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# A Pooled Analysis of the Efficacy and Safety of Methylnaltrexone for Opioid-Induced Constipation in Patients With Advanced Illness: Impact of Baseline Opioid Equivalent Dose

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## INTRODUCTION

- Opioids are commonly prescribed to relieve pain associated with cancer and chronic noncancer pain[1]
- Constipation is one of the leading adverse events (AEs) of opioid use,[2] occurring in an estimated 40% to 80% of opioid users[3,4]
- Patients with opioid-induced constipation (OIC) often have abdominal discomfort and pain, which can lead to a significantly reduced quality of life and nonadherence to pain treatment[2,5]
- The mechanism of OIC involves opioid binding to peripheral μ-opioid receptors in the gastrointestinal tract (GI), leading to abnormal modulation of GI secretion and absorption[3]
  - Moreover, higher doses and/or dosing frequencies are associated with increased likelihood of OIC symptoms[6]
- Peripheral μ-opioid receptor antagonists (PAMORAs) are a class of drugs specifically indicated for the treatment of OIC. With limited ability to cross the blood-brain barrier, PAMORAs are designed to reverse μ-opioid binding in the gut without diminishing the effects of opioid analgesia[3]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) is a United States Food and Drug Administration–approved PAMORA indicated for the treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation; and for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[7]
- Pivotal clinical trials demonstrated superior efficacy of MNTX over placebo (PBO) in achieving rescue-free laxation (RFL) responses within 4 and 24 hours after the first dose, and within 4 hours after ≥2 of the first 4 doses[8-10]
- Using pooled data from the pivotal MNTX trials, this post hoc analysis assessed the effect of baseline opioid equivalent dose (OED) on RFL responses and safety of MNTX for OIC in patients with advanced illness

## METHODS

- This was a post hoc analysis of pooled data from 3 multicenter, double-blind, randomized, PBO-controlled clinical trials of MNTX, including the phase III 301 [NCT00401362][8] and 302 [NCT00402038][8] studies and the phase IV 4000 study [NCT00672477][10] (Figure 1)

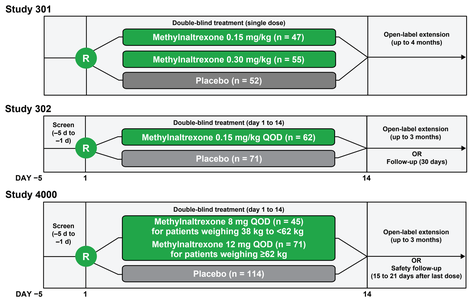
### Patients

- Men and women aged ≥18 years with OIC and a diagnosis of advanced illness (eg, incurable cancer and end-stage organ/system disorders) with a life expectancy of ≥1 month (studies 302 and 4000) or 1 to 6 months (study 301) were eligible
  - OIC was defined as <3 bowel movements during the previous week, and no clinically significant laxation within 24 hours (studies 302 and 4000) or 48 hours (study 301) preceding the first dose of study drug
- Patients were also required to be receiving chronic opioid treatment for discomfort or pain management for ≥3 days (study 301) or ≥2 weeks (studies 302 and 4000), excluding as-needed or rescue doses, and taking a stable regimen for ≥3 days before receiving the first dose of study medication
- For patients taking laxatives, the regimen must have been stable for ≥3 days prior to study drug initiation
- Patients with a history of MNTX treatment (excluding study 4000, where MNTX was allowed after a 7-day washout phase), disease process suggestive of GI obstruction, evidence of fecal impaction, history of fecal ostomy, or any potential nonopioid cause of bowel dysfunction which, in the opinion of the investigator, was the primary cause of constipation, were excluded

### Study Design

- Study 301 included 154 patients randomized in a 1:1:1 ratio to receive a single subcutaneous (SC) injection of MNTX 0.15 mg/kg, MNTX 0.30 mg/kg, or PBO, followed by a 28-day open-label period during which all patients received SC MNTX starting at a dose of 0.15 mg/kg[8]
  - After the 28-day open-label period, patients had the option to continue receiving MNTX in a 3-month open-label extension (OLE) study
- Study 302 included 133 patients randomized in a 1:1 ratio to receive SC injections of MNTX 0.15 mg/kg or PBO every other day (QOD) for 14 days, with the opportunity to increase the dose to 0.30 mg/kg on day 9 in patients with fewer than 3 RFLs[9]
  - After completion of double-blind treatment period, patients could enroll in the 3-month OLE phase, where they could receive MNTX as needed up to every 24 hours
- Study 4000 included patients randomized in a 1:1 ratio to receive SC MNTX 8 mg or 12 mg for patients weighing 38 kg to <62 kg or ≥62 kg, respectively, or PBO, administered QOD for a maximum of 7 doses/14 days, with the option to enroll in a 10-week OLE portion[10]

Figure 1. Study Designs




QOD = every other day.

### Study Assessments

- Outcomes were assessed in patient subgroups stratified by baseline opioid equivalent dose (<80 mg/d, 80 to <150 mg/d, ≥150 mg/d), including:
  - Proportion of patients with RFL within 4 hours after the first treatment dose
  - Proportion of patients with RFL within 24 hours after the first treatment dose
  - Proportion of patients with RFL within 4 hours after ≥2 of the first 4 treatment doses (studies 302 and 4000 only)
- The number and proportion of patients with treatment-emergent adverse events (TEAEs) were also reported

### Statistical Analysis

- Efficacy analyses were performed on the intention-to-treat population, defined as patients who received ≥1 dose of study medication
- Response rates for patients achieving RFL within 4 and 24 hours were compared across treatment groups and by baseline opioid equivalent dose using the Cochran-Mantel-Haenszel test, and *P*-values were generated based on chi-squared tests
- TEAEs were described for each treatment group using summary statistics
- Nominal levels of significance were set at $P < 0.05$, with no adjustments for multiplicity

## RESULTS

### Study Patients

- A total of 518 patients received ≥1 dose of study medication (MNTX, n = 281; PBO, n = 237) across studies and were included in the pooled analyses
- Study completion rates ranged from 78% to 87%, depending on cohort
  - The most frequent reason for discontinuation was death
  - Among patients receiving the highest baseline OED, discontinuations due to death were 8.0% in the PBO group compared with 3.8% for the MNTX group
- Cancer was the most common primary diagnosis across all treatment groups (Table 1)

Table 1. Patient Demographics and Baseline Characteristics Stratified by Baseline Opioid Equivalent Dose

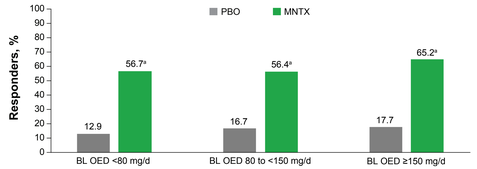
| | Baseline OED <80 mg/d | | Baseline OED 80 to <150 mg/d | | Baseline OED ≥150 mg/d | |
|---|---|---|---|---|---|---|
| | PBO (n = 70) | MNTX (n = 67) | PBO (n = 54) | MNTX (n = 55) | PBO (n = 113) | MNTX (n = 158) |
| Age, mean (SD) | 73.0 (12.8) | 73.7 (11.4) | 69.6 (13.2) | 69.3 (12.7) | 59.5 (13.3) | 61.8 (13.5) |
| Female, n (%) | 35 (50.0) | 38 (56.7) | 24 (44.4) | 29 (52.7) | 61 (54.0) | 70 (44.3) |
| Race, n (%) | | | | | | |
| White | 63 (90.0) | 61 (91.0) | 52 (96.3) | 51 (92.7) | 101 (89.4) | 140 (88.6) |
| ECOG | | | | | | |
| 0-2 | 25 (35.7) | 16 (23.9) | 16 (29.6) | 21 (38.2) | 58 (51.3) | 73 (46.2) |
| 3-4 | 45 (64.3) | 51 (76.1) | 38 (70.4) | 34 (61.8) | 55 (48.7) | 85 (53.8) |
| Median OED, mg/d | 46.0 | 40.0 | 100.0 | 104.0 | 360.0 | 315.0 |
| Primary diagnosis, n (%) | | | | | | |
| Cancer | 33 (47.1) | 46 (64.2) | 33 (61.1) | 31 (56.4) | 91 (80.5) | 124 (78.5) |
| Cardiovascular | 8 (11.4) | 7 (10.4) | 2 (3.7) | 4 (7.3) | 1 (0.9) | 3 (1.9) |
| Neurologic | 4 (5.7) | 3 (4.5) | 1 (1.9) | 4 (7.3) | 6 (5.3) | 6 (3.8) |
| Pulmonary | 13 (18.6) | 2 (3.0) | 5 (9.3) | 3 (5.5) | 7 (6.2) | 9 (5.7) |
| Other | 12 (17.1) | 12 (17.9) | 13 (24.1) | 13 (26.3) | 8 (7.1) | 16 (10.1) |

ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo; SD = standard deviation.

### Efficacy

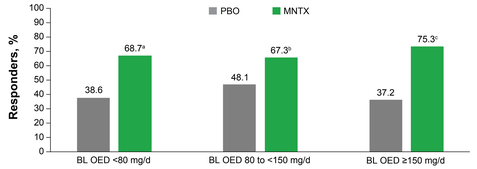
- Significantly greater proportions of patients treated with MNTX compared with PBO had an RFL within 4 and 24 hours after the first dose, regardless of baseline opioid equivalent dose (Figure 2 and Figure 3)
- Furthermore, significantly greater proportions of patients achieved RFL within 4 hours after at least 2 of the first 4 doses with MNTX vs PBO treatment (Figure 4)

Figure 2. Patients Achieving an RFL Response Within 4 Hours After the First Dose of Study Treatment (ITT Population)



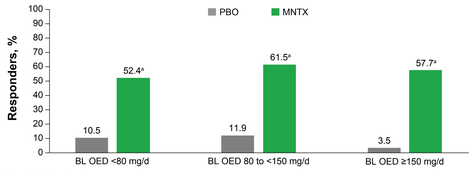

[a]$P < 0.0001$ vs placebo.
BL = baseline; RFL = rescue-free laxation; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo; ITT = intent to treat.

Figure 3. Patients Achieving an RFL Response Within 24 Hours After the First Dose of Study Treatment (ITT Population)




[a]$P < 0.001$ vs placebo.
[b]$P < 0.05$ vs placebo.
[c]$P < 0.0001$ vs placebo.
BL = baseline; RFL = rescue-free laxation; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo; ITT = intent to treat.

Figure 4. Patients Achieving an RFL Response Within 4 hours After ≥2 of the First 4 Doses of Study Treatment (ITT Population – Studies 302 and 4000)




[a]$P < 0.0001$ vs placebo.
BL = baseline; RFL = rescue-free laxation; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo; ITT = intent to treat.

### Safety

- The majority of AEs were GI in nature
  - Abdominal pain and flatulence occurred more frequently in the MNTX group versus the PBO group (Table 2)
- Among patients in the higher baseline opioid equivalent dose subgroups (ie, 80 to 150 mg/d or ≥150 mg/d), a greater proportion of patients had ≥1 TEAE with MNTX vs PBO

Table 2. TEAEs Occurring in >5% of Patients in Any Treatment Group, Stratified by Baseline Opioid Equivalent Dose (Safety Population)

| | Baseline OED <80 mg/d | | Baseline OED 80 to <150 mg/d | | Baseline OED ≥150 mg/d | |
|---|---|---|---|---|---|---|
| n (%) | PBO (n = 70) | MNTX (n = 67) | PBO (n = 54) | MNTX (n = 55) | PBO (n = 113) | MNTX (n = 159) |
| Patients with ≥1 TEAE | 49 (70.0) | 46 (68.7) | 36 (66.7) | 46 (83.6) | 78 (69.0) | 125 (78.6) |
| Abdominal pain[a] | 7 (10.0) | 17 (25.4) | 9 (16.7) | 13 (23.6) | 14 (12.4) | 54 (34.0) |
| Flatulence | 6 (8.6) | 5 (7.5) | 3 (5.6) | 7 (12.7) | 3 (2.7) | 18 (11.3) |
| Nausea | 9 (12.9) | 4 (6.0) | 2 (3.7) | 7 (12.7) | 13 (11.5) | 18 (11.3) |
| Asthenia | 2 (2.9) | 4 (6.0) | 4 (7.4) | 3 (5.5) | 4 (3.5) | 3 (1.9) |
| Peripheral edema | 5 (7.1) | 5 (7.5) | 3 (5.6) | 3 (5.5) | 4 (3.5) | 4 (2.5) |
| Fall | 3 (4.3) | 4 (6.0) | 7 (7.4) | 2 (3.6) | 4 (3.5) | 4 (2.5) |
| Cough | 4 (5.7) | 1 (1.5) | 0 | 1 (1.8) | 0 | 0 |
| Diarrhea | 3 (4.3) | 0 | 3 (5.6) | 1 (1.8) | 9 (8.0) | 8 (5.0) |
| Pain exacerbated | 0 | 1 (1.5) | 3 (5.6) | 0 | 6 (5.3) | 8 (5.0) |
| Arthralgia | 0 | 1 (1.5) | 0 | 4 (7.3) | 5 (4.4) | 2 (1.3) |
| Back pain | 0 | 1 (1.5) | 1 (1.9) | 4 (7.3) | 4 (3.5) | 9 (5.7) |
| Malignant neoplasm progression | 1 (1.4) | 1 (1.5) | 3 (5.6) | 3 (5.5) | 9 (8.0) | 3 (1.9) |
| Dizziness | 1 (1.4) | 0 | 2 (3.7) | 4 (7.3) | 4 (3.5) | 12 (7.5) |
| Headache | 1 (1.4) | 2 (3.0) | 0 | 3 (5.5) | 3 (2.7) | 3 (1.9) |
| Dyspnea | 2 (2.9) | 1 (1.5) | 3 (5.6) | 0 | 3 (2.7) | 2 (1.3) |
| Vomiting[a] | 5 (7.2) | 3 (4.5) | 3 (5.6) | 6 (10.9) | 11 (9.7) | 9 (5.6) |
| Disease progression | 2 (2.9) | 3 (4.5) | 2 (3.7) | 0 | 13 (11.5) | 7 (4.4) |
| Dehydration | 2 (2.9) | 0 | 0 | 2 (3.6) | 6 (5.3) | 1 (0.6) |
| Confusional state | 1 (1.4) | 2 (3.0) | 2 (3.7) | 2 (3.6) | 10 (8.8) | 6 (3.8) |
| Restlessness | 1 (1.4) | 3 (4.5) | 1 (1.9) | 1 (1.8) | 6 (5.3) | 7 (4.4) |

[a]Includes abdominal pain or vomiting not otherwise specified.
MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo; TEAE = treatment-emergent adverse events.

## SUMMARY AND CONCLUSIONS

- **In this post hoc analysis of pooled data from 3 randomized, PBO-controlled trials involving patients with advanced illness and OIC, MNTX was significantly more effective than PBO in achieving RFL responses within 4 and 24 hours after the first dose, regardless of baseline opioid equivalent dose**
- **MNTX was also significantly more effective than PBO at achieving RFL within 4 hours of ≥2 of the first 4 doses in studies 302 and 4000, independent of baseline opioid equivalent dose**
- **Most TEAEs were GI related and were not conspicuously linked to opioid dose**
- **These results demonstrate that MNTX provides effective and safe relief of OIC in patients with advanced illness across a range of baseline opioid equivalent doses**

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## DISCLOSURES

Dr. Sayuk is a consultant and speaker for Salix, Ironwood, Allergan, Alnylam, Takeda, and GI Health Foundation. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US. Dr. Stambler is an employee of Progenics Pharmaceuticals, Inc. a wholly owned subsidiary of Lantheus Holdings, Inc. Dr. Israel is an employee of Bausch Health US, LLC.

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