POSTER NUMBER

83

Safety of Oral Methylnaltrexone in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain: Results From a Phase 3, Randomized, Controlled Trial

Richard Rauck, MD[1]; Neal E. Slatkin, MD[2,3]; Nancy Stambler, DrPH[4]; Sylvia Hanna, MD[3]; Robert J. Israel, MD[3]

[1]The Center for Clinical Research, Winston-Salem, NC; [2]School of Medicine, University of California Riverside, Riverside, CA; [3]Salix Pharmaceuticals, Bridgewater, NJ; [4]Progenics Pharmaceuticals, Inc., New York, NY

INTRODUCTION

- Opioid-induced constipation (OIC) is the most common and bothersome symptom associated with the use of opioid analgesics for the treatment of chronic noncancer pain[1-3]
- OIC, which results from activation of μ-opioid receptors in the gastrointestinal (GI) tract, often leads patients to discontinue opioid therapy or skip doses, which can interfere with pain management[1,4,5]
- Relief from over-the-counter medicines such as laxatives and stool softeners is often inadequate as these treatments do not address the underlying pathophysiology or may themselves cause side effects[1,2,5,6]
- 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]

OBJECTIVE

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

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 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)

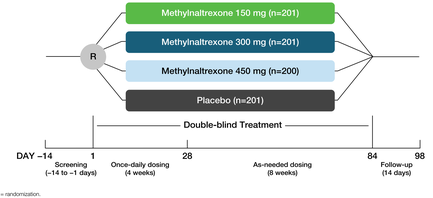
Key Exclusion Criteria

- 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

- Safety assessments included:
  - Treatment-emergent adverse events (TEAEs), severe TEAEs, serious TEAEs, drug-related TEAEs, and TEAEs leading to discontinuation

Statistical Analyses

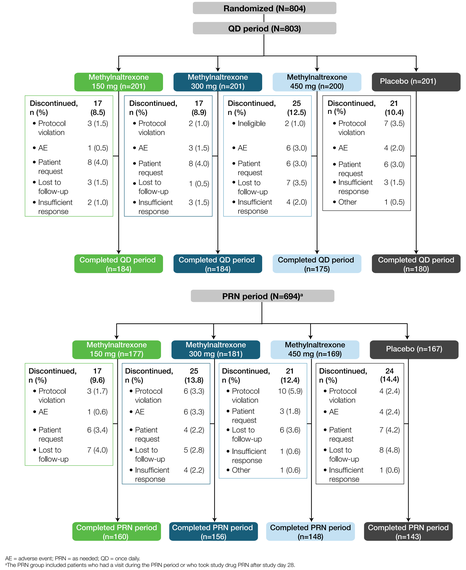
- Safety analyses were performed in the safety population, which consisted of all randomized patients who received ≥1 dose of study drug
- Safety data were summarized using descriptive statistics

RESULTS

Patient Disposition

- Of the 804 randomized patients, 803 received ≥1 dose of study medication: methylnaltrexone 150 mg (n=201), methylnaltrexone 300 mg (n=201), methylnaltrexone 450 mg (n=200), or placebo (n=201) (Figure 2)
  - Overall, 90.0% of patients receiving methylnaltrexone (all doses) and 89.6% of patients receiving placebo completed the once-daily dosing period
  - Among patients who entered the PRN dosing period, 88.0% of patients who received methylnaltrexone (all doses) and 85.6% of patients who received placebo completed the study

Figure 2. Patient Disposition by Dosing Period



AE = adverse event; PRN = as needed; QD = once daily.
[a]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]				
Mean (SD)	200.0 (205.2)	252.6 (298.1)	218.0 (189.1)	209.7 (199.1)
Median (range)	141.1 (30.0–1280.0)	177.5 (47.4–2289.3)	155.6 (27.0–1272.0)	132.0 (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.

TEAEs

- The incidence of TEAEs was 59.0% for patients receiving methylnaltrexone (150 mg, 58.2%; 300 mg, 59.7%; 450 mg, 59.0%) compared with 63.2% for patients receiving placebo
- The most commonly reported TEAEs (incidence ≥2%) for each treatment group are summarized in Table 2
  - 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%)

Table 2. TEAEs in ≥2% of Patients Treated With Methylnaltrexone or Placebo (Safety Population)

Patients reporting TEAEs, n (%)	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
Nausea	13 (6.5)	16 (8.0)	12 (6.0)	18 (9.0)
Abdominal pain	11 (5.5)	16 (8.0)	21 (10.5)	17 (8.5)
Flatulence	11 (5.5)	7 (3.5)	10 (5.0)	9 (4.5)
Vomiting	3 (1.5)	6 (3.0)	7 (3.5)	9 (4.5)
Upper respiratory tract infection	9 (4.5)	7 (3.5)	8 (4.0)	9 (4.5)
Headache	2 (1.0)	8 (4.0)	9 (4.5)	8 (4.0)
Abdominal pain upper	4 (2.0)	6 (3.0)	6 (3.0)	7 (3.5)
Back pain	12 (6.0)	6 (3.0)	5 (2.5)	7 (3.5)
Diarrhea	7 (3.5)	13 (6.5)	16 (8.0)	7 (3.5)
Urinary tract infection	7 (3.5)	8 (4.0)	7 (3.5)	7 (3.5)
Abdominal distension	3 (1.5)	7 (3.5)	7 (3.5)	6 (3.0)
Influenza	4 (2.0)	6 (3.0)	2 (1.0)	5 (2.5)
Abdominal discomfort	2 (1.0)	0	1 (0.5)	4 (2.0)
Arthralgia	7 (3.5)	5 (2.5)	4 (2.0)	4 (2.0)
Hot flush	2 (1.0)	2 (1.0)	2 (1.0)	4 (2.0)
Hyperhidrosis	6 (3.0)	8 (4.0)	6 (3.0)	4 (2.0)
Muscle strain	0	2 (1.0)	1 (0.5)	4 (2.0)
Sinusitis	5 (2.5)	7 (3.5)	2 (1.0)	4 (2.0)
Anxiety	6 (3.0)	9 (4.5)	7 (3.5)	3 (1.5)
Rhinorrhea	5 (2.5)	4 (2.0)	4 (2.0)	3 (1.5)
Tremor	7 (3.5)	4 (2.0)	3 (1.5)	1 (0.5)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
AEs were coded using MedDRA version 13.0. A patient reporting more than 1 AE for a particular MedDRA preferred term or system organ class was counted only once for that MedDRA preferred term or system organ class.

Drug–Related TEAEs

- The incidence of study drug–related TEAEs was similar among treatment groups (22.1% among patients receiving methylnaltrexone [150 mg, 16.9%; 300 mg, 24.4%; 450 mg, 25.0%] and 22.9% among patients receiving placebo)
- The most commonly reported study drug–related TEAEs (incidence ≥1%) are summarized in Table 3
  - The most common drug-related TEAEs were abdominal pain (150 mg, 4.0%; 300 mg, 5.5%; 450 mg, 9.0%; placebo, 5.0%), nausea (150 mg, 3.5%; 300 mg, 5.5%; 450 mg, 5.5%; placebo, 4.0%), and flatulence (150 mg, 4.5%; 300 mg, 3.5%; 450 mg, 5.0%; placebo, 3.0%)

Table 3. Study Drug–Related TEAEs in ≥1% of Patients Treated With Methylnaltrexone or Placebo (Safety Population)

Patients reporting TEAEs, n (%)	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
Abdominal pain	8 (4.0)	11 (5.5)	18 (9.0)	10 (5.0)
Nausea	7 (3.5)	11 (5.5)	11 (5.5)	8 (4.0)
Abdominal pain upper	3 (1.5)	6 (3.0)	4 (2.0)	6 (3.0)
Flatulence	9 (4.5)	7 (3.5)	10 (5.0)	6 (3.0)
Abdominal distension	4 (2.0)	3 (1.5)	6 (3.0)	4 (2.0)
Abdominal discomfort	1 (0.5)	0	1 (0.5)	2 (1.0)
Blood alkaline phosphatase increased	0	0	1 (0.5)	2 (1.0)
Dizziness	1 (0.5)	1 (0.5)	3 (1.5)	2 (1.0)
Fatigue	0	0	0	2 (1.0)
Hot flush	0	0	1 (0.5)	2 (1.0)
Hyperhidrosis	1 (0.5)	3 (1.5)	5 (2.5)	2 (1.0)
Vomiting	0	1 (0.5)	4 (2.0)	2 (1.0)
Headache	1 (0.5)	4 (2.0)	3 (1.5)	1 (0.5)
Diarrhea	0	9 (4.5)	13 (6.5)	1 (0.5)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
AEs were coded using MedDRA version 13.0. A patient reporting more than 1 AE for a particular MedDRA preferred term or system organ class was counted only once for that MedDRA preferred term or system organ class.

Severe and Serious Adverse Events (SAEs)

- While the majority of TEAEs were mild to moderate in intensity, severe TEAEs (defined as grade 3 [severe] or grade 4 [life-threatening or disabling] by Common Terminology Criteria for Adverse Events) were reported by similar percentages of patients in all methylnaltrexone (8.0%–8.5%) and placebo (9%) groups
  - The most common severe AEs with methylnaltrexone overall vs placebo were diarrhea (1.7% vs 1.0%) and abdominal pain (1.2% vs 1.0%), respectively
- The incidence of SAEs was 3% among the 3 methylnaltrexone treatment groups versus 4% in the placebo group during the 12-week double-blind treatment period
- SAEs reported in ≥2 patients included dyspnea (methylnaltrexone 150 mg, n=1; placebo, n=2), noncardiac chest pain (placebo, n=2), chest pain (methylnaltrexone 300 mg, n=2), and suicidal ideation (methylnaltrexone 150 mg, n=1; methylnaltrexone 300 mg, n=1)
- No deaths occurred during the study, and no SAEs were deemed likely to be related to study drug treatment

Discontinuations Due to TEAEs

- TEAEs leading to study discontinuation occurred in 3.0% of patients treated with methylnaltrexone (150 mg, 1.0%; 300 mg, 4.5%; 450 mg, 3.5%) compared with 4.5% of patients receiving placebo
  - Discontinuations due to TEAEs that occurred in ≥2 patients in the methylnaltrexone groups or placebo group, respectively, included diarrhea (n=3 vs n=1), abdominal pain (n=2 vs n=0), and dyspnea (n=2 vs n=0)
  - All but 3 of the TEAEs resulting in study discontinuation (urticaria, placebo; abdominal pain, 300 mg; and vertigo, 450 mg) were resolved by the end of the study
- TEAEs in all treatment groups resulting in study discontinuation are summarized in Table 4

Table 4. TEAEs Leading to Study Discontinuation (Randomized Patient Population)

Study Group	TEAE	Relationship to Methylnaltrexone	Intensity	Outcome
Methylnaltrexone 150 mg (n=201)	Dyspnea	Probably related	Moderate	Resolved
	Nausea	Probably related	Severe	Resolved
Methylnaltrexone 300 mg (n=201)	Pulmonary embolism[a]	Not related	Severe	Resolved
	Diarrhea	Probably related	Severe	Resolved
	Abdominal pain	Possibly related	Severe	Never resolved
	Diarrhea	Probably related	Moderate	Resolved
	Pneumonia[a]	Not related	Moderate	Resolved
	Renal failure, acute[a]	Unlikely related	Severe	Resolved
	ALT increased	Probably related	Moderate	Resolved
	AST increased	Probably related	Moderate	Resolved
	Syncope	Not related	Moderate	Resolved
	Abdominal pain upper	Definitely related	Severe	Resolved
Methylnaltrexone 450 mg (n=200)	Vertigo	Not related	Moderate	Never resolved
	Abdominal pain	Probably related	Moderate	Resolved
	Constipation	Unlikely related	Moderate	Resolved
	Dyspnea	Possibly related	Mild	Resolved
	Hyperhidrosis	Probably related	Mild	Resolved
	Vomiting	Definitely related	Moderate	Resolved
	Diarrhea	Definitely related	Moderate	Resolved
Placebo (n=201)	Urticaria	Probably related	Moderate	Never resolved
	Vomiting	Probably related	Moderate	Resolved
	Nausea	Probably related	Moderate	Resolved
	Diarrhea	Not related	Severe	Resolved
	Pain in extremity	Unlikely related	Mild	Resolved
	Cellulitis	Not related	Severe	Resolved
	Enterocolitis infectious[a]	Not related	Severe	Resolved
	Abdominal distension	Probably related	Moderate	Resolved
	Diabetes mellitus inadequate control[a]	Not related	Severe	Resolved

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.
[a]Event was also considered an SAE. SAEs are sorted by treatment group.

CONCLUSIONS

- In this study, oral methylnaltrexone was well tolerated for the treatment of OIC associated with chronic noncancer pain
- The safety profile of oral methylnaltrexone was comparable to that of placebo at all dose levels tested (methylnaltrexone 150 mg, 300 mg, and 450 mg)
- Few discontinuations due to TEAEs and no study drug–related SAEs occurred during the study

REFERENCES: **1.** Bell TJ, et al. *Pain Med*. 2009;10(1):35-42. **2.** Cook SF, et al. *Aliment Pharmacol Ther*. 2008;27(12):1224-1232. **3.** Kalso E, et al. *Pain*. 2004;112(3):372-380. **4.** Gupta S, et al. *J Opioid Manag*. 2015;11(4):325-338. **5.** Coyne KS, et al. *Clinicoecon Outcomes Res*. 2014;6:269-281. **6.** Pappagallo M. *Am J Surg*. 2001;182(suppl 5A):11S-18S. **7.** Yuan CS, et al. *Clin Pharmacol Ther*. 2000;67(4):398-404. **8.** Yuan CS, Foss JF, *JAMA*. 2000;284(11):1383-1384. **9.** Rauck RL, Hong KJ, North J. *Pain Pract*. 2017;17(3):309-335. **10.** Relistor [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2017.

DISCLOSURES: Dr. Hanna and Dr. Israel are employees of Salix (Valeant) Pharmaceuticals. Dr. Rauck has received research funding from BioDelivery Sciences International, Inc., Boston Scientific Corporation, Inc., Endo Pharmaceuticals Inc., and Mainstay Delivery and is a consultant for Boston Scientific Corporation, Endo Pharmaceuticals Inc., and Pfizer Inc. Dr. Slatkin has been employed by Salix Medical Affairs since July 2016; prior to that time and for the preparation of all work related to the study on which this poster was based, he worked on behalf of Salix as an unpaid consultant; and through February 2016 was also on the Salix Speakers panel. Dr. Stambler is a full-time employee and shareholder of Progenics Pharmaceuticals.

ACKNOWLEDGMENTS: This study was supported by Salix, a Division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ, USA, which has licensed the rights to develop and commercialize Relistor® from Progenics Pharmaceuticals, Inc., New York, NY, USA. Technical editorial and medical writing assistance was provided under the direction of the authors by Lisa Feder, PhD, Echelon Brand Communications, Parsippany, NJ. Funding for this support was provided by Salix.

Research funded by: Salix Pharmaceuticals