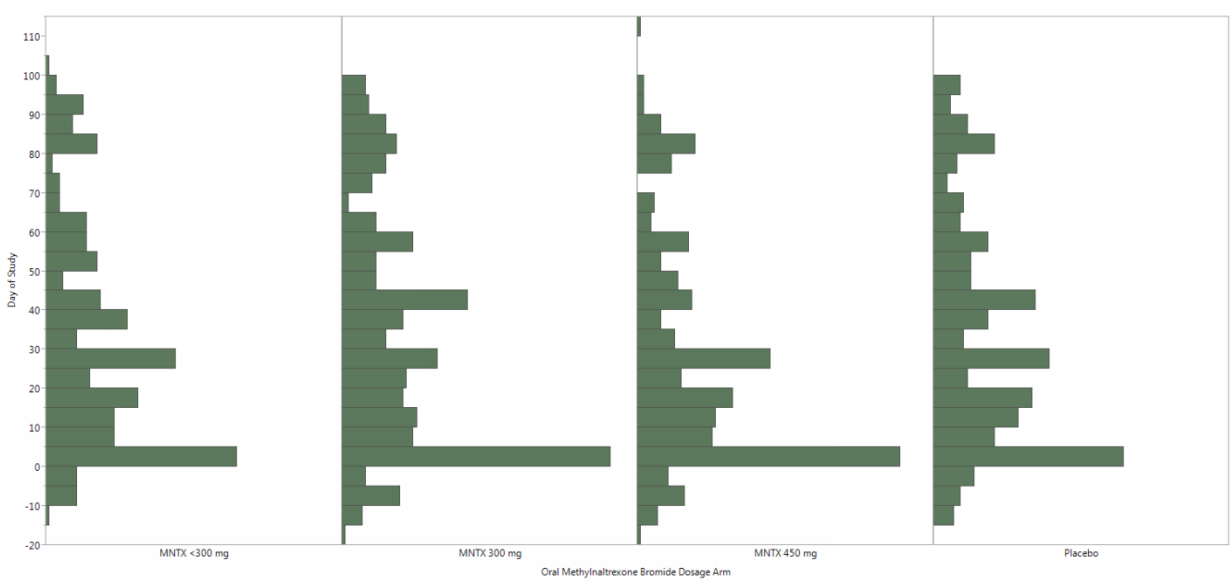
The Applicant defined drug related events as those TEAEs occurring within 14 days of the last dose of MNTX. As previously stated, the applicant did not complete a long-term safety study in support of this application. The double-blind, placebo-controlled portion of the studies were no more than 4-weeks in duration. Dosing after the initial 4-weeks was only on an as-needed basis (PRN), thereby limiting the ability to assess frequency of AEs related to consistent dosing to only 4 weeks. No other explorations of time dependency as related Figure 9 graphs how many subjects in Study MNTX3201 reported an AE (X-axis) as related to the study Day (Y-Axis), for the full duration of the study.

Figure 9: Time Dependency of Reported AEs in the Oral Placebo Controlled OIC Pooled Data



Source: Reviewer's analysis of AE.xpt dataset for NDA 208271

Figure 10: Time Dependency of Reported AEs in Study MNTX 3201.



Source: Reviewer's analysis of AE.xpt dataset for NDA 208271

Similarly, time dependency of AEs was explored for all Oral Placebo-controlled OIC data set as noted in Figure 10.

Reviewer Comments: While AEs were reported throughout the duration of the studies, the majority were reported within the first 10 days of study drug initiation, as shown in Figures 9 and 10. Study MNTX3201 showed a similar pattern with GI events reported throughout the study, but more frequently within the first few days of study drug initiation. This may suggest that tolerability improves with time. The mean and median duration of trial for subjects in Study MNTX3201 by study arm are noted below, and suggest that despite a higher frequency of AEs reported earlier in exposure to study drug, subjects tended to continue with protocol through much of the PRN phase. The mean and median duration of all study arms were comparable.

Mean and Median Duration of Study MNTX3201

Exposure to study Drug (Days)	***150 mg (N=201)***	***300 mg (N=201)***	***450 mg (N=200)***	***Placebo (N=201)***
Mean	***71.5***	***70.0***	***69.1***	***67.4***
Median	***83***	***83***	***83***	***88.0***
Standard Deviation	***24.1***	***24.5***	***26.3***	***25.8***
Standard Error mean	***1.7***	***1.7***	***1.85***	***1.82***

Source: Medical Officer review of POP.xm dataset of Study MNTX3201, using "EXDUR", exposure duration total column

7.5.3 Drug-Demographic Interactions

The applicant analyzed the safety of the Oral Placebo-controlled OIC pool based on age group, gender and opioid equivalence.

Age Group:

In the Oral Placebo-Controlled OIC Pool, 961 patients were <65 (91 %) years of age and 96 patients (9%) were ≥65 years of age. Overall, the rates of TEAEs were similar across age groups (52.4% for all MNTX doses in patients < 65 years compared with 53.1% for all MNTX doses in patients who were ≥ 65 years of age). GI related AEs occurred at higher frequency in a dose dependent manner (abdominal pain, nausea and flatulence) in both age cohorts. See Table 61 for additional details.

Table 61: TEAEs with Incidence ≥5% by Age: Oral Placebo-Controlled OIC Pool

System Organ Class Preferred Term	MNTX < 300 mg (N=327) n (%)	MNTX 300 mg (N=280) n (%)	MNTX 450 mg (N=385) n (%)	MNTX > 450 mg (N=65) n (%)	All MNTX (N=1057) n (%)	Placebo (N=344) n (%)
Subjects with TEAEs,						
< 65 years, n	n=301	n=245	n=353	n=6	n=961	n=304
	153 (50.8)	140 (57.1)	177 (50.1)	34 (54.8)	504 (52.4)	165 (54.3)
≥ 65 years, n	n=26	n=3	n=32	n=	n=9	n=40
	15 (57.7)	19 (54.3)	17 (53.1)	0	51 (53.1)	18 (45.0)
Gastrointestinal						
Abdominal pain						
< 65 years	16 (5.3)	15 (6.1)	28 (7.9)	3 (4.8)	62 (6.5)	17 (5.6)
≥ 65 years	1 (3.8)	3 (8.6)	2 (6.3)	0	6 (6.3)	3 (7.5)
Nausea						
< 65 years	22 (7.3)	17 (6.9)	19 (5.4)	3 (4.8)	61 (6.3)	22 (7.2)
≥ 65 years	1 (3.8)	4 (11.4)	2 (6.3)	0	7 (7.3)	1 (2.5)
Diarrhea						
< 65 years	10 (3.3)	10 (4.1)	16 (4.5)	3 (4.8)	39 (4.1)	10 (3.3)
≥ 65 years	0	5 (14.3)	5 (15.6)	0	10 (10.4)	0
Flatulence						
< 65 years	11 (3.7)	8 (3.3)	13 (3.7)	0	32 (3.3)	12 (3.9)
≥ 65 years	2 (7.7)	4 (11.4)	1 (3.1)	0	7 (7.3)	1 (2.5)
Infections and						
Urinary tract infection						
< 65 years	7 (2.3)	7 (2.9)	8 (2.3)	3 (4.8)	25 (2.5)	8 (2.6)
≥ 65 years	3 (11.5)	2 (5.7)	0	0	5 (5.2)	1 (2.5)

Source: Integrated Summary of Safety Table 57

Gender:

The Applicant evaluated the most frequently reported TEAEs In the Oral Placebo-controlled OIC pool as assessed by gender. 544 males and 857 females were represented in the analysis pool. In general, more women than men were represented as exposed to methylnaltrexone bromide (60.8% vs. 39.2%) and placebo (62.2% vs. 37.8%), with complaints of abdominal pain and nausea reported at a slightly higher frequency by women (Table 62).

Table 62: TEAEs with Incidence ≥5% by Gender: Oral Placebo-Controlled OIC Pool

System Organ Class Preferred Term	MNTX < 300 mg (N=327) n (%)	MNTX 300 mg (N=280) n (%)	MNTX 450 mg (N=385) n (%)	MNTX > 450 mg (N=65) n (%)	All MNTX (N=1057) n (%)	Placebo (N=344) n (%)
Subjects with TEAEs						
Male, n	n=118	n=126	n=145	n=25	n=414	n=130
	55 (46.6)	66 (52.4)	65 (44.8)	14 (56.0)	200 (48.3)	64 (49.2)
Female, n	n=209	n=154	n=240	n=40	n=643	n=214
	113 (54.1)	93 (60.4)	129 (53.8)	20 (50.0)	355 (55.2)	119 (55.6)
Gastrointestinal Disorders						
Abdominal pain						
Male	7 (5.9)	5 (4.0)	9 (6.2)	1 (4.0)	22 (5.3)	7 (5.4)
Female	10 (4.8)	13 (8.4)	21 (8.8)	2 (5.0)	46 (7.2)	13 (6.1)
Nausea						
Male	5 (4.2)	6 (4.8)	8 (5.5)	1 (4.0)	20 (4.8)	7 (5.4)
Female	18 (8.6)	15 (9.7)	13 (5.4)	2 (5.0)	48 (7.5)	16 (7.5)
Diarrhea						
Male	3 (2.5)	3 (2.4)	9 (6.2)	1 (4.0)	16 (3.9)	3 (2.3)
Female	7 (3.3)	12 (7.8)	12 (5.0)	2 (5.0)	33 (5.1)	7 (3.3)

Source: Integrated Summary of Safety Table 58

Opioid Equivalence:

The incidence of TEAEs as related to baseline oral morphine equivalents was analyzed for subjects in the Oral placebo controlled OIC pool who used <150 mg/day (719 subjects) vs. ≥ 150 mg/day (681 subjects). For any subject exposed to oral methylnaltrexone bromide the mean baseline opioid use (as oral morphine equivalents) was 215.2 mg/day compared to 197.9 mg/day in the placebo group.

The overall incidence of TEAEs at any methylnaltrexone dosage was slightly higher in subjects whose opioid use exceeded ≥ 150 mg/day opioid mean equivalents (OME) (56.9% MNTX, 55.8% placebo) compared with subjects who used < 150 mg/day (48.2% MNTX, 51.1% placebo) in the oral placebo-controlled pool. The Applicant noted that the

distribution and incidence of reported TEAEs to OME dosage was similar in the oral-placebo controlled pool.

Within complaints of GI disorders, the reported AEs were similar across OME cohorts, with 10% of subjects receiving MNTX exposed to <150 mg/day OME reporting abdominal pain AEs, compared 9.7% of subjects receiving MNTX and exposed to ≥150 mg/day OME. noted abdominal pain compared with 8.4% of patients receiving placebo. Nausea was noted more frequently in subjects with ≥ 150 mg/day OME (8.5%) compared to those < 150 mg/day OME (4.3%).

Body Weight:

The Applicant also analyzed TEAEs in the Oral Placebo-controlled OIC Pool by weight. For subjects <80 kg, the incidence of any TEAE after exposure to methylnaltrexone bromide was 53.2% in comparison to placebo (50.0%). In those subjects ≥80 kg, any methylnaltrexone exposure resulted in complaints of TEAEs in 52% of subjects, in comparison to placebo (55.1%). While more subjects in the ≥80 kg group on placebo (27.6%) complained of GI related TEAEs than those exposed to methylnaltrexone bromide (23.0%), the highest complaints in the ≥80 kg group in this SOC was at 450 mg related to abdominal pain (12% vs 6.5% placebo). Placebo-treated subjects ≥ 80 kg experienced a higher incidence of nausea (8.4% vs. 3.8%) and vomiting (5.1% vs. 0.8%) compared with placebo-treated subjects < 80 kg. Methylnaltrexone bromide treated subjects at any dosage reported GI complaints more frequently when <80 kg (25.2%) in comparison to ≥ 80 kg (23.0%). However, complaints of abdominal pain (including lower abdominal pain and upper abdominal pain) were more frequent when ≥80 kg (12%) compared to subjects <80 kg at 450 mg methylnaltrexone bromide. This dosage demonstrated the highest complaints of abdominal pain in all study arms in the oral placebo-controlled OIC pool.

Reviewer Comments: In summary, the most frequently reported AEs were in subjects who were Caucasian females and in subjects whose opioid use exceeded ≥ 150 mg/day OME. These groupings were similar to those seen in Study MNTX3356, but are also reflective of demographics of the subjects enrolled in these studies.

7.5.4 Drug-Disease Interactions

Hepatically Impaired Subjects

Patients with unstable or severe hepatic disease were excluded from the Phase 3 study. As noted in Section 7.2.3, the Applicant completed a single study to evaluate dosage in subjects with mild or moderate hepatic impairment. Patients with moderate hepatic

(Child-Pugh Grade B and C) impairment were recommended to lower dosing to 150 mg daily.

Study MNTX1004 compared PK levels of oral methylnaltrexone bromide after a single dose in healthy subjects and subjects with hepatic impairment (Child-Pugh A, B, or C). Impaired liver function led to increases in systemic exposure to oral methylnaltrexone bromide compared to healthy subjects. Mean Cmax values in Child-Pugh B and C subjects were approximately 4-and 5-fold higher, respectively, than healthy subjects, while Cmax was 2-fold higher in subjects with milder disease (Child-Pugh A). Similarly, mean $AUC_{0-\infty}$values were twice as high for Child-Pugh B and C subjects, compared with healthy subjects. Child-Pugh A subjects had a mean $AUC_{0-\infty}$ comparable to healthy subjects.

Renally Impaired Subjects

Patients with unstable or severe renal disease were excluded from the Phase 3 study. The Applicant completed Study MNTX1105, an open-label, multi-center, non-randomized study, to evaluate the PK, safety and tolerability of a single dose of Relistor® SC in subjects with impaired renal function.

In this study, 8 healthy subjects were matched to 3 groups of 8 patients with mild, moderate or severe renal impairment. All received 0.3 mg/kg subcutaneous methylnaltrexone bromide. Severe renal impairment decreased the renal clearance of MNTX by 8- to 9-fold and resulted in a 2-fold increase in total MNTX exposure (AUC). Mean Cmax was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Although not specifically testing during the oral methylnaltrexone bromide development program, there was no indication that oral treatment had a negative effect on renal function in patients with OIC and CNCP.

The current labeling for SC methylnaltrexone bromide indicates decreased dosage (6 mg) in patients with severe renal impairment, where creatinine clearance is less than 30 mL/min as estimated by Cockcroft-Gault..

Reviewer Comments: The PK/PD data and bioavailability data between the SC and oral formulations suggest that there should not be a concern with oral dosing for patients with mild renal impairment. However, for patients with moderate to severe renal impairment, oral administration may considered with caution.

7.5.5 Drug-Drug Interactions

Current labeling for SC methylnaltrexone bromide states that concomitant use with other opioid antagonists should be avoided because of the potential for additive effects of opioid receptor antagonism and increased risk for opioid withdrawal.

The Applicant completed studies of methylnaltrexone and its metabolites to investigate as substrates and inhibitors of the transporters P-gp, BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, and MATE2-K. As a whole, in the Applicant's review of the studies completed, there did not appear to be a clinically significant drug-drug interaction by induction or inhibition of drug metabolizing enzymes or drug transporters by methylnaltrexone at a daily oral dose of 450 mg.

Listing of the most frequent concomitantly taken medications during the Phase 3 study MNTX3201 were reported in Table 63. Analgesics (range from 94.7 - 96.0% and laxatives (61.0 - 65.2%) were the most frequent in all study arms.

Table 63: Concomitant Medications Taken by ≥15% of Subjects in any Treatment Group (Safety Population) for Study MNTX3201

Medication Class Preferred Term	Placebo n (%)	MOA-728 150 mg n (%)	MOA-728 300 mg n (%)	MOA-728 450 mg n (%)	All MOA-728 n (%)
Subjects Randomized (N)	**201**	**201**	**201**	**200**	**602**
Any Concomitant Medications	201 (100.0)	201 (100.0)	201 (100.0)	200 (100.0)	602 (100.0)
Agents Acting on the Renin-Angiotensin System	57 (28.4)	50 (24.9)	53 (26.4)	45 (22.5)	148 (24.6)
Lisinopril	38 (18.9)	26 (12.9)	36 (17.9)	22 (11.0)	84 (14.0)
Analgesics	192 (95.5)	190 (94.5)	188 (93.5)	192 (96.0)	570 (94.7)
Oxycodone	68 (33.8)	61 (30.3)	75 (37.3)	72 (36.0)	208 (34.6)
Morphine	63 (31.3)	64 (31.8)	58 (28.9)	60 (30.0)	182 (30.2)
Vicodin	35 (17.4)	58 (28.9)	46 (22.9)	44 (22.0)	148 (24.6)
*Gabapentin	30 (14.9)	40 (19.9)	36 (17.9)	43 (21.5)	119 (19.8)
Oxycocet	28 (13.9)	27 (13.4)	23 (11.4)	30 (15.0)	80 (13.3)
Laxatives	128 (63.7)	130 (64.7)	131 (65.2)	122 (61.0)	383 (63.6)
Bisacodyl	122 (60.7)	119 (59.2)	121 (60.2)	113 (56.5)	353 (58.6)
Lipid Modifying Agents	65 (32.3)	68 (33.8)	65 (32.3)	65 (32.5)	198 (32.9)
Simvastatin	26 (12.9)	24 (11.9)	19 (9.5)	30 (15.0)	73 (12.1)
Muscle Relaxants	83 (41.3)	87 (43.3)	89 (44.3)	94 (47.0)	270 (44.9)
Cyclobenzaprine	28 (13.9)	24 (11.9)	25 (12.4)	32 (16.0)	81 (13.5)
Carisoprodol	26 (12.9)	19 (9.5)	31 (15.4)	23 (11.5)	73 (12.1)
Other Nervous System Drugs	34 (16.9)	40 (19.9)	37 (18.4)	34 (17.0)	111 (18.4)
Methadone	28 (13.9)	33 (16.4)	31 (15.4)	31 (15.5)	95 (15.8)
Thyroid Therapy	27 (13.4)	25 (12.4)	31 (15.4)	29 (14.5)	85 (14.1)
Levothyroxine	27 (13.4)	24 (11.9)	31 (15.4)	27 (13.5)	82 (13.6)

Source: Table 37: MNTX3201 CSR

Reviewer Comments: *No safety signals were identified related to the use of concomitant medications.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed. Animal carcinogenicity studies had been completed previously for SC methylnaltrexone and are summarized in the most recent FDA approved label (September 2014):

"Two-year oral carcinogenicity studies have been conducted with methylnaltrexone in CD-1 mice at doses up to 200 mg/kg/day (about 81 times the maximum recommended human (MRHD) dose of 0.2 mg/kg/day based on body surface area) in males and 400 mg/kg/day (about 162 times the MRHD of 0.2 mg/kg/day based on body surface area) in females and in Sprague Dawley rats at oral doses up to 300 mg/kg/day (about 243 times the MRHDof 0.2 mg/kg/day based on body surface area). Oral administration of methylnaltrexone for 104 weeks did not produce tumors in mice and rats."

7.6.2 Human Reproduction and Pregnancy Data

Human pregnancy studies were not performed, and all women of child bearing age were required to complete urine/serum pregnancy tests and use appropriate contraception during study enrollment. The most recent FDA approved label for SC methylnaltrexone and are summarized below (September 2014):

"There are no adequate and well-controlled studies with RELISTOR in pregnant women. The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of intravenous methylnaltrexone during organogenesis in rats and rabbits at doses up to 20 times and 26 times, respectively, the maximum recommended human dose (MRHD) of 0.2 mg/kg/day. RELISTOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus"

Reviewer Comments: Labeling will continue to reflect current concerns for fetal opioid withdrawal and fetal developmental concerns, inclusive of opioid withdrawal syndrome in the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please see Dr. Ethan Hausman's review from the Division of Pediatric and Maternal Health (DPMH). The Sponsor has requested a full waiver of pediatric studies under the Pediatric Research Equity Act (PREA). Previous discussions between the Pediatric Review Committee (PeRC) and the Division determined that studies to evaluate

PAMORA in the pediatric population were both impossible and highly impracticable due to the need for at least 4 weeks duration of round-the clock opioid/naltrexone exposure required to develop OIC in chronic non-cancer pain and assess treatment effect. No pediatric data has been submitted for a labeling indication for this application or for the previously marketed formulation.

Reviewer Comments: This reviewer agrees with the Applicant's request for a full waiver, and the Applicant's waiver request was granted on by the Pediatric Review Committee (PeRC) on 17 February2016.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The integrated summary of safety (ISS) reported a single patient from study 2201 (MOA7282201-026-1127) receiving 450 mg oral methylnaltrexone bromide with an accidental overdose of the study drug two weeks after initial exposure. The subject was a 48 year old man with a history of levoscoliosis, hypertension and insomnia. Per the narrative, the subject was prescribed 4 (150 mg) tablets per day, but ingested 8 tables per day. There were no additional reported AEs for this subject and the AE was categorized as "mild" in intensity. The subject was withdrawn from the study per the principal investigator's discretion due to the protocol violation.

For assistance with the analysis of AEs possibly related to opioid withdrawal, DGIEP consulted the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The overall conclusions focused upon Opioid withdrawal syndrome (OWS) to state that Study MNTX3201 was not adequately designed to fully evaluate study subjects for the presence of OWS. However review of the identified cases of OWS in the oral methylnaltrexone bromide clinical development program appeared sufficient to support the Applicant's proposed labeling. There was no comment regarding concerns for oral methylnaltrexone bromide overdose.

Reviewer Comments: The narrative for subject MOA7282201-026-1127 was limited and did not describe any clinical concerns. No specific safety concerns were identified related to oral methylnaltrexone bromide overdose. There is no apparent history of any safety signals upon overdose or drug abuse potential with use of Relistor® SC. This reviewer's interpretation is that the risk is probably low, if present at all.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Initial labeling was completed for use in patients with OIC in the context of cancer related pain unresponsive to conventional therapy in the palliative care setting. A summary of labeling revisions is noted in Table 64.

Table 64: Labeling Revisions for Relistor® SC

Date	Indication for Labeling Revision
24 April 2008	Initial labeling
4 November 2009	Labeling revision to update information on AE to include the following language: The most common (> 5%) adverse reactions reported with RELISTOR are abdominal pain, flatulence, nausea, dizziness, diarrhea and hyperhidrosis.
23 July 2010	Provided for the addition of gastrointestinal perforation warning language to the following sections of the package insert (PI): Warnings and Precautions (5.2 Intestinal Perforation), Adverse Reactions (6.2 Postmarketing Experiences), Patient Counseling Information, as well as to the patient package insert (PPI).
23 August 2013	Provided for the addition of the creating of a **Medication Guide** and **Instructions for Use** sections. Information regarding post-marketing experience added to include the following: *Gastrointestinal: Perforation, cramping, vomiting* *General Disorders and Administrative Site Disorders: Diaphoresis, flushing, malaise, pain. Cases of opioid withdrawal have been reported.*
29 September 2014	This efficacy supplement expanded the approved indication to include the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain

Source: Drugs@FDA.com, Relistor

Since 29 September 2014, there have been safety labeling changes or modifications to postmarketing safety monitoring.

Relistor® SC was initially approved on 24 April 2008 for the treatment of OIC in a palliative care setting and for chronic OIC in patients with non-cancer pain on 29 April 2014. The Applicant provided a summary of spontaneously AEs reported for Relistor® SC during the postmarketing period in NDA 208271. The most commonly reported serious AEs were within the Gastrointestinal disorders SOC, and bowel perforation was the most commonly reported SAE. The most common non-serious AEs reported are within the category of General disorders and administration site condition and (Table 65). There were 14 SAEs related to cardiac disorders, the most frequently reported was tachycardia. (Table 66).

Table 65: Overview of Relistor® SC Postmarketing Adverse Events (28 March 2008 through 27 March 2015)

SOC/MedDRA PTs	Serious		Non Serious		Total	Solicited	
	I	C	I	C	SC	Ser I	Ser C
Blood and lymphatic system disorders	0	1	0	1	2	0	0
Cardiac disorders	1	14	1	2	16	0	0
Eye disorders	0	2	1	2	4	0	0
Gastrointestinal disorders	11	114	32	267	381	0	0
General disorders and administration site conditions	8	87	44	332	419	0	0
Hepatobiliary disorders	0	3	0	1	4	0	0
Immune system disorders	0	1	0	2	3	0	0
Infections and infestations	0	16	0	2	18	0	0
Injury, poisoning and procedural complications	0	9	0	2	18	0	0
Investigations	3	20	3	17	37	0	0
Metabolism and nutrition disorders	2	13	1	5	18	0	0
Musculoskeletal and connective tissue disorders	1	6	2	16	22	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	5	0	1	6	0	0
Nervous system disorders	6	27	7	40	67	0	0
Psychiatric disorders	1	18	0	12	30	0	0
Renal and urinary disorders	0	3	0	2	5	0	0
Reproductive system and breast disorders	0	4	0	1	5	0	0
Respiratory, thoracic and mediastinal disorders	2	10	1	12	22	0	0
Skin and subcutaneous tissue disorders	2	14	3	35	49	0	0
Social circumstances	0	3	0	2	5	0	0
Surgical and medical procedures	0	3	0	8	11	0	0
Vascular disorders	4	16	1	7	23	0	0
Total number of PTs	41	389	100	829	1218	0	0
Total number of Cases	10	117	44	431	548	0	0

Source: Table 60 Integrated Summary of Safety
I = Interval (defined from March 2014 to January 2015 with extrapolation by the Applicant for 12 months, C = Cumulative, SC = Spontaneous Cumulative, Ser I = Serious Interval, Ser C = Serious Cumulative

Table 66: SAEs During Post-marketing use of Relistor

Events reported in Relistor Serious Case Reports from 28Mar2008 to 27Mar2015	
MedDRA System Order Class/Preferred Term	**Sum Count (*) of MedDRA Preferred Terms**
Blood and Lymphatic system disorders	**1**
Cardiac Disorders	**14**
Acute myocardial infarction	1
Atrial fibrillation	1
Cardiac arrest	1
Cardiac failure congestive	1
Cardio-respiratory arrest	1
Cyanosis	2
Sinus arrest	1
Tachycardia	6
Eye disorders	2
Gastrointestinal disorders	114
Gastrointestinal perforation	1
Intestinal perforation	6
Large intestine perforation	5
General disorders and administration site conditions	87
Hepatobiliary disorders	3
Immune system disorders	1
Infections and infestations	16
Investigations	20
Metabolism and nutrition disorders	13
Musculoskeletal and connective tissue disorders	6
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5
Nervous system disorders	
Dizziness	1
Headache	3
Loss of consciousness	1
Migraine with aura	1
Psychiatric disorders	**18**
Renal and urinary disorders	**3**
Reproductive system and breast disorders	**4**
Respiratory, thoracic and mediastinal disorders	**10**
Skin and subcutaneous tissue disorders	**14**
Social circumstances	**3**
Surgical and medical procedures	**3**
Vascular disorders	**16**
Circulatory collapse	1
Flushing	5
Hemorrhage	1

Hypertension	**1**
Hypotension	4
Pallor	1
Shock	2
Vascular occlusion	1
Total MedDRA Preferred Terms	**389**
Total # of serious Case Reports	**117**

Source: modified from Table 61, Integrated Summary of Safety

Reviewer Comment: Post-marketing safety reports are difficult to interpret, as the data is not from controlled studies, After approval of Relistor® SC for use in the treatment of OIC in adults in palliative care unresponsive to laxative therapy, the post-marketing period identified a new signal of bowel perforation. On 23 July 2010 the Relistor® SC label was amended to acknowledge this risk. No additional new safety signals have been subsequently identified.

9 Appendices

Appendix A: Risk Management Plan

Safety concern (Important Identified Risk, Potential Risk, or Missing Information)	Pharmacovigilance activities (routine and additional)	Risk Minimization activities (routine and additional)
Important Identified Risks		
Gastrointestinal effects	Routine Pharmacovigilance and discussion of adverse events in periodic reports	**US Package Insert:** **Warnings and Precautions:** To instruct the prescriber if severe or persistent diarrhea occurs during treatment, patients should be advised to discontinue therapy and consult their healthcare provider **Adverse Reactions:** GI AEs of abdominal pain, nausea, diarrhea, (b) (4) are cited in the Adverse Reactions section of the US PI describing common adverse reactions (≥1%) observed in the Advanced Illness and Non-Cancer Pain study populations. **Ongoing monitoring of safety data:** Ongoing monitoring of clinical trials and postmarketing reports will include a targeted review for reports of GI AEs observed in the setting of Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous Relistor treatment).
Gastrointestinal Perforation	Routine Pharmacovigilance and discussion of adverse events in periodic reports New reports of GI perforation will be reviewed in real time and any change in the profile or risk factors for GI perforation will lead to a more detailed examination as appropriate. Any new safety information concerning this risk will be communicated through updates to the product label	**US Package Insert:** **Contraindications:** Informs the prescriber that use of Relistor is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction. **Warnings and Precautions:** Instructs the prescriber to consider the overall risk benefit in patients with known or suspected lesion of the GI tract and monitor for severe, persistent or worsening abdominal pain; and to discontinue if symptoms develop. **GI Perforation:** Background and risk information on Gastrointestinal Perforation (GI) observed in the setting of subcutaneous administration to Advanced Illness patients is detailed in section 5.1 of the US PI (Warnings and Precautions, Gastrointestinal Perforation) and applies to all patient populations and routes of administration as follows: Cases of gastrointestinal perforation have been reported in adult patients with opioid induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease,

		Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using Relistor in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue Relistor in patients who develop this symptom **Ongoing monitoring of safety data:** (Noted as above)
Opioid Withdrawal Symptoms	Routine Pharmacovigilance and discussion of adverse events in periodic reports Planned surveillance (see Potential Risks below): Concerns about the potential for drugs in the pharmacologic class of opioid receptor antagonists to cause opioid withdrawal symptoms and a potential link between the hemodynamic and autonomic nervous system effects of opioid withdrawal and cardiovascular events were examined in the FDA Anesthetic and Analgesic Drug Products Advisory Committee on 11-12 June 2014. Evaluation of Major Adverse Cardiovascular (MACE) events is captured as a separate safety concern in this RMP under the heading of Potential Risk.	**US Package Insert:** **Warnings and Precautions** Instruct that symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with Relistor. Prescribers are also advised that patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia with instructions to: -Take into account the overall risk-benefit profile when using Relistor in such patients.-Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients. **Ongoing monitoring of safety data:** Ongoing monitoring of clinical trials and postmarketing reports will include a targeted review for reports of opioid withdrawal like symptoms (inclusive of events experienced by the mother, fetus/neonate/infant) in the setting of Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous RELISTOR treatment).
Potential Risks		
Concomitant use with other opioid antagonists	Routine Pharmacovigilance and discussion of adverse events in periodic reports	**Drug Interactions** The Drug Interactions section (7.1) advises prescribers to avoid concomitant use of Relistor with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

		Ongoing monitoring of safety data: Ongoing monitoring of post marketing reports will include a targeted review for events observed in the setting of Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous Relistor treatment) concurrent with other opioid antagonists.
Major Adverse Cardiovascular Events (MACE) (Potential Risk and identified by FDA as "new safety information)	Routine Pharmacovigilance and discussion of adverse events in periodic reports **Planned surveillance:** (b) (4) post marketing requirement (PMR) for an observational epidemiologic study comparing SC RELISTOR to other treatments of OIC in patients with chronic non-cancer pain. (b) (4)	(b) (4) **Ongoing monitoring of safety data:** Ongoing monitoring of clinical trials and post marketing reports will include a targeted review for cardiovascular events observed in the setting of Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous Relistor treatment). In accordance with the 24-Apr- 2008 FDA approval letter for Relistor SC in AI, adverse events related to the cardiac and hepatic organ class as well as reports of dehydration will continue to be submitted as 15-day reports, per reporting regulation 21 CFR 314.80.
Potential for off-label use	Routine Pharmacovigilance and discussion of adverse events in periodic reports	**US Package Insert:** Indications and Usage explicitly states the indication and appropriate adult patient populations for use of Relistor. The safety and effectiveness of Relistor have not been established in pediatric patients. Sales force detailing and product promotion materials are developed to clearly communicate the indication and appropriate populations for use and are intended to help

		guide healthcare professionals to use Relistor only in the indicated patient populations. Balancing statements such as "(b) (4) have been included in the indication statements of promotional literature and advertisements
Potential for Misuse	Routine Pharmacovigilance and discussion of adverse events in periodic reports	**US Package Insert:** As Relistor has no intrinsic opioid agonist activity, there is no potential for direct abuse of the medication. However, as constipation is a major side effect of chronic opioid abuse, and chronic opioid abusers rarely develop tolerance to constipation, abusers may wish to acquire Relistor to alleviate this side effect. There is a possibility that Relistor might be seen as an attractive medication for relieving the constipating side effects of opioid abuse. To date, post marketing spontaneous reports with Relistor do not suggest that the product is subject to misuse for illegal purposes. During development of risk management measures, experts in the fields of opioid addiction and narcotic diversion were consulted to determine if there is a potential for misuse that would require enhanced pharmacovigilance and/or risk minimization activities. The final report from experts revealed no additional pharmacovigilance or risk minimization activities were indicated. **Ongoing monitoring of safety data:** Ongoing monitoring of clinical trials and post marketing reports will include a targeted review for misuse observed with Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous Relistor treatment).
Missing Information		
Pregnant and Lactating women and Pediatric Use	Routine Pharmacovigilance and discussion of adverse events in annual periodic report	**US Package Insert:** **Use in Specific Populations:** **Pregnancy:** Prescribers are advised that there are no adequate and well controlled studies with Relistor in pregnant women. The use of Relistor during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. **Lactation** Prescribers are advised that it is not known whether Relistor is present in human milk. However, methylnaltrexone bromide is present in rat milk. Because of the potential for serious adverse reactions, including opioid withdrawal in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**

		Prescribers are advised that the safety and effectiveness of Relistor have not been established in pediatric patients. **Ongoing monitoring of safety data:** Ongoing monitoring of clinical trials and post marketing reports will include a targeted review for misuse observed with Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous Relistor treatment).

Source: Modified from Section 1.16.1 Module 1 Administrative Information NDA 208271

Appendix B: Summary of Regulatory meetings for oral MNTX

4 November 2014 Meeting Clinical Comments:

Question 1: Based on the efficacy and safety of SC MNTX in OIC in non-cancer pain patients (Studies 3356 and 3358), comparability of pharmacokinetic/pharmacodynamic relationships for SC and oral MNTX, and demonstrated efficacy of the oral MNTX formulation (Study 3201), does the Division concur that these data establish sufficient basis for submission and substantive review of the proposed sNDA for oral MNTX?

FDA Response to Question 1:
As noted by FDA during our 7 March 2012 meeting, current standards for the design of trials for new drugs to treat OIC in NCP have changed since the completion of the trials listed above. However, we acknowledge that, as described in the label, Relistor SC was approved based on a primary endpoint of the proportion of patients with ≥ 3 spontaneous bowel movements (SBMs) per week during the 4-week double-blind period. In order for Study 3201 to support the approval of an oral Relistor formulation, the results of the pre-specified analyses supporting the proposed dose would first need to be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product. The results of these key analyses of clinical endpoints considered suitable for purposes of labeling would need to be robust (e.g., analyses comparable to the analyses presented in subcutaneous methylnaltrexone product labeling for the indication of OIC in chronic pain).

We do not agree that the pre-specified primary endpoint of Study 3201 is appropriate for labeling as it does not adequately define an overall responder for a chronic condition and is likely not to be readily interpretable to patients or practitioners. These will be review issues during the NDA review if you choose to submit the completed single oral methylnaltrexone trial as the major trial supporting the NDA. Note that key support for this approach would be persuasive safety data indicating that the oral formulation is better tolerated than the SC formulation (i.e., evidence that you have identified an effective alternative oral dosing formulation with evidence of improved safety compared to the available SC formulation).

7 March, 2012 Meeting Clinical Comments:

Sponsor Question:
Does the Agency concur that efficacy data from the phase 3 study 3201, double-blind efficacy study 3356, open-label study 3358, and additional supportive studies are sufficient to allow for a substantive review of this NDA?

FDA Response to Question 1:
No, we do not concur.
We have the following concerns regarding study 3201:

- A clinically relevant endpoint was not evaluated over an adequate treatment duration (i.e. 12 weeks)
- Primary endpoint assessing RFBM within 4 hours of dosing is not acceptable
- The 150 mg dose regimen failed to demonstrate a positive result assessed by your primary endpoint based upon your proposed Hochberg multiplicity adjustment procedure
- Only the 450 mg dose regimen demonstrated a positive result assessed by an overall responder analyses and using the proposed Hochberg multiplicity adjustment procedure.
- Since not all three doses showed significant results and Hochberg procedure is not a separable procedure, no alpha level was left to test secondary endpoints.

Because the definitive relative bioavailability between SC MNTX and the to-be-marketed oral formulation and the final dose for marketing is not available at this point, it is not clear whether efficacy and/or safety of SC MNTX 12 mg in patients with non-cancer pain could be supportive of the efficacy and/or long term safety of oral MNTX.

In addition, we note that the to-be-marketed formulation is different from the formulation used in study 3201 and will be manufactured at a different site. Bioequivalence should be demonstrated between the to-be-marketed formulation and the phase 3 formulation. You should include appropriate bridging studies between the various oral formulations and the to-be-marketed formulation if studies conducted using other oral formulations are to be used to support safety and efficacy of the to-be-marketed formulation at the time of your NDA submission.

Given the above concerns, we recommend that you conduct two independent phase 3 trials to demonstrate efficacy and safety of the proposed oral product in the target population. To support an indication for treatment of opioid-induced constipation (OIC) in patients with *chronic* non-cancer pain, the duration of the double-blind treatment period should be at least 12 weeks (see additional comments #1).

Additional Discussion:
Salix provided additional discussion points relative to the FDA preliminary comments (see handout attachment). FDA reinforced content of preliminary comments, no agreements or new comments were provided during the discussion.

FDA agreed to consider a follow-up discussion in the future regarding trial design for as needed dosing. [Post-meeting comments: Trial design for as needed dosing should be conducted in double blind manner.]

Question 2: Does the Agency concur that the proposed safety pools, safety database and ISS analysis plan are sufficient to provide a substantive review of this NDA?

FDA Response to Question 2: No we do not concur. Please see our response to question 1. The to-be-marketed formulations and doses should be pooled together. Safety data using other formulations (i.e., SC, (b) (4) would be considered supportive and should be presented separately.

Question 3: Does the Agency have questions or recommend any additional analyses beyond those specified in the ISS analysis plan?

FDA Response to Question 3: We do not have any additional comments or recommendations at this time. Please see our response to question 1.

Question 4: Does the Agency concur with the proposed recommended dose of 150 mg (1 MNTX tablet), 300 mg (2 MNTX tablets) or 450 mg (3 MNTX tablets) orally QD?

FDA Response to Question 4: See our response to question 1.

4 April 2011 Meeting Comments:

Sponsor Question: Based on the in silico data presented on (b) (4) and (b) (4) the Sponsor believes that (b) (4) similar to (b) (4) does not present significant genotoxic risk and is of low concern for human safety. Therefore, the Sponsor proposes to control (b) (4) in the MNTX oral drug product as a specified identified degradation product at the lower value of NMT (b) (4) % or (b) (4) mg total daily intake (TDI) in accordance with ICH Q3B(R2). Does the Agency agree?

FDA Response:
We agree, based on our expectation that the human daily dose of MNTX will not be more than 2 g. For daily doses greater than 2 g, the limit should be (b) (4) %.

Appendix C: Patient- and Clinician – Reported Outcomes

- Weekly averages of BSS scores of RFBMs. The BSS is a 7-point scale rating the characteristics of the stool sample. The range is from Type 1, separate hard lumps, like nuts (hard to pass) to Type 7, watery, no solid pieces, entirely liquid. The BSS is a recognized, general measure of stool consistency or form.
- Weekly number of quality RFBMs (i.e. RFBMs with BSS types 3 and 4).
- Weekly number of complete RFBMs, i.e., RFBMs with a sensation of complete evacuation. Measures of the sense of complete evacuation were recorded for each bowel movement using the Sense of Complete Evacuation Scale, which is a subject assessment tool.
- Weekly average of Straining Scale of RFBMs. The Straining Scale is a 5-point subject assessment tool to rate the amount of straining: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.
- Proportion of subjects with improvement in BSS of RFBMs by ≥ 1 level weekly.
- Proportion of subjects with improvement in Straining Scale of RFBMs by ≥ 1 level weekly.
- Weekly average of daily stool consistency score.
- Proportion of subjects with diarrhea or watery RFBMs (BSS Type 6 or 7) by week.
- Monthly average percentage of RFBMs with BSS Type 3 or 4.
- Monthly average percentage of RFBMs classified as diarrhea or watery stools.
- Monthly average percentage of RFBMs with Straining Scale scores of 0 or 1.
- Monthly average percentage of RFBMs with a sensation of complete evacuation.
- Subject's and clinician's global clinical impression of change (GCIC). The GCIC is assessed using a 7-point scale designed to assess subject's and clinician's impression of the subject's change in bowel status while on study drug. The scale ranges from 1 (Much Worse) to 7 (Much Better). This scale was completed by the subject and by the clinician at the end of QD dosing (Visit 4) and end of treatment (Visit 7).
- Change from baseline in abdominal, rectal, and stool symptoms domain scores and overall score of Patient Assessment of Constipation – Symptoms (PAC-SYM) at each time point and end of treatment. The PAC-SYM is a 12 item survey that measures the severity of constipation symptoms across 3 domains: stool symptoms, rectal symptoms, and abdominal symptoms, and overall. The PAC-SYM scale is used primarily to evaluate chronic constipation.
- Change from baseline in the physical discomfort, psychosocial, worries and concerns, and satisfaction domain scores and total score of the Patient Assessment of Constipation – Quality of Life (PAC-QoL) at each time point and end of treatment. The PAC-QoL is a 28-item survey that measures constipation-specific quality of life across 4 domains: worries and concerns, physical discomfort, psychosocial discomfort, and satisfaction.

- Change from baseline in general health scale of European Quality of Life-5 Dimensions (EQ-5D) at each time point and end of treatment. The EQ-5D is a 5-item standardized instrument for use as a measure of patient reported outcomes. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D items include general health, measured on a visual analog scale (0 to 100), and 5 dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression), each measured on a 3-point scale: where 1 = no problem, 2 = some problem, and 3 = unable to perform or extreme impairment.
- Improvement from baseline (defined as ≥ 1 point decrease from baseline) in each of the 5 EQ-5D dimensions to each time point and end of treatment.
- Change from baseline to each time point and end of treatment in each of the 4 domain scores of the Work Productivity and Activity Impairment General Health V2.0 (WPAI:GH). The WPAI:GH is a 6-item questionnaire to quantify lost time from work and loss in productivity for health problems. The WPAI:GH yields 4 types of scores: absenteeism (work time missed), “presenteeism” (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. Outcomes are expressed as 4 impairment percentages in domain scores, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

Appendix D: Proportion of Subjects Achieving at ≥ 3 RFBMs and an increase of at Least 1 RFBM from Baseline (Responder Endpoint) – Weeks 1-12

Proportion (%) of Subjects Achieving at least 3 RFBMs per week (Observed Case) Intention-to-Treat Population (ITT)	**Dose MNTX**			
	150 mg 201	**300 mg 201**	**450 mg 200**	**Placebo 201**
Week 1				
Yes-n/N (%)	109/201 (54.2%)	119/201 (59.2%)	124/100 (62.0%)	101/201 (50.2%)
% Difference (vs. Placebo)	4.0%	9.0%	11.8%	
95% CI for % Diff. (vs Placebo)	(-5.8%, 13.7%)	(-0.7%, 18.6%)	(2.1%, 21.4%)	
P-value (vs. Placebo)	0.3986	0.731	0.0109	
Week 2				
Yes-n/N (%)	106/201 (52.7%)	114/201 (56.7%)	123/200 (61.5%)	102/201 (50.7%)
% Difference (vs. Placebo)	2.0%	6.0%	10.8%	
95% CI for % Diff. (vs Placebo)	(-7.8%, 11.8%)	(-3.8%, 15.7%)	(1.1%, 20.4%)	
P-value (vs. Placebo)	0.6341	0.2352	0.0285	
Week 3				
Yes-n/N (%)	110/201 (54.7%)	120/201 (59.7%)	110/200 (55.0%)	19/201 (54.2%)
% Difference (vs. Placebo)	0.5%	5.5%	0.8%	
95% CI for % Diff. (vs Placebo)	(-9.2%, 10.2%)	(-4.2%, 15.1%)	(-9.0%, 10.5%)	
P-value (vs. Placebo)	0.8478	0.3039	0.7532	
Week 4				
Yes-n/N (%)	106/201 (52.7%)	112/201 (55.7%)	112/201 (55.7%)	101/1201 (50.2%)
% Difference (vs. Placebo)	2.5%	5.5%	6.8%	
95% CI for % Diff. (vs Placebo)	(-7.3%, 12.3%)	(-4.3%, 15.2%)	(-3.0%, 16.5%)	
P-value (vs. Placebo)	0.6009	0.2612	0.1519	
Week 5				
Yes-n/N (%)	101/167 (60.5%)	102/177 (57.6%)	107/181 (59.1%)	101/167 (60.5%)
% Difference (vs. Placebo)	-2.9%	-1.4%	5.8%	
95% CI for % Diff. (vs Placebo)	(-13.2%, 7.5%)	(-11.7%, 8.9%)	(-4.5%, 16.1%)	
P-value (vs. Placebo)	0.6261	0.7673	0.1869	
Week 6				
Yes-n/N (%)	105/177 (59.3%)	108/181 (59.3%)	114/169 (67.5%)	92/167 (55.1%)
% Difference (vs. Placebo)	4.2%	4.6%	12.4%	

95% CI for % Diff. (vs Placebo)	(-6.2%, 14.7%)	(-5.8%, 15.0%)	(2.0%, 22.7%)	
P-value (vs. Placebo)	0.4194	0.4187	0.0189	
Week 7				
Yes-n/N (%)	107/177 (60.5%)	110/181 (60.8%)	114/169 (67.5%)	88/167 (52.7%)
% Difference (vs. Placebo)	7.8%	8.1%	14.8%	
95% CI for % Diff. (vs Placebo)	(-2.7%, 18.2%)	(-2.3%, 18.5%)	(4.4%, 25.1%)	
P-value (vs. Placebo)	0.1502	0.1337	0.0045	
Week 8				
Yes-n/N (%)	106/177 (59.9%)	109/181 (60.2%)	105/169 (62.1%)	86/167 (51.5%)
% Difference (vs. Placebo)	8.4%	8.7%	10.6%	
95% CI for % Diff. (vs Placebo)	(-2.1%, 18.9%)	(-1.7%, 19.1%)	(0.1%, 21.2%)	
P-value (vs. Placebo)	0.1348	0.1092	0.0393	
Week 9				
Yes-n/N (%)	101/177 (57.1%)	102/181 (56.4%)	118/169 (69.8%)	91/167 (54.5%)
% Difference (vs. Placebo)	2.6%	1.9%	15.3%	
95% CI for % Diff. (vs Placebo)	(-7.9%, 13.1%)	(-8.6%, 12.3%)	(5.1%, 25.6%)	
P-value (vs. Placebo)	0.5728	0.7587	0.0023	
Week 10				
Yes-n/N (%)	100/177 (56.5%)	110/181 (60.8%)	107/169 (63.3%)	94/167 (56.3%)
% Difference (vs. Placebo)	0.2%	4.5%	7.0%	
95% CI for % Diff. (vs Placebo)	(-10.3%, 10.7%)	(-5.9%, 14.8%)	(-3.4%, 17.5%)	
P-value (vs. Placebo)	0.9547	0.4195	0.1541	
Week 11				
Yes-n/N (%)	102/177 (57.6%)	100/181 (55.2%)	105/169 (62.1%)	85/167 (50.9%)
% Difference (vs. Placebo)	6.7%	4.4%	11.2%	
95% CI for % Diff. (vs Placebo)	(-3.8%, 17.2%)	(-6.1%, 14.8%)	(0.7%, 21.8%)	
P-value (vs. Placebo)	0.1955	0.4604	0.0392	
Week 12				
Yes-n/N (%)	105/177 (59.3%)	100/181 (55.2%)	101/169 (59.8%)	82/167 (49.1%)
% Difference (vs. Placebo)	10.2%	6.1%	10.7%	
95% CI for % Diff. (vs Placebo)	(-0.3%, 20.7%)	(-4.3%, 16.6%)	(0.1%, 21.3%)	
P-value (vs. Placebo)	0.0509	0.2841	0.0425	

Table 14.2.4.3a from Study MNTX3201 (Efficacy Data)

Appendix E

Unadjusted and Multiplicity Adjusted P-Values for the Hierarchical Testing of Primary and Key Secondary Efficacy Endpoints

Hypothesi	Raw p-value (two-sided)	Adjusted p-value
Primary efficacy endpoint[a]		
Hypothesis H_1 – 150 mg versus placebo	0.1692	0.5076
Hypothesis H_2 – 300 mg versus placebo	0.0016*	0.0048*
Hypothesis H_3 – 450 mg versus placebo	< 0.0001*	< 0.0001*
Key secondary efficacy endpoint #1[b]		
Hypothesis H_4 – 150 mg versus placebo	0.3076	0.9228
Hypothesis H_5 – 300 mg versus placebo	0.0339	0.1526
Hypothesis H_6 – 450 mg versus placebo	0.0043*	0.0194*
Key secondary efficacy endpoint #2[c]		
Hypothesis H_7 – 150 mg versus placebo	0.6920	0.9228
Hypothesis H_8 – 300 mg versus placebo	0.0274	0.1526
Hypothesis H_9 – 450 mg versus placebo	0.0237	0.1067

Source: Table 16 MNTX3201 Clinical Study Report

Notes: The asterisk identifies the p-values that are significant at the two-sided 0.0167 level for raw p-values and at the two-sided
0.05 level for adjusted p-values. The adjusted p-values were calculated based on the truncated Hochberg-based gatekeeping procedure with Bonferroni procedures for both primary and key secondary #1 endpoints and regular Hochberg for the key
secondary endpoint #2.

a The primary endpoint is the average percentage of dosing days that resulted in RFBMs within 4 hours of dosing during
Weeks 1 – 4.

b Key secondary endpoint 1 is the proportion of responders, and a responder was defined as a subject who had
3 RFBMs/week, with an increase of 1 5)%0/ZHHN RYHU EDVHOLQH, IRU 3 of the first 4 weeks of treatment.

c Key secondary endpoint 2 is the change from baseline in the weekly number of RFBMs over the first 4 weeks of dosing.

9.1 Literature Review/References

As noted in Footnotes

9.2 Labeling Recommendations

The Applicant's label included all the required sections and was appropriately formatted. The Applicant's proposed label was reviewed, and discussions regarding labeling recommendations are ongoing at the time of this review. The final approved labeling will be appended if an approval letter is granted.

9.3 Advisory Committee Meeting

There was no Advisory Committee meeting during the review cycle for NDA 208271. Given previous concern for MACE with other PAMORA, a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) was convened on June 11, 2014 to discuss the cardiovascular safety of five peripherally active mu-opioid receptor antagonists in various stages of development, including Relistor® SQ. This AC was discussed in Section 2.5 above.

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

/s/

DINA J ZAND
06/02/2016

LAURIE B MULDOWNEY
06/03/2016