Many patients develop some degree of opioid-induced constipation (OIC), and unlike other GI-related adverse effects (eg, nausea), patients typically do not develop tolerance to OIC across time, or they develop tolerance very slowly. Severe OIC may result in opioid dose reduction or limitations on upward titration, potentially affecting adequate pain control. Guidelines recommend that health care providers proactively manage opioid-associated adverse effects.

Although randomized controlled data are generally lacking, stool softeners and stimulant laxatives may be prescribed at the initiation of opioid therapy. However, these treatments are nonspecific and do not target the underlying pathophysiology of OIC, including opioid inhibition of peristalsis. Methylnaltrexone blockade of peripherally acting μ-opioid receptor antagonists has restricted ability to cross the blood-brain barrier, and it antagonizes the negative opioid-induced effects on the GI tract, such as delayed gastric emptying and prolongation of oral-cecal transit time. Methylnaltrexone is indicated for the treatment of OIC in adults with chronic noncancer pain and for the treatment of OIC in patients with advanced illness receiving palliative care who have had an inadequate response to laxative therapy. The efficacy and safety of methylnaltrexone in patients with chronic noncancer pain were demonstrated in a 4-week, randomized, placebo-controlled trial, with efficacy and tolerability maintained for up to an additional 8 weeks in an open-label extension (OLE) phase. To assess the reproducibility of efficacy and safety findings from the RCT, data from placebo-treated patients who crossed over to methylnaltrexone treatment in the OLE phase were analyzed.

**Background and Objectives:** In patients with chronic noncancer pain, subcutaneous methylnaltrexone for opioid-induced constipation (OIC) was examined in a randomized controlled trial (RCT) followed by an open-label extension (OLE). This study examined the reproducibility of RCT findings by analyzing data from placebo-treated patients who crossed over to methylnaltrexone.

**Methods:** Adults with less than 3 weekly rescue-free bowel movements (RFBMs), taking 50 mg or more of an oral morphine equivalent per day, were randomized to receive methylnaltrexone 12 mg or placebo for 4 weeks, followed by open-label methylnaltrexone 12 mg as needed for 8 weeks.

**Results:** A total of 134 placebo-treated patients (median morphine equivalent dose, 150 mg/d; mean of 1.1 RFBM per week) crossed over to methylnaltrexone in OLE. During the RCT, 9.7% of placebo-treated patients experienced an RFBM within 4 hours of first dose and 9.0% of all placebo injections resulted in an RFBM within 4 hours compared with 45.9% and 34.5%, respectively, with methylnaltrexone treatment in the OLE. When expressed as percentage of patients experiencing 3 or more RFBMs per week and a 1-RFBM increase over baseline, weekly values ranged from 35% to 40% during placebo treatment; at week 5 of OLE methylnaltrexone, this percentage increased to more than 70% and remained relatively stable throughout the OLE. The most common adverse events during methylnaltrexone treatment were abdominal pain (9.7% vs 1.5% for placebo) and nausea (5.2% vs 6.7%).

**Conclusions:** Findings during placebo treatment further establish the profile of OIC and support that little or no gastrointestinal tolerance develops across time. Findings under open-label conditions established the reproducibility and durability of methylnaltrexone for OIC.

**Methods**

**Study Population**

This study included adults with chronic noncancer pain (≥2 months’ duration before screening) who had been taking opioids and had a stable medical status for at least 1 month (average daily dose ≥50 mg oral morphine equivalent for ≥2 weeks with no anticipated changes) and who had OIC (<3 rescue-free bowel movements [RFBMs] per week with ≥1 of the following signs or symptoms for ≥25% of bowel movements: hard or lumpy stools, straining during bowel movements, or sensation of incomplete evacuation). Patients were excluded if they had a history of inflammatory bowel disease, irritable bowel syndrome, or megacolon during the previous 6 months, were scheduled to undergo surgery during the study period, had evidence of bowel obstruction or fecal incontinence, history of rectal bleeding unrelated to hemorrhoids or fissures, or a history of chronic constipation before starting opioid therapy. Patients discontinued all laxative use before enrollment; rescue laxatives (bisacodyl tablets taken ≥4 hours after study drug administration, with only 1 dose allowed within a 24-hour period) were permitted if the patient had no bowel movements for 3 consecutive days during the RCT or OLE. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice according to the Declaration of Helsinki, and all patients provided written informed consent.
Study Design and Assessments

Details on the design of the RCT have been previously published. Briefly, the RCT was a phase 3, double-blind, placebo-controlled, multicenter study (ClinicalTrials.gov identifier, NCT00529087) conducted at 91 sites in the United States and Canada. Patients were randomly assigned 1:1:1 to receive subcutaneous methylnaltrexone (Relistor; Salix Pharmaceuticals, Inc, Raleigh, North Carolina) 12 mg once daily (qd), methylnaltrexone 12 mg once every other day (qod), or placebo for 4 weeks. Patients who completed the RCT were eligible to enter an OLE phase and received subcutaneous methylnaltrexone 12 mg as needed (prn; maximum, qd) for 8 weeks, followed by a 14-day posttreatment follow-up period.

Efficacy outcomes were evaluated during the RCT and OLE using daily patient diaries, which included the number and time of bowel movements, stool consistency (Bristol Stool Form Scale), straining during a bowel movement (0 = none to 4 = very severe), sense of complete evacuation (yes/no), and rescue laxative use. The coprimary efficacy end points in the RCT were the percentage of patients experiencing an RFBM within 4 hours of the first dose and the percentage of injections resulting in an RFBM within

**TABLE 1.** Patient Demographics and Baseline Characteristics

| Characteristics                                      | Placebo Crossover (n = 134) | RCT Methylnaltrexone qd (n = 150)† | RCT Methylnaltrexone qod (n = 148)† |
|------------------------------------------------------|-----------------------------|------------------------------------|------------------------------------|
| Mean age (SD), y                                      | 50.3 (10.8)                 | 48.0 (10.7)                        | 48.6 (11.0)                        |
| Range                                                | 25–83                       | 24–78                              | 23–73                              |
| Sex (male), %                                        | 64.2                        | 62.0                               | 57.4                               |
| Race, n (%)                                          |                             |                                    |                                    |
| White                                                | 119 (88.8)                  | 139 (92.7)                         | 133 (89.9)                         |
| Black                                                | 12 (9.0)                    | 7 (4.7)                            | 10 (6.8)                           |
| Other                                                | 3 (2.2)                     | 4 (2.6)                            | 5 (3.4)                            |
| Mean BMI (SD), kg/m²                                  | 30.2 (8.0)                  | 30.3                               | 28.9                               |
| Range                                                | 15.7–66.2                   | 16.8–56.5                          | 15.7–54.7                          |
| Primary pain condition, n (%)                         |                             |                                    |                                    |
| Back pain                                            | 78 (58.2)                   | 96 (64.0)                          | 83 (56.1)                          |
| Other                                                | 56 (41.8)                   | 54 (36.0)                          | 65 (43.9)                          |
| Mean oral morphine equivalents (SD), mg/d             | 214.6 (199.3)               | 214.4 (156.6)                      | 225.2 (205.1)                      |
| Median                                               | 150.0                       | 161.0                              | 154.8                              |
| Mean OIC duration (SD), mo                            | 78.3 (70.15)                | 76.4 (60.3)                        | 76.1 (74.1)                        |
| Mean baseline bowel movements per week (SD)           | 1.1 (0.8)                   | 1.0 (0.8)                          | 0.9 (0.7)                          |

*At baseline of RCT.
†Data from Michna et al.© 2015 American Society of Regional Anesthesia and Pain Medicine. Unauthorized reproduction of this article is prohibited.

BMI indicates body mass index; OIC, opioid-induced constipation; qd, every day; qod, every other day; RCT, randomized controlled trial; SD, standard deviation.
4 hours of dose administration. Secondary efficacy end points included the percentage of patients experiencing 3 or more RFBMs per week and at least a 1-RFBM increase from baseline in the weekly RFBM rate ("responders"), the percentage of patients experiencing 3 or more RFBMs per week, the weekly RFBM rate, and the percentage of weekly injections resulting in an RFBM within 4 hours of dose administration. An RFBM was defined as a bowel movement not occurring within 24 hours of rescue laxative use. Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications.

Statistical Analyses

The RCT methylnaltrexone population included all patients randomized to treatment who received at least 1 dose of methylnaltrexone. The placebo crossover population included all patients who completed the RCT trial and received at least 1 dose of methylnaltrexone during the OLE. Data were analyzed using an observed case analysis. For between-group comparisons during the RCT, P values were calculated using the Wilcoxon rank sum test. Descriptive statistics were used for the placebo crossover population analyses.

RESULTS

A total of 460 patients received methylnaltrexone 12 mg qd (n = 150), methylnaltrexone 12 mg qod (n = 148), or placebo (n = 162) in the 4-week RCT (Fig. 1). Of the 162 patients who had received placebo in the RCT, 134 were enrolled in the OLE and crossed over to methylnaltrexone 12 mg prn treatment. The most common pain condition among the 134 patients in the placebo crossover population was back pain (58.2%), and the mean number of bowel movements per week at RCT baseline was 1.1 (Table 1).

A total of 13 (9.7%) of 134 patients had experienced an RFBM within 4 hours of the first placebo dose during the RCT; however, 61 (45.9%) of the 134 patients experienced an RFBM within 4 hours of the first methylnaltrexone dose in the OLE. When response was expressed according to the percentage of patients experiencing 3 or more RFBMs per week and an increase of 1 or more RFBMs over baseline, weekly values ranged from 35% to 40% during placebo treatment in the RCT, suggesting a lack of tolerance development to OIC across time (Fig. 3A). However, when patients crossed over from placebo to methylnaltrexone treatment, the percentage increased to more than 70% within the first week (week 5) and remained relatively stable throughout the study. The percentage of patients experiencing 3 or more RFBMs per week and an increase of 1 or more RFBMs over baseline observed in the placebo crossover population during the OLE was consistent with data observed for those patients who had received methylnaltrexone qd or qod during the RCT and continued receiving methylnaltrexone during the OLE (Fig. 3B).

The number of RFBMs per week increased slightly but significantly during placebo treatment in the RCT, from 1.1 RFBMs per week to a range of 2.3 to 2.7 per week (P < 0.001); the results were significantly lower than data for patients who were treated with methylnaltrexone qd during the RCT (1.0 RFBM per week at baseline vs 4.3 to 4.6 during the RCT; P < 0.05 versus placebo at all weeks; Fig. 3B). When placebo-treated patients crossed over to receive methylnaltrexone prn in the OLE, weekly RFBMs increased to levels of approximately 4 within 1 week, remained stable through week 12, and the weekly data were consistent with results from patients who had received methylnaltrexone during both the RCT and the OLE (Fig. 3B). The trend in improvement observed with the placebo crossover population was also observed when the percentage of weekly injections resulting in an RFBM within 4 hours of dose administration was assessed (Fig. 3C). In the placebo group in the RCT, only approximately 10% of weekly injections resulted in an RFBM within 4 hours of dose administration; however, when patients crossed over to methylnaltrexone prn in the OLE, this percentage increased to 35% to 40%. Improvements observed in the placebo crossover population were consistent with results from patients who had received methylnaltrexone during both the RCT and OLE (Fig. 3C).

Overall, AEs were reported in 32.8% of 134 patients during placebo treatment in the 4-week RCT versus 43.3% of 134 patients during 8 weeks of methylnaltrexone treatment in the OLE (Table 2). Abdominal pain, nausea, and urinary tract infections were the most common AEs during the OLE. Serious AEs were reported in 1 patient (0.7%) during placebo treatment (musculoskeletal chest pain) in the RCT and 4 patients (3.0%) during methylnaltrexone treatment in the OLE (pneumonia in 2 patients; gastroenteritis and hypertension in 1 patient; and mental status change in 1 patient); none were considered by investigators to be drug related.

DISCUSSION

Methylnaltrexone is a peripherally acting μ-opioid receptor antagonist that targets the underlying pathophysiology of OIC: opioid agonism of μ-opioid receptors in the GI tract. Opioids
can interfere with normal GI motility, thereby reducing productive peristalsis, increasing fluid absorption from the GI tract, and decreasing intestinal secretions, which leads to drier harder stool. Subcutaneous methylnaltrexone has been shown in an RCT to be well tolerated and to provide significant relief from OIC when administered once daily or every other day for the treatment of OIC in patients with chronic noncancer pain. The current post hoc analysis examined the repeatability of these findings by evaluating the tolerability and response of patients who were initially treated with placebo during the RCT and crossed over to treatment with methylnaltrexone 12 mg prn for up to 12 weeks. This methodology minimized the risk of heterogeneity with the analyses by having each patient function as his or her own control.

The current analysis reaffirmed the data from the RCT and demonstrated that a higher percentage of patients achieved an RFBM within 4 hours of the first dose of methylnaltrexone during the OLE compared with their first dose of placebo in the RCT. As well, other efficacy analyses, including the percentage of weekly responders (≥3 RFBMs per week and ≥1 RFBM increase over baseline) and weekly number of RFBMs, improved when patients crossed over to receive methylnaltrexone prn compared with their experience with placebo treatment during the RCT. Furthermore, responder rates achieved when patients crossed over to methylnaltrexone treatment in the OLE (53.7%–70.9%) were consistent with results observed during the 4-week RCT for patients receiving methylnaltrexone qd (61.2%–66.4%) or qod (45.6%–60.5%) and results for the methylnaltrexone-treated patients who continued to receive methylnaltrexone in the OLE (56.3%–69.4% and 49.4%–67.5% for qd and qod dosing, respectively). This is the first OIC study to evaluate drug efficacy during an RCT and an OLE crossover period, and differences in “responder” definitions prevent comparisons with other studies; however, an RCT of oral μ-opioid receptor antagonist alvimopan that used a definition similar to the one used in the current study (ie, patients who had ≥3 spontaneous bowel movements per week and a mean increase from baseline of ≥1 spontaneous bowel movement per week) showed that responder rates with alvimopan 1 mg/d were only slightly higher (72%) than response rates in the current study. A separate RCT of alvimopan using the identical definition of responder reported no significant difference with alvimopan 1 mg/d compared with placebo. Lower response rates in patients with noncancer

FIGURE 3. Percentage of patients with both a weekly number of rescue-free bowel movements (RFBMs) of 3 or more and an increase of 1 or more RFBMs from baseline by week (A); average weekly number of RFBMs by week (B); and percentage of weekly injections resulting in an RFBM within 4 hours of dose administration by week (C). *Statistically significant difference versus placebo (P < 0.05) during the randomized controlled trial (RCT). MNTX indicates methylnaltrexone; OLE, open-label extension; prn, as needed; qd, once a day; qod, every other day.
and chronic noncancer pain, and that administration does not result in the development of opioid tolerance across time.

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REFERENCES
1. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil. 2014;26:1386–1395.
2. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manage. 2008;35:214–228.
3. Thomas J. Opioid-induced bowel dysfunction. J Pain Symptom Manage. 2008;35:103–113.
4. Chou R, Fanciullo GJ, Fine PG, et al. American Pain Society–American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113–130.
5. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther. 2005;7:R1046–R1051.
6. Clemens KE, Klaschik E. Managing opioid-induced constipation in advanced illness: focus on methylnaltrexone bromide. Ther Clin Risk Manag. 2010;6:77–82.
7. Mc Nicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain. 2003;4:231–256.
8. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European patient survey (PROBE 1). Pain Med. 2009;10:35–42.
9. Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: results from a population-based survey. Aliment Pharmacol Ther. 2008;27:1224–1232.
10. Manara L, Bianchi G, Ferretti P, Tavani A. Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites. J Pharmacol Exp Ther. 1986;237:945–949.
11. Tavani A, Bianchi G, Ferretti P, Manara L. Morphine is most effective on gastrointestinal propulsion in rats by intraperitoneal route: evidence for local action. Life Sci. 1980;27:2211–2217.
12. Russell J, Bass P, Goldberg LI, Schuster CR, Merz H. Antagonism of gut, but not central effects of morphine with quaternary narcotic antagonists. Eur J Pharmacol. 1982;78:255–261.
13. Bader S, Jaroslawski K, Blum HE, Becker G. Opioid-induced constipation in advanced illness: safety and efficacy of methylnaltrexone bromide. Clin Med Insights Oncol. 2011;5:201–211.
14. Rosow CE, Gomery P, Chen TY, Stefanovich P, Stambler N, Israel R. Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. Clin Pharmacol Ther. 2007;82:48–53.
15. Murphy DB, Sutton JA, Prescott LF, Murphy MB. Opioid-induced delay in gastric emptying: a peripheral mechanism in humans. Anesthesiology. 1997;87:765–770.
16. Yuan CS, Foss JF, O’Connor M, Toledano A, Roizen MF, Moss J. Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: a double-blind randomized placebo-controlled trial. Clin Pharmacol Ther. 1996;59:469–475.

| TABLE 2. Summary of AEs (Placebo Crossover Population) |
|-----------------------------------------------|
| AEs (%) | Placebo Treatment During RCT | Methylnaltrexone Treatment During OLE |
|-----------------------------------------------|
| Any AEs | 44 (32.8) | 58 (43.3) |
| Serious AEs | 1 (0.7) | 4 (3.0) |
| Deaths | 0 | 0 |
| Most common AEs* | | |
| Nausea | 9 (6.7) | 7 (5.2) |
| Abdominal pain | 2 (1.5) | 13 (9.7) |
| Diarrhea | 4 (3.0) | 6 (4.5) |
| Upper abdominal pain | 5 (3.7) | 4 (3.0) |
| Urinary tract infection | 2 (1.5) | 7 (5.2) |
| Hyperhidrosis | 1 (0.7) | 6 (4.5) |
| Back pain | 1 (0.7) | 4 (3.0) |
| Hypertension | 0 | 5 (3.7) |
| Rhinorrhea | 1 (0.7) | 4 (3.0) |
| Influenza | 0 | 4 (3.0) |
| Sinusitis | 0 | 4 (3.0) |

*Reported in 5% or more patients.

AE indicates adverse event; OLE, open-label extension; RCT, randomized controlled trial.
17. Relistor (methylnaltrexone bromide) subcutaneous injection [package insert]. Raleigh, NC: Salix Pharmaceuticals, Inc; 2014.

18. Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. *J Pain*. 2011;12:554–562.

19. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920–924.

20. Jansen JP, Lorch D, Langan J, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J Pain*. 2011;12:185–193.

21. Irving G, Pénzes J, Ramjattan B, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J Pain*. 2011;12:175–184.

22. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*. 2014;370:2387–2396.

23. Slatkin NE, Lynn R, Su C, Wang W, Israel RJ. Characterization of abdominal pain during methylnaltrexone treatment of opioid-induced constipation in advanced illness: a post hoc analysis of two clinical trials. *J Pain Symptom Manage*. 2011;42:754–760.

24. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol*. 2009;7:39–46.

25. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*. 2008;358:2332–2343.

26. Chen W, Chung HH, Cheng JT. Opiate-induced constipation related to activation of small intestine opioid μ2-receptors. *World J Gastroenterol*. 2012;18:1391–1396.

27. Pasternak GW. Molecular insights into mu opioid pharmacology: from the clinic to the bench. *Clin J Pain*. 2010;26(suppl 10):S3–S9.

28. Ling GS, Paul D, Simantov R, Pasternak GW. Differential development of acute tolerance to analgesia, respiratory depression, gastrointestinal transit and hormone release in a morphine infusion model. *Life Sci*. 1989;45:1627–1636.