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Cumulative Laxation Response With Methylnaltrexone: Implications for Hospitalized Patients With Advanced Illness and Opioid-Induced Constipation

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INTRODUCTION

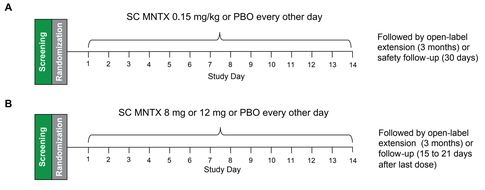
- Constipation is a frequent complication in severely and critically ill patients,[1-3] with prevalence rates among patients admitted to critical care facilities as high as 76% to 83%[1,3]
- Although constipation in severely ill patients is multifactorial, the use of opioid analgesics may be an important risk factor[1,4]
- Conventional laxatives fail to provide adequate relief of opioid-induced constipation (OIC) symptoms in many patients[5-7]
  - Stimulant and osmotic laxatives and stool softeners do not address the distinct underlying mechanism of OIC, which involves opioid agonism of peripheral μ-opioid receptors throughout the lower gastrointestinal (GI) tract[5-7]
  - Without adequate relief, patients may reduce or discontinue opioid dosing, resulting in suboptimal analgesia[7-9]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA), is a selective peripherally acting μ-opioid receptor antagonist (PAMORA) that decreases the constipating effect of opioid therapy without attenuating opioid analgesia[10-13]
  - MNTX tablets and subcutaneous (SC) injections have been approved by the US Food and Drug Administration for treatment of OIC in adults with chronic noncancer pain
  - MNTX SC is the only PAMORA indicated for treatment of OIC in adults with advanced cancer-related illness or pain caused by active cancer who require opioid dosage escalation for palliative care
- The objective of this analysis was to determine the effects of repeat dosing with MNTX on rescue-free laxation (RFL) in patients with advanced illness who were refractory to current laxative regimens

METHODS

Study Design

- This post hoc analysis included pooled data from a pivotal multicenter, double-blind, randomized, placebo-controlled clinical trial and a randomized, placebo-controlled postmarketing study conducted in adults with OIC and advanced illness (study 302 [NCT00402038][12]; study 4000 [NCT00672477][14])
  - Study 302: Patients received SC injections of MNTX 0.15 mg/kg or placebo every other day for 14 days, with permissible dose escalation to 0.30 mg/kg on day 9 for patients who had <3 bowel movements (BMs) not associated with rescue medication (**Figure 1A**)
  - Study 4000: Patients weighing ≥38 to <62 kg received SC MNTX 8 mg or placebo, and those weighing ≥62 kg received SC MNTX 12 mg or placebo; both groups were treated every other day for up to 14 days (**Figure 1B**)

Figure 1. Schematic Study Design Diagrams for Study 302 (A) and Study 4000 (B)



MNTX = methylnaltrexone; PBO = placebo; SC = subcutaneous.

Study Population

- Eligible patients were men and women aged ≥18 years with OIC and a diagnosis of advanced illness (eg, incurable cancer, congestive heart failure, chronic obstructive pulmonary disease, and end-stage acquired immunodeficiency disease) with a life expectancy ≥1 month
  - OIC: <3 BMs during the previous week and no clinically significant laxation during the 24 hours preceding the first dose of study drug or no clinically significant laxation within 48 hours prior to first dose of study drug
- Patients must have been receiving chronic opioid therapy for ≥2 weeks in a stable opioid regimen (no dose reduction ≥50%) for ≥3 days prior to study drug initiation
- Patients must have been taking conventional laxatives (eg, stool softeners plus senna or equivalent) in a stable regimen for ≥3 days prior to study drug initiation
- Patients were excluded if they had prior MNTX treatment (study 302) or prior MNTX treatment within 7 days of the study dose (study 4000), possible GI obstruction/fecal impaction, or possible nonopioid cause of bowel dysfunction contributing to constipation that, in the opinion of the investigator, was the primary cause of the constipation

Study Assessments

- Baseline assessments included demographics and disease/treatment characteristics such as primary diagnosis, functional status, and daily opioid dosage (morphine equivalents)
  - Functional status was assessed using World Health Organization (WHO) performance status (study 302) and Eastern Cooperative Oncology Group (ECOG) performance status (study 4000)[15]
    - For the current post hoc analysis, WHO performance status was mapped to the equivalent ECOG performance status categories (**Table 1**)

Table 1. Mapping of World Health Organization (WHO) Performance Status to Eastern Cooperative Oncology Group (ECOG) Performance Status

Scale Rating	WHO Performance Scale	ECOG Performance Scale[15]
0	Able to carry out all normal activity without restriction	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work, with less than 50% of waking hours in bed or chair	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled, not capable of any self-care, and confined to bed or chair	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

- Pooled efficacy endpoints
  - Achievement of RFL (laxation without use of laxative, enema, or suppository) within 4 and 24 hours of initial study drug dose
  - Cumulative laxation rates after the first and second study drug doses and after the first, second, and third study drug doses
  - Median time to RFL
  - RFL response rates stratified by WHO/ECOG performance status
- Pooled safety assessments
  - Change from baseline in pain intensity (study drug effects on opioid analgesia) assessed on an 11-point scale (0=no pain, 10=worst imaginable pain)
  - Treatment-emergent adverse events (TEAEs)

Statistical Analysis

- Efficacy and pain scores were analyzed for the intent-to-treat (ITT) population, defined as all patients who received ≥1 dose of study medication, which also defined the safety population
- RFL responses at 4 and 24 hours were compared by treatment group and by WHO/ECOG performance status scores using the Cochran-Mantel-Haenszel test
  - *P*-values were generated based on chi-square tests
- RFL was calculated using Kaplan-Meier time-to-event methods
- Comparison between treatment groups of mean change from baseline in pain scores was based on t-tests
- Summary statistics were used to describe TEAEs by treatment group
- Nominal significance levels were set at $P<0.05$, with no adjustments for multiplicity
- All analyses were conducted using SAS® version 9.4

RESULTS

Study Population

- Study population demographics and baseline characteristics are summarized in **Table 2**
- The pooled analysis was based on 364 patients (placebo=185, MNTX=179)
  - Median age was 66 years in both treatment groups
  - The study population was approximately 52% female and 94% white
- The most common primary diagnoses were cancer (63.4%), cardiovascular disorders (11.3%), and pulmonary disease (7.4%)
- Median baseline opioid consumption (morphine mg equivalents/day) was higher in the MNTX group (156 mg [range: 0–4,427 mg]) than in the placebo group (130 mg [range: 0–10,160 mg])

Table 2. Study Population Demographics, WHO/ECOG Performance Status, Median Opioid Consumption, and Primary Diagnoses

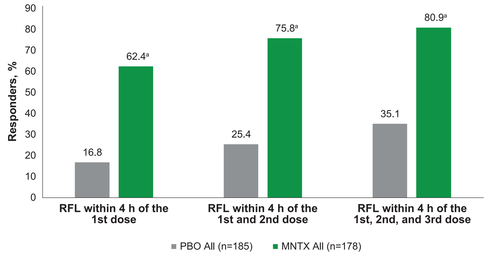
Characteristic	Placebo (n=185)	MNTX (n=178)[a]	Total (N=363)
Age, years, median (range)	66.0 (32 – 98)	66.0 (27 – 101)	66.0 (27 – 101)
Gender, n (%)			
Male	89 (48.1)	87 (48.9)	176 (48.5)
Female	96 (51.9)	91 (51.1)	187 (51.5)
Race, n (%)			
White	173 (93.5)	168 (94.4)	341 (93.9)
Black or African American	8 (4.3)	6 (3.4)	14 (3.9)
American Indian/Alaskan native	1 (0.5)	1 (0.6)	2 (0.6)
Asian	0	1 (0.6)	1 (0.3)
Other	3 (1.6)	2 (1.1)	5 (1.4)
Body weight, kg, mean (SD)	72.6 (24.0)	71.2 (19.7)	71.9 (22.0)
WHO/ECOG performance status score, n (%)			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	21 (11.4)	21 (11.8)	42 (11.6)
2	57 (30.8)	54 (30.3)	111 (30.6)
3	78 (42.2)	73 (41.0)	151 (41.6)
4	27 (14.6)	27 (15.2)	54 (14.9)
Daily opioid dose, morphine equivalents, mg/day			
Median (range)	130.0 (0 – 10,160)	156.0 (0 – 4,427)	145.7 (0 – 10,160)
Primary diagnosis, n (%)			
Cancer	114 (61.6)	116 (65.2)	230 (63.4)
Cardiovascular disease	20 (10.8)	21 (11.8)	41 (11.3)
Pulmonary disease (nonmalignant)	13 (7.0)	14 (7.9)	27 (7.4)
COPD	5 (2.7)	9 (5.1)	14 (3.9)
Alzheimer's disease/dementia	4 (2.2)	4 (2.2)	8 (2.2)
Neurologic disease	3 (1.6)	4 (2.2)	7 (1.9)
Failure to thrive	3 (1.6)	0	3 (0.8)
ALS	1 (0.5)	1 (0.6)	2 (0.6)
Multiple sclerosis	2 (1.1)	0	2 (0.6)
Arthritis	0	1 (0.6)	1 (0.3)
Stroke	0	1 (0.6)	1 (0.3)
Other	20 (10.8)	7 (3.9)	27 (7.4)

[a]One female patient from study 302 was excluded from this table and the efficacy analyses (but not the TEAE summary statistics) because she received MNTX before being randomized to the MNTX group.
ALS = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; SD = standard deviation; WHO = World Health Organization.

Efficacy

- MNTX, compared with placebo, significantly increased the proportion of patients with RFL response within 4 hours after the first dose and cumulatively within 4 hours after the first and second doses and after the first, second, and third doses ($P<0.0001$ for all comparisons) (**Figure 2**)
  - Cumulative RFL responses with MNTX increased from 62.4% within 4 hours of the first dose to 80.9% within 4 hours of the third dose, compared with 16.8% and 35.1%, respectively, with placebo

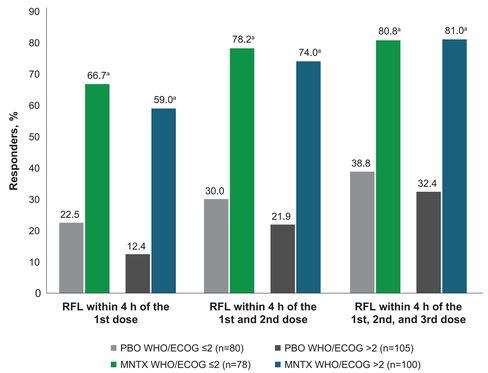
Figure 2. Patients Treated With MNTX or Placebo in the Overall Population With Cumulative RFL Response Within 4 Hours (ITT)



[a]$P<0.0001$ for MNTX vs placebo.
ITT = intent to treat; MNTX = methylnaltrexone; PBO = placebo; RFL = rescue-free laxation.

- Similar results were observed when cumulative RFL responses were analyzed by baseline WHO/ECOG performance status ≤2 or >2 (**Figure 3**)

Figure 3. Patients Treated With MNTX or Placebo With Cumulative RFL Response Within 4 Hours (ITT) Based on WHO/ECOG Status



[a]$P<0.0001$ for MNTX vs placebo.
ITT = intent to treat; MNTX = methylnaltrexone; PBO = placebo; RFL = rescue-free laxation; WHO/ECOG = World Health Organization/Eastern Cooperative Oncology Group performance status.

- Median time to RFL was significantly shorter with MNTX compared with placebo at the 4- and 24-hour time points following initial dosing (4 hours: 1.11 vs >4 hours: median not achieved; 24 hours: 1.11 vs 23.58 hours; $P<0.0001$ for both comparisons)
  - Median time to RFL remained significantly shorter with MNTX compared with placebo at the 24-hour time point in patients with baseline WHO/ECOG performance status ≤2 (0.87 vs 17.79 hours; $P<0.0001$) or >2 (1.46 vs >24 hours; $P<0.0001$)

Safety

- MNTX treatment did not reduce the efficacy of opioid analgesia
  - Across all patients, mean changes from baseline in current and worst pain scores 1 day and 7 days after dosing were zero or negative (indicating reduced pain) and similar between MNTX (current pain: −0.4 at 1 day and −0.5 at 7 days; worst pain: −0.7 at 1 day and −0.7 at 7 days) and placebo (current pain: −0.3 at 1 day and −0.2 at 7 days; worst pain: −0.6 at 1 day and −0.4 at 7 days)
    - Mean changes from baseline in pain scores were similar with MNTX and placebo regardless of WHO/ECOG baseline performance status (≤2 or >2)
- TEAEs decreased from treatment day 1 to treatment day 2
- The most common TEAEs were GI in nature (ie, abdominal pain, flatulence, nausea, and vomiting) (**Table 3**)

Table 3. TEAEs Reported in >2% of Patients in Any Treatment Group by Treatment Day (Safety Population)

	Treatment Day 1		Treatment Day 2	
System Organ Class Preferred Term, n (%)	**Placebo (n=185)**	**MNTX (n=179)**	**Placebo (n=170)**	**MNTX (n=160)**
Patients with ≥1 TEAE	27 (14.6)	47 (26.3)	24 (14.1)	36 (22.5)
Abdominal pain[a]	8 (4.3)	23 (12.8)	7 (4.1)	13 (8.1)
Flatulence	3 (1.6)	5 (2.8)	3 (1.8)	2 (1.3)
Nausea	4 (2.2)	5 (2.8)	3 (1.8)	3 (1.9)
Vomiting[b]	1 (0.5)	4 (2.2)	1 (0.6)	2 (1.3)
Back pain	0	4 (2.2)	0	0

[a]Includes the following system organ class preferred terms: abdominal pain and abdominal pain not otherwise specified.
[b]Includes the following system organ class preferred terms: vomiting and vomiting not otherwise specified.
MNTX = methylnaltrexone; TEAE = treatment-emergent adverse event.

CONCLUSIONS

- **In this pooled analysis of a diverse population of severely ill patients with OIC despite laxative treatment, MNTX significantly increased RFL responses within 4 hours after the initial dose compared with placebo**
- **Results for MNTX efficacy measures compared with placebo, including cumulative RFL response and median time to RFL, were consistent regardless of baseline WHO/ECOG performance status (≤2 or >2), indicating that MNTX efficacy is not affected by varying degrees of baseline functional performance**
- **MNTX treatment did not negatively affect opioid analgesia; mean pain scores remained constant or declined slightly in both treatment groups regardless of WHO/ECOG performance status**
- **MNTX was generally well tolerated; the most common side effects were consistent with restored laxation and decreased from treatment day 1 to treatment day 2**
- **Repeat dosing of MNTX is an effective treatment for OIC that may be safely administered in the hospital to patients with advanced illness regardless of baseline performance status[2]**
- **This patient population is typical of patients hospitalized with OIC in terms of their relatively severe medical morbidities, the failure of ongoing conventional laxative therapy, and for many, their impaired functional status. The latter was not a barrier to successful treatment with MNTX**

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DISCLOSURES

Dr. Farchadi has nothing to disclose. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US since July 2016; an unpaid consultant for Salix prior to July 2016; and a speaker for Salix through February 2016. Dr. Stambler is a full-time employee and shareholder of Progenics Pharmaceuticals. Dr. Israel is an employee of Bausch Health US, LLC. Dr. Matus has nothing to disclose.

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