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Effect of Baseline Characteristics on Outcomes of Oral Methylnaltrexone for Opioid-Induced Constipation

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INTRODUCTION

- Patient characteristics may affect the efficacy of treatments for opioid-induced constipation (OIC) and the incidence of opioid withdrawal symptoms in patients receiving treatment for OIC
  - Characteristics such as age may affect the efficacy of drugs, particularly drugs that pass the blood-brain barrier, because with aging the brain becomes increasingly vulnerable to various insults that may reflect a higher permeability of this barrier[1,2]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, Bridgewater, NJ, USA) is a selective, peripherally acting μ-receptor antagonist that is restricted from crossing the blood-brain barrier and specifically improves gastrointestinal transit without affecting the analgesic effects of the opioid[3-5]
  - MNTX tablets and subcutaneous (SC) injection are approved 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
  - MNTX SC injection is approved for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[3]
- In a phase 3, randomized, double-blind trial, oral MNTX demonstrated significant reductions in OIC symptoms versus placebo[6]
- No significant changes from baseline in Objective Opioid Withdrawal Scale (OOWS) or Subjective Opioid Withdrawal Scale (SOWS) scores were observed in patients in other clinical studies of MNTX[7]

OBJECTIVE

- This post hoc analysis evaluated the potential impact of baseline characteristics such as sex, age, and baseline opioid daily dose on efficacy endpoints and opioid withdrawal indicators in patients treated with oral MNTX from a phase 3 trial

METHODS

Key Inclusion Criteria

- Aged ≥18 years, chronic noncancer pain for ≥2 months, and receiving a daily dose ≥50 mg of oral morphine equivalents per day for ≥14 days before screening
- History of OIC for ≥30 days confirmed during screening and defined as <3 rescue-free bowel movements (RFBM) per week on average (ie, no laxative use within 24 hours prior to bowel movement) and ≥1 of the following:
  - ≥25% of RFBMs categorized as type 1 or type 2 on the Bristol Stool Form Scale
  - Straining during ≥25% of RFBMs
  - ≥25% of RFBMs with a sensation of incomplete evacuation
- Laxative therapy for ≥30 days before screening (discontinued during screening)

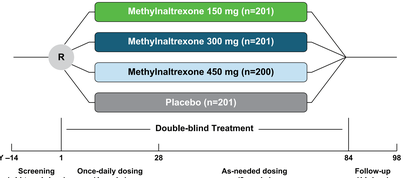
Key Exclusion Criteria

- History of mechanical bowel obstruction or megacolon or clinically significant gastrointestinal disorders (eg, fecal incontinence, rectal prolapse, fecal ostomy, and inflammatory bowel disease)
- Rectal bleeding not associated with hemorrhoids or fissures within 60 days of screening
- Planned surgery during the study

Study Design

- This was a post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study (NCT01186770)
- After a 14-day screening period, patients were randomized (1:1:1:1) to receive oral MNTX 150 mg, 300 mg, 450 mg, or placebo once daily for 4 weeks, followed by as-needed (PRN) dosing (not to exceed once daily) for 8 weeks (Figure 1)[6]
  - Throughout the 12-week study, patients received the same dose of MNTX or placebo, and double-blinding was maintained
- Patients who completed the 12-week treatment period were to return for a follow-up visit 14 days after the last dose of study drug

Figure 1. Study Design



R = randomization.

Assessments and Statistical Analyses

- Data were analyzed by sex, age group (<65 years of age vs ≥65 years of age) and baseline opioid morphine-equivalent daily doses (high [average dose ≥150 mg/d] vs low [average dose <150 mg/d]) for the following efficacy endpoints:
  - Average percentage of dosing days that resulted in RFBMs within 4 hours of dosing during weeks 1 to 4
    - An RFBM was defined as a bowel movement without laxative use within 24 hours prior to bowel movement
  - Proportion of patients who responded to study drug during weeks 1 to 4
    - Responder 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 first 4 weeks of dosing
- The impact of baseline characteristics on opioid withdrawal symptoms was assessed using the 13-item OOWS, completed by a trained clinician, and the 19-item SOWS, completed by the patient[8]
  - Items on OOWS were scored as 0 (absent) or 1 (present), with a total score from 0 to 13
  - Items on SOWS were scored as 0 (not at all), 1 (a little), 2 (moderate), 3 (quite a bit), or 4 (extremely), with a total score from 0 to 76
  - Changes in opioid withdrawal indicators were assessed at baseline (day 1 predose); days 1 (1 hour postdose), 14, and 28 (QD period); and days 42, 56, and 84 (PRN period)
  - OOWS and SOWS were assessed with and without abdominal cramping
- An analysis of covariance model with treatment as the main effect and sex and age group (<65 years of age vs ≥65 years of age) as covariates was used to compare percentage of dosing days with an RFBM within 4 hours of dosing and weekly number of RFBMs for each MNTX group versus placebo during weeks 1 through 4

RESULTS

Patients

- Demographic and baseline characteristics of the overall study population (N=803) were similar across all treatment groups (Table 1)

Table 1. Demographic and Baseline Characteristics (ITT Population[a])

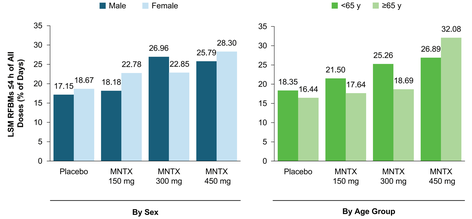
Characteristic	Placebo (n=201)	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)
Age, y				
Mean (SD)	52.6 (10.3)	50.9 (10.3)	51.5 (10.5)	51.4 (10.5)
Median (min, max)	53.0 (23, 78)	52.0 (18, 79)	52.0 (24, 82)	52.0 (23, 78)
Age group, n (%)				
<65 years	179 (89.1)	186 (92.5)	182 (90.5)	181 (90.5)
≥65 years	22 (10.9)	15 (7.5)	19 (9.5)	19 (9.5)
Sex, n (%)				
Male	71 (35.3)	68 (33.8)	87 (43.3)	72 (36.0)
Female	130 (64.7)	133 (66.2)	114 (56.7)	128 (64.0)
Baseline MED[b], mg/d				
Median (min, max)	132.0 (42.6, 1077.3)	141.1 (30.0, 1280.0)	177.5 (47.4, 2289.3)	155.6 (27.0, 1272.0)

ITT = intent to treat; MED = morphine-equivalent dose; SD = standard deviation.
[a]The ITT population included all randomized patients who received ≥1 dose of study drug.
[b]Baseline opioid dose was defined as the average daily oral MED during the screening period.

Percentage of Dosing Days That Resulted in RFBMs Within 4 Hours of Dosing

- Baseline sex or age had no significant effect on the percentage of dosing days that resulted in a RFBM within 4 hours of dosing during weeks 1 through 4 in any treatment group (Figure 2)

Figure 2. Mean Percentage of Dosing Days That Resulted in RFBMs Within 4 Hours of Dosing During Weeks 1 to 4



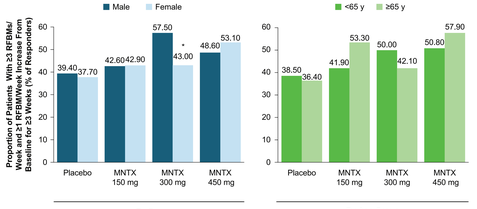
LSM = least squares mean; MNTX = methylnaltrexone; RFBM = rescue-free bowel movement.

- The percentage of dosing days that resulted in a RFBM within 4 hours of dosing during weeks 1 to 4 was significantly greater in patients treated with MNTX 300 mg and 450 mg versus placebo ($P<0.05$ for both comparisons; analysis of covariance model with treatment as the main effect and sex and age group as covariates)

Proportion of Responders

- Baseline sex or age had no significant effect on the proportion of patients who responded to study drug during weeks 1 to 4 except in the MNTX 300 mg group (males 57.5% vs females 43.0%, $P<0.05$) (Figure 3)

Figure 3. Proportion of Patients Who Responded During Weeks 1 to 4

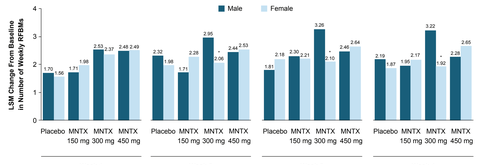


*P<0.05 vs males. MNTX = methylnaltrexone; RFBM = rescue-free bowel movement.

Change From Baseline in Weekly Number of RFBMs

- Sex did not significantly affect the change in weekly number of RFBMs from baseline over the first 4 weeks of dosing in the placebo, MNTX 150 mg, and MNTX 400 mg groups (Figure 4)
  - However, a significantly greater change from baseline in the number of weekly RFBMs was observed in males versus females in the MNTX 300 mg group during weeks 2 to 4 ($P<0.05$) (Figure 4)

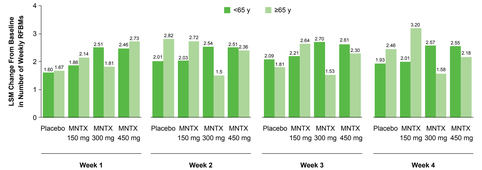
Figure 4. Change in Weekly Number of RFBMs From Baseline Over Weeks 1 to 4, By Sex



*P<0.05 vs males. LSM = least squares mean; MNTX = methylnaltrexone; RFBM = rescue-free bowel movement.

- Age had no significant effect on the change in weekly number of RFBMs from baseline over weeks 1 to 4 (Figure 5)

Figure 5. Change From Baseline in the Number of RFBMs During Weeks 1 to 4 by Age Group



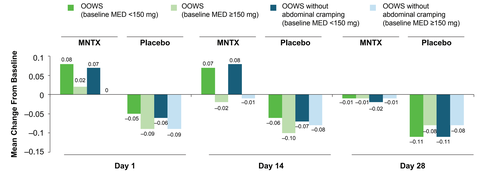
LSM = least squares mean; MNTX = methylnaltrexone; RFBM = rescue-free bowel movement.

- The weekly number of RFBMs was significantly higher in patients treated with MNTX 300 mg and 450 mg versus placebo at week 1 ($P<0.05$ for both comparisons; analysis of covariance model with treatment as the main effect and sex and age group as covariates)

Opioid Withdrawal Symptoms

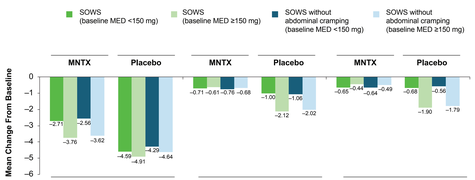
- No significant differences in mean change from baseline in OOWS (Figure 6) and SOWS (Figure 7) scores were observed between patients with a low baseline opioid dose (<150 mg) versus a high baseline opioid dose (≥150 mg) on postdose days 1, 14, or 28, whether or not abdominal cramping was excluded from the analysis in either the MNTX group or the placebo group

Figure 6. Change in Mean OOWS Score by Baseline Daily Opioid Use



MED = morphine-equivalent dose; MNTX = methylnaltrexone; OOWS = Objective Opioid Withdrawal Scale.

Figure 7. Change in Mean SOWS Score by Baseline Daily Opioid Use



MED = morphine-equivalent dose; MNTX = methylnaltrexone; OOWS = Objective Opioid Withdrawal Scale.

CONCLUSIONS

- **Once-daily oral MNTX is effective for the treatment of OIC in adults with chronic noncancer pain**
- **The demonstrated efficacy of oral MNTX is independent of patient sex and age**
- **Oral MNTX did not appear to be associated with opioid withdrawal symptoms**

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DISCLOSURES

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