Subcutaneous Methylnaltrexone for Treatment of Opioid-Induced Constipation in Cancer versus Noncancer Patients: An Analysis of Efficacy and Safety Variables from Two Studies

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Purpose: Methylnaltrexone inhibits opioid-induced constipation (OIC) by binding to peripheral µ-opioid receptors without impacting central opioid receptor mediated analgesia. This analysis compared methylnaltrexone efficacy and safety among advanced illness patients with and without active cancer and OIC.

Patients and Methods: This post hoc analysis included two multicenter, randomized, double-blind, placebo-controlled studies in adults with advanced illness and OIC who received subcutaneous methylnaltrexone. Efficacy endpoints included the proportion of patients achieving rescue-free laxation (RFL), time to RFL, weekly laxations within 24 hours after dosing, rescue laxative use, and pain scores. Adverse events were monitored for safety.

Results: After pooling, 178 patients received methylnaltrexone (n = 116 with cancer) and 185 received placebo (n = 114 with cancer). Median baseline daily opioid morphine equivalents (mg/d) were higher in cancer (methylnaltrexone: 180; placebo: 188) versus noncancer patients (methylnaltrexone: 120; placebo: 80). The proportions of patients achieving RFL within 4 hours after ≥2 of the first 4 doses were significantly greater with methylnaltrexone (cancer: 56.9%; noncancer: 58.1%) versus placebo (cancer: 5.3%; noncancer: 11.3%; P < 0.0001). The median time to laxation within 24 hours after the first methylnaltrexone dose was significantly shorter in cancer and noncancer patients versus placebo (cancer: 0.96 vs 22.53 hours, P < 0.0001; noncancer: 1.25 vs >24 hours, P = 0.0002). The mean number of weekly laxations within 24 hours after dosing by week 2 was significantly higher in methylnaltrexone- vs placebo-treated cancer and noncancer patients (cancer: 7.9 vs 4.9, P < 0.0001; noncancer: 8.4 vs 5.0, P < 0.0001). Methylnaltrexone reduced rescue laxative use without impacting pain scores. Consistent with previous data, methylnaltrexone was well tolerated in cancer and noncancer patients, and the AE profile did not suggest symptoms of opioid withdrawal.

Conclusion: Methylnaltrexone reduced RFL time in advanced-illness patients with and without active cancer, while maintaining pain control with opioid treatment despite higher baseline opioid use among cancer patients.

Keywords: methylnaltrexone, opioid-induced constipation, µ-opioid receptor antagonist, cancer, chronic pain

Introduction

Moderate to severe pain occurs in patients with cancer and, despite their inherent risks, management often includes opioid analgesics.¹,² Opioid-induced constipation (OIC) is a common adverse effect of opioid analgesics, affecting up to 60% of...
patients being managed for cancer-related pain with opioids. When daily opioid therapy is prolonged in cancer patients, the likelihood of OIC increases. The development of OIC may limit opioid use, thereby compromising effective analgesia in patients with chronic pain. OIC also impacts quality of life in patients with cancer. In a trial of Japanese patients, quality of life measured 2 weeks after initiation of a strong opioid was significantly reduced among cancer patients with OIC compared with those without OIC.

The use of traditional laxatives often fails to adequately manage symptoms associated with OIC because the underlying opioid receptor-mediated mechanism remains untargeted. OIC occurs as a result of an opioid binding to peripheral μ-opioid receptors in the gastrointestinal tract, leading to abnormal modulation of gastrointestinal secretion and absorption. These considerations have led to the development of the peripherally acting μ-opioid receptor antagonist (PAMORA) class of agents to specifically address OIC. However, constipation in patients with cancer is often multifactorial and may arise from several sources in addition to opioid use. For instance, constipation may be a consequence of cancer-related physiologic dysfunction (eg, gastrointestinal obstruction, tumors, autonomic dysfunction), concomitant medications (eg, anticholinergics, antiemetics, chemotherapy), dehydration, immobility, diet, or metabolic causes (eg, hypercalcemia, hypokalemia), among other factors. Hence, the response of constipated opioid-treated cancer patients to a PAMORA may differ from that of other opioid-treated patients having serious and advanced noncancer illnesses.

A number of reports have indicated that opioids and activation of μ-opioid receptors (MOR) may be an overall risk factor for survival in patients with advanced cancer. In addition to the negative impact of OIC on the symptoms and healthcare resource utilization in cancer patients, the presence of constipation has itself emerged as a potential survival risk factor for such patients. As such, the control of opioid-mediated constipation takes on even greater significance. Indeed, in a retrospective analysis of the treatment of advanced illness patients with OIC, Janku et al found that peripheral μ-opioid inhibition played a role in enhancing cancer survival, an effect potentially directly related to improved gut function. These findings also complement preclinical studies showing that activation of the tumor based MOR has been directly implicated as a risk factor in cancer progression through a variety of mechanisms including MOR-related angiogenesis, an effect shown in several studies to be inhibited by a peripheral u-opioid antagonist.

To the extent that OIC may not only be a distressing symptom in cancer patients, but a factor contributing to decreased survival, it is important to establish the efficacy of peripheral opioid antagonism in treating this symptom. Methylnaltrexone (Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) is a selective, peripherally acting μ-opioid receptor antagonist (PAMORA) that improves gastrointestinal transit in opioid-treated patients. Since methylnaltrexone has restricted ability to cross an intact blood–brain barrier due to high polarity and low lipid solubility, it is able to act on opioid receptors in the gastrointestinal tract without affecting the analgesic effects of the opioid. Methylnaltrexone tablets and subcutaneous (SC) injection are approved for the treatment of OIC in adults with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation. Methylnaltrexone SC injection is the only PAMORA 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.

In two previously completed primary studies in patients with advanced illnesses including cancer, SC methylnaltrexone demonstrated robust efficacy and was well tolerated in treating OIC without affecting central analgesia or precipitating opioid withdrawal. To our knowledge, though, no prospective studies have assessed the efficacy and safety of PAMORAs or laxatives for the treatment of OIC in patients with cancer in the United States, and there are no published studies that compare SC methylnaltrexone use among patients with and without cancer. This post hoc analysis evaluated data from two similarly designed multidose studies and characterized the baseline demographics and efficacy and safety endpoints of patients with and without cancer, receiving opioids, and treated with methylnaltrexone or placebo. Results may provide a basis for future studies to assess additional clinical benefits of methylnaltrexone in cancer patients.

Methods

Study Design

Two multicenter, double-blind, randomized, placebo-controlled studies (302 [NCT00402038] and 4000
tic agents (eg, milk of magnesia, polyethylene glycol, sodium), stimulants (eg, senna and bisacodyl) and osmo
taking laxatives, including stool softeners (eg, docusate
48 hours before the first dose of study drug. For patients
study drug or (2) no clinically significant laxation within
significant laxation in the 24 hours before the first dose of
movements during the previous week and no clinically
permitted) for ≥3 days before the first dose. Patients
be receiving opioids routinely for discomfort or pain
management for ≥2 weeks before the first dose of the
study drug, and to be taking a stable regimen (defined as
no reduction in dose of ≥50%; increases in dose were
allowed) for ≥3 days before the first dose. Patients
were required to have OIC, defined as (1) <3 bowel
movements during the previous week and no clinically
significant laxation in the 24 hours before the first dose of
study drug or (2) no clinically significant laxation within
48 hours before the first dose of study drug. For patients
taking laxatives, including stool softeners (eg, docusate
sodium), stimulants (eg, senna and bisacodyl) and osmo-
tic agents (eg, milk of magnesia, polyethylene glycol,
lactulose, and sorbitol), the regimen was to be stable for
≥3 days prior to the first dose of study drug, and patients
were permitted to continue these laxatives throughout the
study.
Patients were excluded if they had a history of methyl-
naltrexone treatment, any disease process suggestive of
mechanical bowel obstruction, evidence of fecal impac-
tion, active diverticular disease, fecal ostomy, and any
potential nonopioid cause of bowel dysfunction, which in
the opinion of the investigator might have been primarily
responsible for constipation. Additionally, patients with
surgically acute abdomens were not eligible for study
302, and patients who received vinca alkaloids (eg, vin-
cristine, vinblastine, or vinorelbine) during the 4 months
before screening were not eligible for study 4000.
Assessments
Patients were stratified by those with active cancer and those
without cancer. In order to show that methylaltrexone
worked quickly and to determine the temporal relationship
between drug administration and response, the following
efficacy endpoints were chosen: (1) the proportion of patients
with RFL within 4 hours after ≥2 of the first 4 doses; (2) the
proportion of patients with RFL within 4 hours after the first
dose; (3) the time to first RFL assessed at 4 hours and 24
hours; (4) the number of laxations within 24 hours after
dosing by week 2; (5) the proportion of patients with ≥3
rescue-free bowel movements per week in both weeks 1 and
2; (6) the proportion of patients using rescue laxatives; and
(7) pain scores. The weekly number of laxations was set to
missing for the week where bowel movement assessment
was missing for more than 3 days. Current and worst levels
of pain were evaluated after the first dose of study medication
and on day 7 and graded on a scale of 0 (none) to 10 (worst
possible pain).
Safety was evaluated in all patients who received a dose of study drug and included the incidence, severity,
and type of adverse events (AEs). All AEs were coded
according to the Medical Dictionary for Drug Regulatory
Affairs version 6.0 (study 302) or 14.0 (study 4000).
Statistical Analyses
Data were pooled from both studies and patients were stra-
tified by those with active cancer and those without cancer.
Efficacy analyses were performed on the intent-to-treat (ITT) analysis set, which was defined as patients who received ≥1 dose of study drug. Data were analyzed using chi-square tests for RFL response and use of rescue laxatives; log-rank tests for time to first RFL response censored at 48 hours or the time of the next dose of study mediation; and Wilcoxon rank-sum tests for weekly number of laxations. Kaplan–Meier survival curves were used to compare the time to laxation onset between treatments for cancer and noncancer patients. The nominal level of significance was 0.05, with no adjustment for multiplicity.

**Ethical Considerations**
Both studies were designed and conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each patient prior to their participation in the trial. Study protocols and informed consent forms received institutional review board approval from respective investigational sites before the study began (Supplementary Information).

**Results**

**Patients**
In the pooled population, a total of 178 patients received methylnaltrexone and 185 patients received placebo; 65.2% (n=116) of patients in the methylnaltrexone group and 61.6% (n=114) of patients in the placebo group had cancer. Demographics and baseline characteristics are shown in Table 1. Patients with cancer were taking higher median daily doses of opioid morphine equivalents (methylnaltrexone: 180 mg/d; placebo: 188 mg/d) at baseline compared with those without cancer (methylnaltrexone: 120 mg/d; placebo: 80 mg/d). Almost all (98.6%) patients were using laxatives at baseline, with similar laxative use between groups. There were no notable differences in current and worst pain scores between study populations at baseline.

**Effect on Laxation**
In patients with and without cancer, methylnaltrexone induced a significantly greater RFL response within 4 hours after the first dose of treatment compared with placebo ($P < 0.0001$; Figure 1). Significant differences in RFL after ≥2 of the first 4 doses of study drug were also observed (Figure 1B). The probability of having an RFL within 4 and 24 hours after the first dose of study medication was significantly greater following methylnaltrexone treatment in both cancer and noncancer patients compared with placebo (Figure 2). The median times to laxation within 24 hours after the first dose of study medication were 0.96 hours and 22.53 hours in cancer patients who received methylnaltrexone and placebo, respectively ($P < 0.0001$), and 1.25 hours and >24 hours in noncancer patients who received methylnaltrexone and placebo, respectively ($P=0.0002$). These data indicate that most cancer and noncancer patients who received methylnaltrexone and responded to treatment did so within the first hour after the first dose of study drug. The mean weekly number of laxations within 24 hours after dosing were similar in methylnaltrexone-treated patients with and without cancer by week 2 of the study and were higher in both cancer and noncancer patients who received methylnaltrexone versus placebo (Figure 3). Among cancer and noncancer groups, significantly higher proportions of patients receiving methylnaltrexone versus placebo achieved ≥3 RFL per week in both weeks 1 and 2 on study (Figure 4).

**Rescue Medication Use and Pain Scores**
Smaller proportions of methylnaltrexone-treated patients in both the cancer and noncancer groups required the use of rescue laxatives compared with cancer and noncancer patients receiving placebo. However, these differences did not reach significance (Figure 5). There were no significant changes in current pain scores from baseline to day 7 post-dose among patients treated with methylnaltrexone or placebo in both the cancer ($P = 0.7043$) and noncancer groups ($P = 0.6075$). Among patients with cancer, current pain scores were 3.6 at baseline and 2.9 at day 7 post-dose for those receiving methylnaltrexone and 3.5 at baseline and 3.2 at day 7 post-dose for those receiving placebo. Baseline and day 7 post-dose current pain scores for patients without cancer were 4.4 and 3.6, respectively, among those receiving methylnaltrexone and 4.0 and 3.5, respectively, among those receiving placebo. Similarly, worst pain scores were not significantly different from baseline to day 7 post-dose in cancer ($P = 0.9200$) and noncancer ($P = 0.7800$) patients treated with methylnaltrexone or placebo. Among patients with cancer, worst pain scores were 5.1 at baseline and 4.0 at day 7 post-dose for those receiving methylnaltrexone and 5.2 at baseline and 4.3 at day 7 post-dose for those receiving placebo. For those without cancer, worst pain scores at baseline and day 7 post-dose were 5.6 and 4.7, respectively, for methylnaltrexone and 5.4 and 4.4, respectively, for placebo.
Adverse Events

Overall, slightly higher proportions of cancer patients (methylnaltrexone group: 87.9% [n = 102]; placebo group: 79.8% [n = 91]) versus noncancer patients (methylnaltrexone group: 69.8% [n = 44]; placebo group: 70.4% [n = 50]) experienced TEAEs. Table 2 shows TEAEs occurring in >5% of patients in any treatment group. The most frequently occurring TEAEs in cancer patients who received methylnaltrexone or placebo included abdominal pain (24.1% [n = 28] and 9.6% [n = 11], respectively), disease progression (8.6% [n = 10] and 14.0% [n = 16], respectively), and nausea (14.7% [n = 17] and 14.0% [n = 16], respectively). Similar TEAEs were reported in the noncancer cohort. The most frequently occurring TEAEs reported in noncancer patients receiving methylnaltrexone or placebo included abdominal pain (17.5% [n = 11] and 11.3% [n = 8], respectively), nausea (4.8% [n = 3] and 9.9% [n = 7], respectively), and diarrhea (4.8% [n = 3] and 8.5% [n = 6], respectively). Serious AEs were reported more commonly in methylnaltrexone-treated patients with cancer (17.2% [n = 20]) compared with those without cancer (7.9% [n = 5]). Serious AEs of disease progression (methylnaltrexone, 7.8% [n = 9]; placebo, 11.4% [n = 13]) and malignant neoplasm progression (methylnaltrexone, 5.2% [n = 6]; placebo, 10.5% [n = 12]) were reported in cancer patients. Other serious AEs occurring in ≥2 cancer patients were fall (methylnaltrexone, 0%; placebo, 1.8% [n = 2]), spinal cord compression (methylnaltrexone, 0%; placebo, 1.8% [n = 2]), and dyspnea (methylnaltrexone, 0%; placebo, 1.8% [n = 2]). Serious AEs occurring in ≥2 noncancer patients were aggravated congestive cardiac failure (methylnaltrexone, 1.6% [n = 1]; placebo, 1.4% [n = 1]).
[n = 1]) and concomitant disease progression (methylnaltrexone, 3.2% [n = 2]; placebo, 1.4% [n = 1]).

**Discussion**

Nearly two-thirds of patients included in this pooled post hoc analysis had cancer. Baseline characteristics were similar between cancer and noncancer patients, with the exception that cancer patients were receiving a higher dose of opioid morphine equivalents at baseline. Despite this, along with several nonopioid-related factors that could contribute to constipation in cancer patients (eg, cancer-related physiologic dysfunction, concomitant medications, dehydration, immobility, diet, or metabolic causes), the percentage of patients achieving a laxation response was similar in cancer and noncancer patients and significantly greater than
Methylnaltrexone induced laxation within 4 hours after administration of the first dose in the majority of patients with and without cancer, versus less than 20% of patients who received placebo. Similar results were obtained within 4 hours after at least 2 of the first 4 doses of methylnaltrexone. The laxation effect of methylnaltrexone was achieved rapidly within 1 hour among the majority of patient responders. Overall, the time to RFL was significantly reduced after treatment with methylnaltrexone compared with placebo. The mean number of weekly laxations within 24 hours of study drug administration by week 2 was significantly higher with methylnaltrexone versus placebo. Among both cancer and noncancer groups, significantly higher proportions of patients receiving methylnaltrexone versus placebo achieved ≥3 RFL per week in both weeks 1 and 2. These results show that methylnaltrexone effectively reduces OIC in cancer patients, despite the likelihood that nonopioid-related factors contributed to constipation in this population and support the use of SC methylnaltrexone in patients with active cancer taking opioids for cancer-related pain.

The laxation response associated with methylnaltrexone decreased the need for rescue laxatives in both patients with and without cancer. Importantly, there were no significant changes from baseline to day 7 post-dose in current or worst pain scores for cancer and noncancer patients receiving methylnaltrexone or placebo. These results demonstrate
that methylnaltrexone therapy allowed patients to continue their opioid treatment without experiencing an increase in pain while reducing their constipation.

Consistent with prior studies in patients with advanced illnesses, this study showed that methylnaltrexone was well tolerated in cancer and noncancer patients.\textsuperscript{13,29–31} Adverse events and serious AEs occurred more frequently in cancer patients, likely as a result of their underlying disease and treatment. Although AEs such as abdominal pain and nausea occurred more frequently with methylnaltrexone, this may have been due to the increased laxation response observed with treatment.\textsuperscript{33} The AE profile of methylnaltrexone does not suggest symptoms associated with opioid withdrawal, confirming the drug’s selective effect for peripheral \(\mu\)-opioid receptors.\textsuperscript{30,31,33}

Serious AEs of disease progression and malignant neoplasm progression were reported in cancer patients during these studies. It is important to note that these patients were taking higher doses of opioids at baseline than noncancer patients, and that, in advanced cancer patients, peripheral \(\mu\)-opioid receptors may play a role in disease progression.\textsuperscript{24,25,34}

Indeed, cellular, animal and human data suggest that targeting these receptors may have potential as anticancer therapy.\textsuperscript{17,24,25,35} Based on this evidence, Janku et al examined the potential effects of methylnaltrexone on survival.\textsuperscript{24} Findings revealed significantly longer overall survival times for cancer patients treated with methylnaltrexone versus placebo, and even greater benefits were observed in those patients who had a laxation response to methylnaltrexone. No treatment-related differences in overall survival were observed in noncancer patients. Collectively, these findings may suggest a direct effect of methylnaltrexone on cellular tumor targets related to peripheral \(\mu\)-opioid receptors\textsuperscript{24} that could result in the slowing of disease progression. It is unclear if other factors related to OIC relief such as indirect effects on gut function and immunosuppression may be involved in mitigating cancer progression.\textsuperscript{21,22,24,36,37} Moreover, constipation may be a risk factor for reduced survival as it relates to patients’ global quality of life,\textsuperscript{21,36} performance status, including decreased appetite and anorexia-cachexia syndrome,\textsuperscript{21,22} as well as increased intestinal permeability.\textsuperscript{38}

Data from the current post hoc analysis cannot provide conclusions regarding the effect of opioids on cancer and survival, but they do indicate that methylnaltrexone was safe

| Table 2 Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in Any Treatment Group (Pooled ITT Population) |
|---|
| **Cancer Patients** | **Cancer Patients** | **Noncancer Patients** | **Noncancer Patients** |
| **Using PBO** | **Using MNTX** | **Using PBO** | **Using MNTX** |
| (n = 114) | (n = 116) | (n = 71) | (n = 63) |
| n (%) | n (%) | n (%) | n (%) |
| Abdominal pain | 11 (9.6) | 28 (24.1) | 8 (11.3) | 11 (17.5) |
| Nausea | 16 (14.0) | 17 (14.7) | 7 (9.9) | 3 (4.8) |
| Flatulence | 6 (5.3) | 12 (10.3) | 4 (5.6) | 4 (6.3) |
| Back pain | 3 (2.6) | 10 (8.6) | 0 | 2 (3.2) |
| Disease progression | 16 (14.0) | 10 (8.6) | 1 (1.4)* | 0 |
| Abdominal pain NOS | 6 (5.3) | 9 (7.8) | 3 (4.2) | 2 (3.2) |
| Confusional state | 9 (7.9) | 9 (7.8) | 2 (2.8) | 0 |
| Peripheral edema | 8 (7.0) | 9 (7.8) | 4 (5.6) | 3 (4.8) |
| Pyrexia | 3 (2.6) | 7 (6.0) | 4 (5.6) | 1 (1.6) |
| Fall | 8 (7.0) | 7 (6.0) | 3 (4.2) | 3 (4.8) |
| Dizziness | 3 (2.6) | 7 (6.0) | 4 (5.6) | 2 (3.2) |
| Vomiting NOS | 7 (6.1) | 7 (6.0) | 2 (2.8) | 1 (1.6) |
| Diarrhea | 9 (7.9) | 6 (5.2) | 6 (8.5) | 3 (4.8) |
| Malignant neoplasm progression | 13 (11.4) | 6 (5.2) | 0 | 1 (1.6)* |
| Vomiting | 8 (7.0) | 5 (4.3) | 2 (2.8) | 0 |
| Asthenia | 8 (7.0) | 4 (3.4) | 2 (2.8) | 3 (4.8) |
| Abdominal distention | 7 (6.1) | 4 (3.4) | 4 (5.6) | 2 (3.2) |
| Dehydration | 6 (5.3) | 3 (2.6) | 2 (2.8) | 0 |
| Pain exacerbated | 6 (5.3) | 2 (1.7) | 1 (1.4) | 0 |

Notes: *One patient with lymphoma was classified in the noncancer group because the diagnosis of lymphoma was not recorded in the baseline medical history. Treatment-emergent adverse events are listed in order of descending incidence in the cancer patients using MNTX group.

Abbreviations: ITT, intent to treat; MNTX, methylnaltrexone; NOS, not otherwise specified; PBO, placebo.
and effective in an advanced cancer population and that no differences in laxation response to methylnaltrexone were observed between cancer and noncancer patients. These preliminary results provide a basis for a better understanding of the clinical effects of methylnaltrexone in cancer patients who are receiving opioids and help to support future studies of methylnaltrexone as a potential treatment for cancer.

This post hoc analysis has some limitations. The two studies pooled in this analysis were not initially designed to compare outcomes for cancer versus noncancer patients. In addition, the trials were of short duration given the patients’ advanced illnesses. The effect of methylnaltrexone over a 10-week open-label extension was found to be generally consistent with that of a 2-week randomized controlled trial, though again patients were not stratified by cancer/noncancer. Given the advanced-illness diagnoses in this population, these patients were inherently very ill; AEs observed during the study could possibly be attributable to underlying disease.

Conclusions

Treatment with methylnaltrexone resulted in significantly higher proportions of both cancer and noncancer patients with OIC achieving laxation responses within 4 hours of administration compared with placebo. Additionally, among those achieving a laxation response, laxation occurred significantly faster with methylnaltrexone than placebo and was associated with a reduced need for rescue laxatives and no significant changes in pain. Methylnaltrexone was also generally well tolerated in all patient groups. These results show that methylnaltrexone effectively reduces OIC in cancer patients as well as noncancer patients, despite the several nonopioid-related factors that may contribute to constipation in the prior population, and support the approval and use of SC methylnaltrexone for OIC in patients with active cancer taking opioids for cancer-related pain.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available at this time due to the proprietary nature of this information. Requests for additional information should be made to the corresponding author.

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Previous presentations

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Disclosure

Dr. Chamberlain has nothing to disclose. Dr. Israel is an employee of Bausch Health US, LLC, which has a proprietary interest in methylnaltrexone. Dr. Rhiner has received a grant from Wyeth Pharmaceuticals for the 302 study mentioned in this manuscript and was reimbursed by Salix Pharmaceuticals for travel expenses related to poster presentations at the 2018 World Congress on Regional Anesthesia & Pain Medicine and the 2018 Palliative and Supportive Care in Oncology meeting. Dr. Slatkin is an employee of Salix Pharmaceuticals since July 2016, has received personal fees from Salix Pharmaceuticals for consulting/speaking between 2012 and 2016, and has received a grant from Progenics Pharmaceuticals for the 302 study mentioned in this manuscript. Dr. Stambler is an employee of Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings Inc., New York, NY. The authors report no other conflicts of interest in this work.

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