POSTER NUMBER 141

Oral Methylnaltrexone Is Efficacious and Well Tolerated for the Treatment of Opioid-Induced Constipation in Patients With Chronic Noncancer Pain Taking Concomitant Methadone

Lynn R. Webster, MD[1]; Joseph R. Harper, PharmD[2]; Robert J. Israel, MD[2]

[1]PRA Health Sciences, Salt Lake City, UT, USA; [2]Salix Pharmaceuticals, Raleigh, NC, USA

INTRODUCTION

- In patients, including those with chronic noncancer pain (CNCP), opioids activate receptors in the gastrointestinal (GI) tract and slow GI transit, leading to constipation[1]
- Stool softeners and laxatives do not disrupt the interaction of opioids with their GI receptors and therefore may be ineffective for opioid-induced constipation (OIC)[2,3]
- An oral formulation of methylnaltrexone, a μ-opioid receptor antagonist, was approved in July 2016 by the US Food and Drug Administration for the treatment of OIC in adults with CNCP; results of a phase 3, randomized, double-blind trial of this drug demonstrated a significant reduction in OIC symptoms versus placebo, and that it was well tolerated[4]
- Other oral agents for the treatment of patients with OIC have reported potential reductions in efficacy (eg, lubiprostone)[5] or increased adverse events (AEs) among patients who were receiving methadone (eg, naloxegol)[6]

OBJECTIVE

- To evaluate the safety and efficacy of oral methylnaltrexone for OIC in a subgroup of adults with CNCP that received methadone

METHODS

Patients and Study Design

- Post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled trial: 14-day screening period, a 28-day once-daily (QD) treatment period, a 56-day as needed (PRN) period, and a 14-day follow-up period (double-blinding maintained throughout study)
- Adults with OIC who had been receiving ≥50 mg/d of oral morphine equivalents for ≥14 days for the treatment of CNCP for ≥2 months
  - OIC was confirmed during screening and defined as <3 rescue-free bowel movements (RFBMs) per week associated with ≥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; or ≥25% of RFBMs with a sensation of incomplete evacuation
- Eligible patients were randomly assigned to receive oral methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo QD for 4 weeks followed by 8 weeks of oral methylnaltrexone PRN
- Laxative therapy was discontinued at the start of the screening phase; however, rescue laxative therapy (ie, up to 3 oral bisacodyl tablets daily) was permitted for patients who did not have a bowel movement for 3 consecutive study days

Assessments and Statistical Analyses

- Time of all bowel movements and rescue laxative use was recorded daily via a telephone interactive voice-response system
- Primary endpoint: the mean percentage of dosing days that resulted in an RFBM within 4 hours of dosing during the 4-week QD period
- Secondary endpoints: time to first RFBM after the first dose, the percentage of responders (ie, had ≥3 RFBMs/week, with an increase of ≥1 RFBM/week from baseline for at least 3 of the 4 weeks) during the QD period, and the change in weekly number of RFBMs from baseline during the QD period

RESULTS

- Overall, 120 patients reported concomitant use of methadone (Table 1)
- Compared with placebo (15.1%), a significantly greater mean percentage of dosing days resulted in an RFBM within 4 hours of dosing during the QD period with oral methylnaltrexone 300 mg (33.6%; $P < 0.01$) and oral methylnaltrexone 450 mg (38.2%; $P < 0.001$), but not oral methylnaltrexone 150 mg (19.9%; $P = 0.4$)

RESULTS

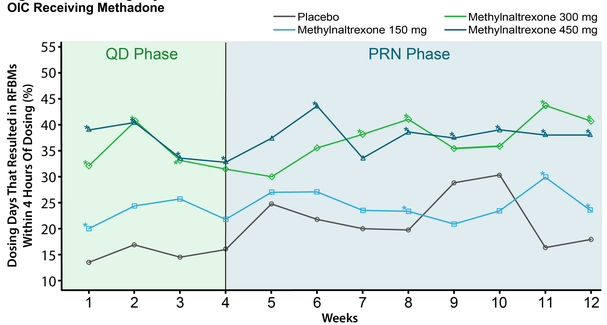
Table 1. Demographic and Baseline Characteristics

Parameter	Oral Methylnaltrexone 150 mg (n = 33)	Oral Methylnaltrexone 300 mg (n = 30)	Oral Methylnaltrexone 450 mg (n = 31)	Placebo (n = 26)
Age, mean, y (range)	47.0 (18-68)	48.1 (24-66)	50.8 (25-71)	47.3 (24-61)
Sex, n (%)				
Male	12 (36.4)	17 (56.7)	10 (32.3)	13 (50.0)
Female	21 (63.6)	13 (43.3)	21 (67.7)	13 (50.0)
Race, n (%)				
White	29 (87.9)	26 (86.7)	28 (90.3)	25 (96.2)
Black	3 (9.1)	2 (6.7)	3 (9.7)	1 (3.8)
Other	1 (3.0)	2 (6.7)	0	0
Primary pain condition				
Back pain	24 (72.7)	20 (66.7)	19 (61.3)	18 (69.2)
Joint/extremity pain	1 (3.0)	3 (10.0)	1 (3.2)	1 (3.8)
Arthritis	2 (6.1)	1 (3.3)	3 (9.7)	4 (15.4)
Neurologic/neuropathic pain	2 (6.1)	2 (6.7)	3 (9.7)	0
Fibromyalgia	3 (9.1)	2 (6.7)	3 (9.7)	1 (3.8)
Other	1 (3.0)	2 (6.7)	2 (6.5)	2 (7.7)
Median baseline MED, mg/d (range)	186.8 (60-1140)	269.8 (72-2289)	225.0 (90-720)	170.3 (60-600)
RFBMs per week, mean (SD)	1.5 (1.0)	1.3 (1.0)	1.4 (0.8)	1.3 (1.5)

MED = morphine equivalent dose; RFBMs = rescue-free bowel movements; SD = standard deviation.

- When assessed by week, improvement in the mean percentage of dosing days resulting in an RFBM within 4 hours of dosing observed during the QD period was maintained with oral methylnaltrexone 300 mg and 450 mg during the PRN period (Figure 1)

Figure 1 . QD Dosing Days That Resulted in an RFBM Within 4 Hours in Patients With CNCP and OIC Receiving Methadone

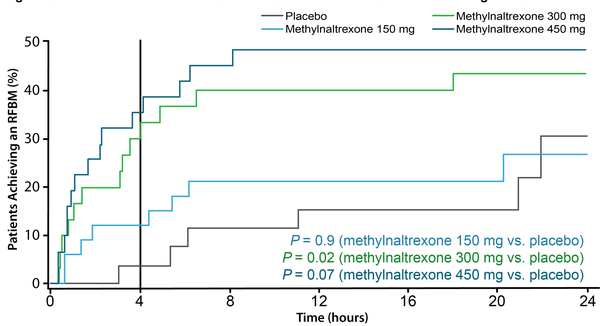


*$P < 0.05$ vs placebo. OIC = opioid-induced constipation; QD = once daily; RFBMs = rescue-free bowel movements.

RESULTS

- The time to achieve a first RFBM was shorter for both of the 2 higher doses of methylnaltrexone; however, a significant difference versus placebo was reported only with methylnaltrexone 300 mg ($P = 0.02$; Figure 2)

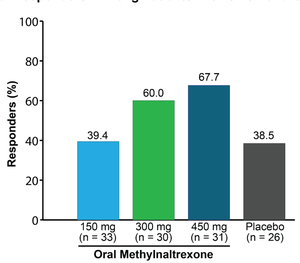
Figure 2. Time to Achieve First RFBM in Patients With CNCP and OIC Receiving Methadone



Patients were censored at 24 hours or the time of the second dose.
CNCP = chronic noncancer pain; OIC = opioid-induced constipation; RFBM = rescue-free bowel movement.

- The percentage of responders was greater versus placebo for methylnaltrexone 300 mg and 450 mg during the QD period; however, differences were not significant ($P \geq 0.05$; Figure 3)

Figure 3. Percentage of Responders* Among Patients With CNCP and OIC Receiving Methadone



*Responder was defined as a patient who had ≥3 RFBMs/week, with an increase of ≥1 RFBM/week from baseline for at least 3 of the first 4 weeks of the treatment period. $P \geq 0.05$ versus placebo for all methylnaltrexone doses.
CNCP = chronic noncancer pain; OIC = opioid-induced constipation.

RESULTS

- Change from baseline in mean number of weekly RFBMs during the QD period was significantly greater with oral methylnaltrexone 450 mg (least-squares mean difference [95% confidence interval], 1.2 [0.1-2.3], $P = 0.04$)
- Oral methylnaltrexone was generally well tolerated (Table 2)

Table 2. Adverse Events* in Patients With CNCP and OIC Receiving Methadone

Patients, n (%)	Oral Methylnaltrexone 150 mg (n = 33)	Oral Methylnaltrexone 300 mg (n = 30)	Oral Methylnaltrexone 450 mg (n = 31)	Placebo (n = 26)
Any AE	21 (63.6)	21 (70.0)	23 (74.2)	12 (46.2)
Abdominal pain	4 (12.1)	4 (13.3)	10 (32.3)	0
Nausea	2 (6.1)	5 (16.7)	5 (16.1)	0
Diarrhea	1 (3.0)	3 (10.0)	4 (12.9)	0
Flatulence	3 (9.1)	2 (6.7)	1 (3.2)	2 (7.7)
Hyperhidrosis	3 (9.1)	3 (10.0)	1 (3.2)	0
URTI	2 (6.1)	1 (3.3)	0	3 (11.5)
Fall	3 (9.1)	1 (3.3)	0	0
Upper abdominal pain	0	3 (10.0)	0	0

*Reported in ≥8.0% of patients in any treatment group during QD, PRN, and follow-up periods.
AE = adverse event; OIC = opioid-induced constipation; PRN = as needed; QD = once daily; URTI = upper respiratory tract infection.

- Only 2 patients discontinued from the study because of AEs: 1 patient treated with oral methylnaltrexone 300 mg discontinued because of upper abdominal pain, and 1 patient treated with oral methylnaltrexone 450 mg discontinued because of vertigo

CONCLUSION

- **Oral methylnaltrexone, particularly the 450-mg dose, was efficacious and well tolerated for treating OIC in patients with CNCP who received concomitant methadone**

REFERENCES

1. Clemens KE, Klaschik E. *Ther Clin Risk Manag.* 2010;6:77-82.
2. Bell TJ, et al. *Pain Med.* 2009;10(1):35-42.
3. Cook SF, et al. *Aliment Pharmacol Ther.* 2008;27(12):1224-1232.
4. Rauck RL, et al. Presented at: Digestive Disease Week; May 19-22, 2012: San Diego, CA.
5. Amitiza® [package insert]. Bethesda, MD: Sucampo Pharma Americas, LLC; 2013.
6. Movantik® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.

DISCLOSURES: LRW has received some form of financial support from AstraZeneca, Cara Therapeutics, Depomed, Inc., Egalet Corporation, Grünenthal USA, Jazz Pharmaceuticals, Kaléo, Inc, Kempharm, Inc., Mallinckrodt Pharmaceuticals, Orexo, Pain Therapeutics, Pfizer Inc, Scilex Pharmaceuticals, Shionogi, Inc., Teva Pharmaceutical Industries Ltd, and Trevena, Inc. JRH is an employee of Salix Pharmaceuticals. RJI is an employee of Salix Pharmaceuticals or its affiliates.

ACKNOWLEDGEMENTS: Funding for this study was provided by Salix Pharmaceuticals. Technical editorial and medical writing assistance was provided under the direction of the authors by Mary Beth Moncrief, PhD, and Jillian Gee, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Salix Pharmaceuticals.

Research funded by: Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America