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Treatment-Emergent Adverse Events Related to Cardiac Safety in a Phase 3, Randomized, Controlled Trial of Oral Methylnaltrexone in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain

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INTRODUCTION

- Opioid-induced constipation (OIC), a consequence of μ-opioid receptor activation in the gastrointestinal (GI) tract, is the most common symptom associated with the use of opioid analgesics for the treatment of chronic noncancer pain[1-4]
- Over-the-counter laxatives are often inadequate to relieve the symptoms of OIC, which are often bothersome enough that patients discontinue or reduce opioid therapy[1,4-6]
- Methylnaltrexone (Relistor®, Salix Pharmaceuticals, Bridgewater, NJ) is a selective, peripherally acting μ-opioid receptor antagonist that improves GI motility and transit time without affecting μ-opioid receptor–associated analgesia[7-9]
- Currently available as a subcutaneous injection for the treatment of OIC, methylnaltrexone was approved for oral administration by the US Food and Drug Administration in 2016[10]
  - In a phase 3, randomized, double-blind, placebo-controlled trial, oral methylnaltrexone administered once daily was well tolerated and significantly improved the mean percentage of dosing days that resulted in a rescue-free bowel movement (RFBM) within 4 hours of dosing compared with placebo (P=0.002 with methylnaltrexone 300 mg; P<0.0001 with methylnaltrexone 450 mg) during a 4-week treatment period[9]
- Although opioid antagonists used to treat OIC are not generally associated with a higher risk for cardiovascular (CV) events, it is important to monitor cardiac safety in clinical trials because increased CV risk has been observed with 1 peripherally acting opioid antagonist[11-13]

OBJECTIVE

- To evaluate the cardiac safety of oral methylnaltrexone versus placebo for the treatment of OIC in adult patients with chronic noncancer pain

METHODS

Key Inclusion Criteria

- Aged ≥18 years, chronic noncancer pain for ≥2 months, and receiving ≥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 RFBMs 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)

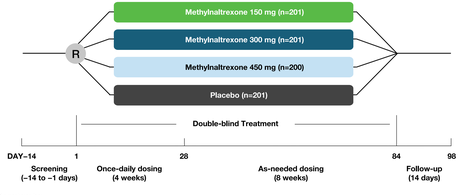
Key Exclusion Criteria

- History of mechanical bowel obstruction or megacolon or clinically significant GI 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 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 methylnaltrexone 150 mg, 300 mg, 450 mg, or placebo once daily (QD) for 4 weeks, followed by as-needed (PRN) dosing (not to exceed QD) for 8 weeks (Figure 1)
  - Throughout the study, patients received the same dose of methylnaltrexone or placebo and double-blinding was maintained
  - Patients were followed for 14 days after the double-blind period

Figure 1. Study Design



R = randomization.

Safety Assessments

- Changes from baseline in vital signs, evaluated at baseline and weeks 2, 4, 6, 8, and 12 (reported separately)
- Changes from baseline in electrocardiogram (ECG) measurements, including incidence of abnormal ECGs, evaluated at screening and week 4 (reported separately)

Statistical Analyses

- Safety analyses were performed in the safety population, which consisted of all randomized patients who received ≥1 dose of methylnaltrexone or placebo
- Safety data were summarized using descriptive statistics
- Comparisons of each methylnaltrexone dose versus placebo for change from baseline in ECG parameters (ie, corrected QT intervals: QTcF [Fridericia correction], QTcB [Bazett correction], QTcL [linear regression correction]) were performed using analysis of covariance with treatment as effect and baseline as a covariate; a 90% confidence interval for the treatment difference was reported

Concomitant Medications

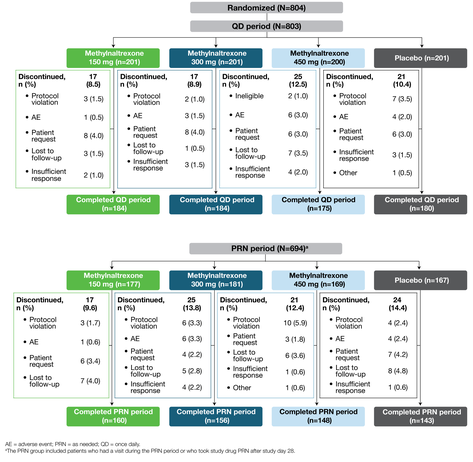
- Rescue laxative therapy (≤3 oral bisacodyl tablets per day) was permitted for patients who did not have a bowel movement for 3 consecutive study days (if bowel movements did not resume within 24 hours, an enema or additional bisacodyl tablets were allowed)
- Prohibited medications included prokinetic agents, stool softeners, 5-HT$_3$ receptor antagonists, partial opioid agonists, or combination opioid agonists/antagonists

RESULTS

Patient Disposition

- Of the 804 randomized patients, 803 received ≥1 dose of methylnaltrexone 150 mg (n=201), methylnaltrexone 300 mg (n=200), or placebo (n=201) (Figure 2)
  - Overall, 90.0% of patients treated with methylnaltrexone (all doses) and 89.6% of patients treated with placebo completed the QD-dosing period
  - Among patients who entered the PRN dosing period, 88.0% who received methylnaltrexone (all doses) and 85.6% who received placebo completed the study

Figure 2. Patient Disposition by Dosing Period



AE = adverse event; PRN = as needed; QD = once daily.
*The PRN group included patients who had a visit during the PRN period or who took study drug PRN after study day 28.

Baseline Characteristics

- Demographics and baseline characteristics were similar among the treatment groups (Table 1)

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

Characteristic	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
Mean age (SD), years	50.9 (10.3)	51.5 (10.5)	51.4 (10.5)	52.6 (10.3)
Age group, n (%)				
<65 years	186 (92.5)	182 (90.5)	181 (90.5)	179 (89.1)
≥65 years	15 (7.5)	19 (9.5)	19 (9.5)	22 (10.9)
Sex, n (%)				
Male	68 (33.8)	87 (43.3)	72 (36.0)	71 (35.3)
Female	133 (66.2)	114 (56.7)	128 (64.0)	130 (64.7)
Race, n (%)				
White	164 (81.6)	158 (78.6)	172 (86.0)	166 (82.6)
Black/African American	30 (14.9)	38 (18.9)	25 (12.5)	27 (13.4)
Other	7 (3.5)	5 (2.5)	3 (1.5)	8 (4.0)
Ethnicity, n (%)				
Hispanic or Latino	14 (7.0)	18 (9.0)	12 (6.0)	8 (4.0)
Not Hispanic or Latino	187 (93.0)	183 (91.0)	188 (94.0)	193 (96.0)
Mean weight (SD), kg	89.5 (24.8)	91.8 (24.5)	87.8 (23.1)	89.9 (24.0)
Primary pain condition, n (%)				
Back pain	132 (65.7)	136 (67.7)	135 (67.5)	145 (72.1)
Joint/extremity pain	13 (6.5)	16 (8.0)	11 (5.5)	10 (5.0)
Arthritis	20 (10.0)	15 (7.5)	19 (9.5)	12 (6.0)
Neurologic/neuropathic pain	16 (8.0)	13 (6.5)	16 (8.0)	11 (5.5)
Fibromyalgia	15 (7.5)	8 (4.0)	11 (5.5)	12 (6.0)
Other	5 (2.5)	13 (6.5)	8 (4.0)	11 (5.5)
Baseline MED, mg/d[b]				
Median (range)	141.1 (50.0–1280.0)	177.5 (47.4–2289.3)	155.6 (27.0–1272.0)	132 (42.6–1077.3)
Mean RFBMs per week (SD)	1.46 (0.91)	1.35 (0.89)	1.37 (0.79)	1.49 (1.05)
<3 average RFBMs per week, n (%)				
Yes	191 (95.0)	195 (97.0)	195 (97.5)	188 (93.5)
No	10 (5.0)	6 (3.0)	5 (2.5)	13 (6.5)

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

Incidence of Cardiac Disorders

- The incidence of cardiac disorders was low and was similar in the methylnaltrexone and placebo treatment groups (Table 2)
  - No patient discontinued from the study due to cardiac treatment-emergent adverse events (TEAEs)
- Cardiac disorders reported as serious adverse events (SAEs) occurred in 1 patient in the placebo group and no patients in the methylnaltrexone groups

Table 2. TEAEs Related to Cardiac Disorders (Safety Population)

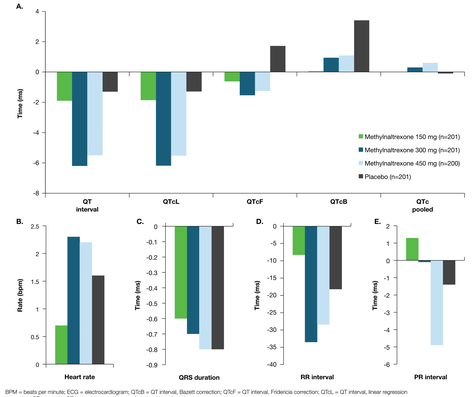
Patients reporting cardiac disorder, n (%)	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
Atrial flutter	0	0	0	1 (0.5)
Tachycardia	0	0	0	1 (0.5)
Angina pectoris	0	1 (0.5)	0	0
Arrhythmia	1 (0.5)	0	0	0
Atrial fibrillation	1 (0.5)	0	0	0
Atrioventricular block first degree	0	0	1 (0.5)	0
Bradycardia	0	1 (0.5)	0	0
Bundle branch block left	0	1 (0.5)	0	0
Bundle branch block right	0	1 (0.5)	0	0
Extrasystoles	0	1 (0.5)	0	0
Left atrial dilatation	0	1 (0.5)	0	0
Palpitations	2 (1.0)	1 (0.5)	0	0
Sinus tachycardia	0	0	1 (0.5)	0
Ventricular extrasystoles	0	1 (0.5)	1 (0.5)	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
AEs were coded using MedDRA version 13.0. A patient reporting more than one AE for a particular MedDRA preferred term or system organ class was counted only once for that MedDRA preferred term or system organ class.

Changes From Baseline in ECG Parameters

- At week 4, mean changes from baseline in ECG parameters were minimal and comparable among the methylnaltrexone and placebo treatment groups (Figure 3 and Table 3)

Figure 3. Mean Changes From Baseline in ECG Parameters at Week 4: (A) QT Interval; (B) Heart Rate; (C) QRS Duration; (D) RR Interval; and (E) PR Interval



BPM = beats per minute; ECG = electrocardiogram; QTcB = QT interval, Bazett correction; QTcF = QT interval, Fridericia correction; QTcL = QT interval, linear regression correction; QTc pooled = QT interval corrected on pooled data from all study centers.

Table 3. Baseline ECG Parameters (Safety Population)

Baseline ECG parameters	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
QT interval, ms	398.4	400.8	398.8	394.0
QTcL, ms	398.4	400.8	398.8	394.0
QTcF, ms	414.8	414.5	413.5	411.5
QTcB, ms	424.0	422.0	421.9	421.3
QTc pooled	419.6	418.5	417.3	420.3
Heart rate, bpm	69.2	67.9	68.6	69.8
QRS period, ms	90.5	91.1	92.1	90.1
RR interval, ms	891.8	910.8	903.4	883.9
PR interval, ms	158.9	163.2	166.7	160.6

BPM = beats per minute; ECG = electrocardiogram; QTcB = QT interval, Bazett correction; QTcF = QT interval, Fridericia correction; QTcL = QT interval, linear regression correction; QTc pooled = QT interval corrected on pooled data from all study centers.

Potentially Clinically Important ECG Results

- Changes in ECG parameters that may be clinically important were similar among the methylnaltrexone and placebo treatment groups (Table 4)

Table 4. ECG Results of Potential Clinical Relevance

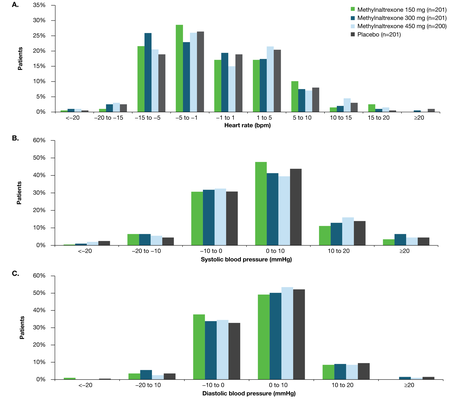
Postbaseline ECG abnormalities, n (%)	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
Postbaseline abnormal ECG finding	76 (37.8)	78 (38.8)	73 (36.5)	64 (31.8)
QT interval, ms	22 (10.9)	15 (7.5)	14 (7.0)	11 (5.5)
Increases from baseline >30	19 (9.5)	14 (7.0)	11 (5.5)	11 (5.5)
Increases from baseline >60	2 (1.0)	3 (1.5)	2 (1.0)	2 (1.0)
QTcL, ms	22 (10.9)	15 (7.5)	14 (7.0)	11 (5.5)
Increases from baseline >30	19 (9.5)	14 (7.0)	11 (5.5)	11 (5.5)
Increases from baseline >60	2 (1.0)	3 (1.5)	2 (1.0)	2 (1.0)
QTcF, ms	12 (6.0)	11 (5.5)	8 (4.0)	11 (5.5)
Increases from baseline >30	5 (2.5)	7 (3.5)	7 (3.5)	9 (4.5)
Increases from baseline >60	1 (0.5)	2 (1.0)	3 (1.5)	3 (1.5)
QTcB, ms	12 (6.0)	27 (13.4)	17 (8.5)	19 (9.5)
Increases from baseline >30	6 (3.0)	18 (9.0)	7 (3.5)	13 (6.5)
Increases from baseline >60	1 (0.5)	1 (0.5)	4 (2.0)	4 (2.0)

ECG = electrocardiogram; QTcB = QT interval, Bazett correction; QTcF = QT interval, Fridericia correction; QTcL = QT interval, linear regression correction.

Changes From Baseline in Hemodynamic Parameters

- At 1 hour after the first dose, changes from baseline in hemodynamic parameters were minimal and comparable in the methylnaltrexone and placebo treatment groups (Figure 4)

Figure 4. Categorical Changes From Baseline in (A) Heart Rate, (B) Systolic Blood Pressure, and (C) Diastolic Blood Pressure 1 Hour Postdose*



*Categories include the lower limit of the interval (eg, 0 to 10 means 0 to <10).

Most Commonly Reported TEAEs

- Overall, the safety profile of oral methylnaltrexone (59.0%) was comparable to that of placebo (63.2%) at all dose levels tested (150 mg, 58.2%; 300 mg, 59.7%; 450 mg, 59.0%)
- The most common TEAEs were abdominal pain (150 mg, 5.5%; 300 mg, 8.0%; 450 mg, 10.5%; placebo, 8.5%), nausea (150 mg, 6.5%; 300 mg, 8.0%; 450 mg, 6.0%; placebo, 9.0%), and diarrhea (150 mg, 3.5%; 300 mg, 6.5%; 450 mg, 8.0%; placebo, 3.5%)

CONCLUSIONS

- In this study, oral methylnaltrexone was well tolerated for the treatment of OIC in patients with chronic noncancer pain, with a low incidence of TEAEs related to cardiac safety that was comparable with placebo
- Changes from baseline in ECG and hemodynamic parameters were minimal and did not suggest an increased cardiac safety risk with methylnaltrexone versus placebo

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