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ORIGINAL RESEARCH

Impact of Patient Subgroups on the Efficacy and Safety of Methylnaltrexone for Opioid-Induced Constipation in Patients with Advanced Illness

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Purpose: We evaluated the impact of baseline patient characteristics on safety and efficacy of methylnaltrexone, a peripherally acting μ-opioid receptor antagonist, in patients with advanced illness with opioid-induced constipation (OIC).

Patients and Methods: This analysis pooled data from 2 randomized, double-blind, placebo-controlled studies (study 302: NCT00402038; study 4000: NCT00672477) in patients with advanced illness, including cancer, and OIC. Patients were randomized to receive subcutaneous methylnaltrexone (study 302: 0.15 mg/kg; study 4000: 8 or 12 mg based on weight) or placebo every other day for 2 weeks. The proportions of patients achieving rescue-free laxation within 4 or 24 hours after the first dose of study drug were assessed in patient subgroups stratified by baseline age, Eastern Cooperative Oncology Group (ECOG) performance status, cancer status, laxative type, and opioid requirement. Treatment-emergent adverse events (TEAEs) were evaluated.

Results: Overall, 363 patients were included in this analysis (methylnaltrexone, 178; placebo, 185). Mean (SD) age was 66.3 (13.7) years and 48.5% were men overall. A significantly greater proportion of patients receiving methylnaltrexone versus placebo achieved rescue-free laxation within 4 hours (111/178 [62.4%] vs 31/185 [16.8%]; $P<0.0001$) and 24 hours (135/178 [75.8%] vs 81/185 [43.8%]; $P<0.0001$) of the first dose. These trends were consistent across all subgroups. Most patients experienced ≥1 TEAE in the overall population (methylnaltrexone, 82.1%; placebo, 76.2%), which remained consistent when stratified by baseline characteristics. More than half of TEAEs were gastrointestinal in nature. Abdominal pain was more common in patients receiving methylnaltrexone than placebo across baseline characteristic subgroups.

Conclusion: Methylnaltrexone treatment was superior to placebo in achieving rescue-free laxation within 4 and 24 hours after the first dose, irrespective of patients' cancer status, baseline ECOG performance status, or baseline opioid or laxative use. The methylnaltrexone safety profile remained consistent across baseline characteristic subgroups.

Keywords: methylnaltrexone, opioid-induced constipation, μ-opioid receptor antagonist

Introduction

Opioid-induced constipation (OIC) is a condition associated with abdominal discomfort and pain and is a common adverse event of opioid use.[1–3] Patients often develop tolerance to other side effects of opioid use, such as nausea and vomiting, but some patients do not develop tolerance to constipation with opioid use.[4] Additionally, OIC is associated with disruption of opioid therapy when patients skip or discontinue opioid doses, longer duration of opioid therapy, greater use of healthcare resources, and higher healthcare costs.[5] Therefore, an effective treatment is important for alleviating the burden of OIC.

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OIC is believed to occur because of opioid binding to peripheral μ-opioid receptors in the gastrointestinal tract, leading to abnormal modulation of mucosal secretion and fluid absorption.[1] Peripherally acting μ-opioid receptor antagonists (PAMORAs) block μ-opioid receptors in the gastrointestinal tract. PAMORAs have limited ability to cross the blood–brain barrier, thereby reversing μ-opioid binding in the gut without compromising the effects of opioid analgesia.[1,6]

Methylnaltrexone is a PAMORA approved for the treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to previous cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation, and for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.[7] Pivotal clinical trials in patients with serious and advanced illnesses demonstrated the superior efficacy of methylnaltrexone over placebo in achieving rescue-free laxation responses within 4 and 24 hours after the first dose and within 4 hours after ≥2 of the first 4 doses.[8,9] Whether certain patient characteristics, such as age and cancer status, influence the likelihood that a patient will respond to methylnaltrexone remains unknown. Using pooled data from 2 pivotal methylnaltrexone trials, we conducted a post hoc analysis to evaluate whether baseline patient characteristics impact safety, tolerability, and efficacy of methylnaltrexone among patients with advanced illness and OIC.

Methods

Study Design

This was a post hoc analysis of pooled data from 2 multicenter, double-blind, randomized, placebo-controlled clinical trials of methylnaltrexone, including the phase 3 302 (NCT00402038) study and the phase 4 4000 study (NCT00672477) (Figure 1).[9,10] In study 302, patients were randomized 1:1 to receive subcutaneous injections of methylnaltrexone 0.15 mg/kg or placebo every other day (QOD) for 14 days, with the opportunity to increase the dose to 0.30 mg/kg on day 9 in patients with <3 rescue-free laxations at the discretion of the investigator.[9] After completion of the double-blind treatment period, patients could enroll in the 3-month open-label extension phase, in which they could receive methylnaltrexone as needed up to every 24 hours. Study 4000 included patients randomized 1:1 to receive subcutaneous methylnaltrexone 8 mg or 12 mg for patients weighing 38 kg to <62 kg or ≥62 kg, respectively, or placebo administered QOD for a maximum of 7 doses/14 days, with the option to enroll in a 10-week open-label extension portion.[10] The 2 studies were approved by either a central or a local institutional review board and followed Good Clinical Practice and Declaration of Helsinki principles. Each patient provided written informed consent before enrollment in the studies.

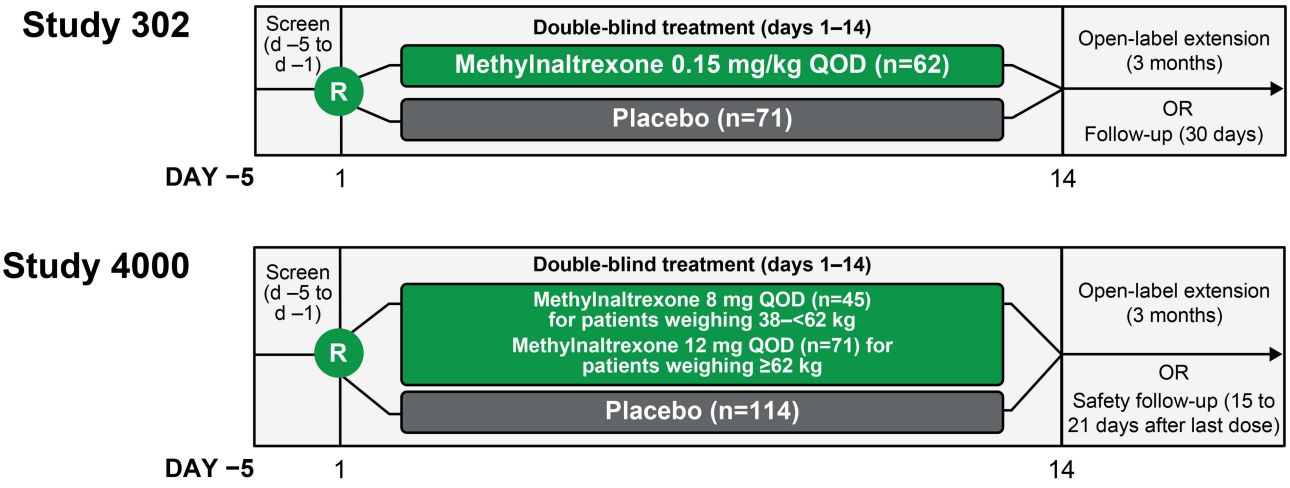

Figure 1 Study design.
Abbreviations: d, day; QOD, every other day; R, randomization.

Study Population

In both studies, eligible patients were aged ≥18 years with a diagnosis of advanced illness, which was defined as terminal disease incurable cancer or other end-stage diseases with a life expectancy of ≥1 month. Patients were receiving opioids routinely for discomfort or pain management for ≥2 weeks and taking a stable regimen of opioids (defined as no reduction in opioid dose of ≥50%) and laxatives for ≥3 days before the first dose. OIC was defined as either <3 bowel movements during the previous week and no clinically significant laxation in the 24 hours before the first dose of study drug or no clinically significant laxation within 48 hours before the first dose of study drug.

Exclusion Criteria

Key exclusion criteria included history of methylnaltrexone treatment, any disease process suggestive of mechanical bowel obstruction, an indwelling peritoneal catheter, clinically active diverticular disease, evidence of fecal impaction, peritonitis, acute surgical abdomen, any potential nonopioid cause of bowel dysfunction (in the opinion of the investigator), body weight <38 kg, and history of fecal ostomy.

Assessments

Efficacy assessments in both studies included the proportion of patients achieving rescue-free laxation within 4 or 24 hours after the first dose of study drug or within 4 hours of ≥2 of the first 4 doses and median time to rescue-free laxation within 4 or 24 hours after the first dose. Rescue-free laxation was defined as a bowel movement without use of any rescue medication or procedure within 4 hours before the bowel movement. In the current analysis, outcomes were assessed in patient subgroups stratified by baseline age (<65 vs ≥65), cancer status, Eastern Cooperative Oncology Group (ECOG) performance status (≤2 vs >2), opioid requirement (oral morphine equivalent dose <80 mg/day, 80 to <150 mg/day, and ≥150 mg/day), and laxative type (osmotic agents, stimulants, or stool softeners). Patients could receive more than one type of laxative. The ECOG performance status scale is a measure of a patient's functioning with scores ranging from 0 (fully active, able to carry on all predisease performance without restriction) to 5 (dead).[11] Data were collected from patient diaries in study 4000 and electronic health records in both studies. Treatment-emergent adverse events (TEAEs), gastrointestinal TEAEs, and abdominal pain were evaluated at all postbaseline visits in the pooled population and in the patient subgroups defined by age, cancer status, ECOG performance status, opioid requirement, and laxative type.

Statistical Analysis

Efficacy analyses for both studies were performed on the intention-to-treat population, defined as patients who received ≥1 dose of study medication. Response rates for patients achieving rescue-free laxation within 4 and 24 hours were compared across treatment groups using the Cochran-Mantel-Haenszel test, and *P*-values based on chi-squared tests were generated to compare placebo and methylnaltrexone. Time to rescue-free laxation was estimated using Kaplan–Meier methods and compared using Log rank tests. Nominal levels of significance were set at $P<0.05$, with no adjustments for multiplicity. Safety analyses were performed on the safety population, which consisted of patients who received ≥1 dose of study medication and 1 patient who received methylnaltrexone in an unblinded fashion and was included only in the safety analyses. TEAEs were described for each treatment group using summary statistics.

Results

Baseline Characteristics

A total of 364 patients received ≥1 dose of study medication. One patient received methylnaltrexone in an unblinded fashion and was included only in the safety analysis. Thus, the pooled efficacy analyses included 363 patients (methylnaltrexone, 178; placebo, 185). Overall, patients had a mean age of 66.3 years, 48.5% were men, and approximately two-thirds had a cancer diagnosis; most patients had an ECOG performance status score ≥2. The mean oral morphine equivalent dose was 374.5 mg/day, and almost all patients were taking ≥1 laxative at baseline. Demographic and clinical characteristics were similar between the methylnaltrexone and placebo groups (Table 1).

Table 1 Patient Demographic and Baseline Characteristics (Intention-to-Treat Population)

Characteristic	Placebo (n = 185)	Methylnaltrexone (n = 178)	Total (N = 363)
Age, mean (SD), years	66.1 (13.9)	66.5 (13.4)	66.3 (13.7)
Age category, n (%)			
<65 years	89	83	172
≥65 years	96	95	191
Sex, n (%)			
Male	89 (48.1)	87 (48.9)	176 (48.5)
Female	96 (51.9)	91 (51.1)	187 (51.5)
Race, n (%)			
American Native or Alaskan Native	1 (0.5)	1 (0.6)	2 (0.6)
Asian	0	1 (0.6)	1 (0.3)
Black or African American	8 (4.3)	6 (3.4)	14 (3.9)
White	173 (93.5)	168 (94.4)	341 (93.9)
Other	3 (1.6)	2 (1.1)	5 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	11 (5.9)	11 (6.2)	22 (6.1)
Not Hispanic or Latino	174 (94.1)	167 (93.8)	341 (93.9)
Weight, mean (SD), kg	72.6 (24.0)	71.2 (19.7)	71.9 (22.0)
Primary diagnosis, n (%)			
Cancer	114 (61.6)	116 (65.2)	230 (63.4)
Cardiovascular disease	20 (10.8)	21 (11.8)	41 (11.3)
Neurologic disease	10 (5.4)	10 (5.6)	20 (5.5)
Pulmonary disease	18 (9.7)	23 (12.9)	41 (11.3)
Other	23 (12.4)	8 (4.5)	31 (8.5)
ECOG PS, n (%)			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	21 (11.4)	21 (11.8)	42 (11.6)
2	57 (30.8)	54 (30.3)	111 (30.6)
3	78 (42.2)	73 (41.0)	151 (41.6)
4	27 (14.6)	27 (15.2)	54 (14.9)
OED, MME/d			
Mean (SD)	372.8 (1016.9)	376.3 (699.9)	374.5 (874.7)
Median (range)	130 (0–10,160)	156 (0–4427)	146 (0–10,160)

(*Continued*)

Table 1 (Continued).

Characteristic	Placebo (n = 185)	Methylnaltrexone (n = 178)	Total (N = 363)
OED categories, n (%)			
<80 MME/day	57	42	99
80 to <150 MME/day	42	39	81
≥150 MME/day	86	97	183
Laxatives used at baseline, n (%)			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	48 (25.9)	56 (31.5)	104 (28.7)
2	69 (37.3)	65 (36.5)	134 (36.9)
3	40 (21.6)	27 (15.2)	67 (18.5)
≥4	26 (14.1)	27 (15.2)	53 (14.6)
Type of laxative, n[a]			
Osmotic agent	82	85	167
Stimulant	149	136	285
Stool softener	98	92	190

Note: [a]Patients could receive >1 laxative type.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MME, morphine milligram equivalent; OED, opioid equivalent dose.

Efficacy

A significantly greater proportion of patients receiving the first dose of methylnaltrexone versus placebo achieved rescue-free laxation within 4 hours (111/178 [62.4%] vs 31/185 [16.8%]; $P<0.0001$) and 24 hours (135/178 [75.8%] vs 81/185 [43.8%]; $P<0.0001$). This pattern was consistent across patient subgroups stratified by baseline age, cancer status, ECOG performance status, opioid requirement, and laxative type (Figure 2A and B). Additionally, a significantly greater proportion of patients treated with methylnaltrexone versus placebo achieved rescue-free laxation within 4 hours of ≥2 of the first 4 doses across all subgroups (methylnaltrexone, 52.4%–69.2%; placebo, 4.1%–14.3%; $P<0.001$ for all) (Figure 2C).

Overall median time to rescue-free laxation for the 4-hour interval was 1.1 hours for methylnaltrexone and >4 hours for placebo ($P<0.0001$). For the 24-hour interval, median time to rescue-free laxation was 1.1 hours for methylnaltrexone and 23.6 hours for placebo ($P<0.0001$). Median time to rescue-free laxation was significantly shorter ($P<0.05$) with methylnaltrexone than with placebo for both the 4-hour and 24-hour intervals regardless of baseline age, cancer status, ECOG performance status, OED, and laxative type (Table 2).

Safety

Most of the patients in both treatment groups (methylnaltrexone, 82.1%; placebo, 76.2%) experienced ≥1 TEAEs, which were mostly gastrointestinal (eg, abdominal pain, nausea, flatulence) (Table 3). The overall incidence of TEAEs was similar between methylnaltrexone and placebo and generally similar across subgroups, although patients who had a cancer diagnosis had a slightly higher incidence of TEAEs than those without cancer (Figure 3). The most common TEAEs were gastrointestinal (including nausea, abdominal pain, and flatulence) and were reported in 38.0–62.4% of patients receiving methylnaltrexone or placebo across subgroups (Figure 4A). Abdominal pain was more common in patients receiving methylnaltrexone than placebo across subgroups (methylnaltrexone, 15.8%–29.5%; placebo, 8.8–14.6%) (Figure 4B).

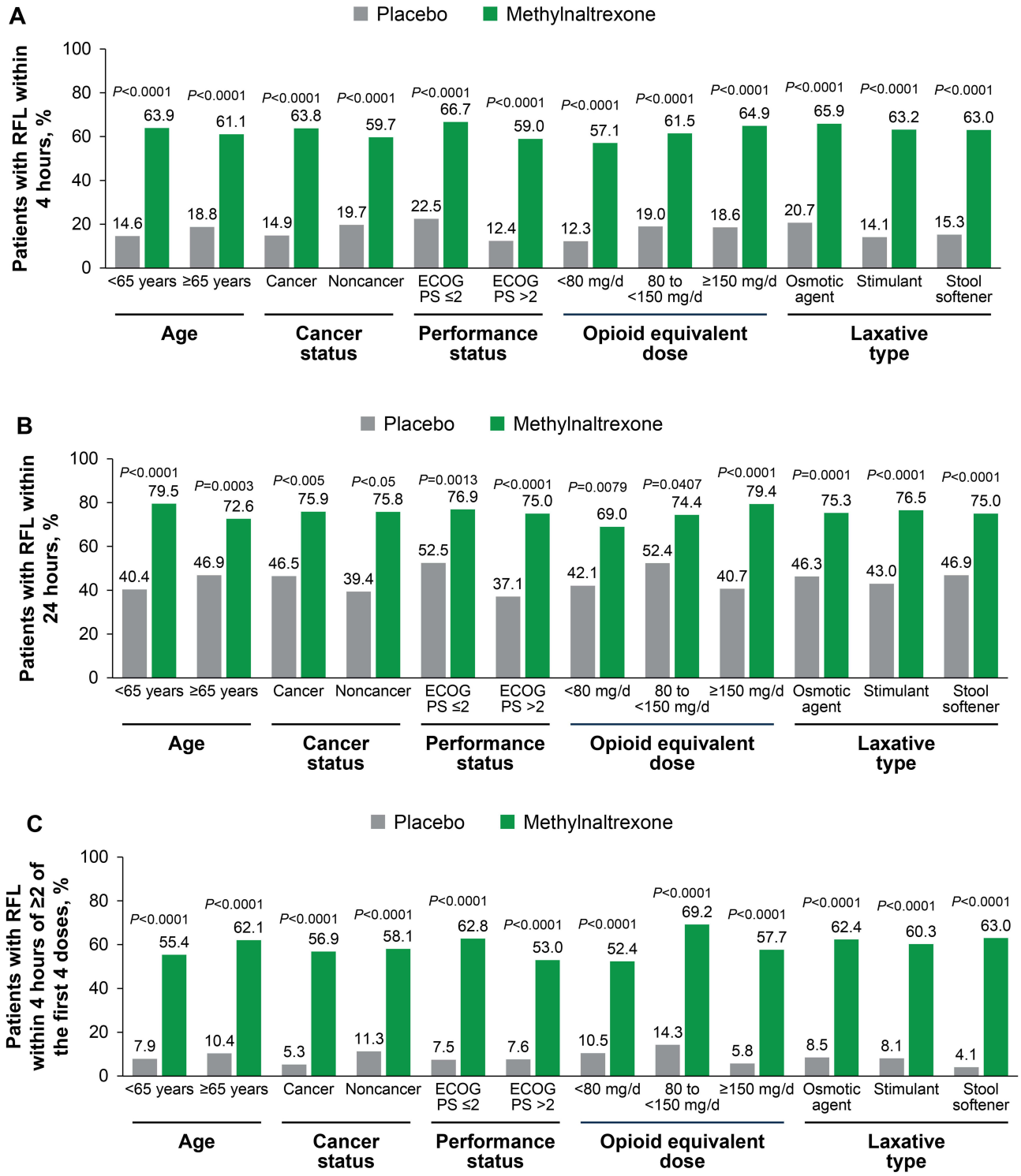

Figure 2 Rescue-free laxation (**A**) within 4 hours after the first dose, (**B**) within 24 hours after the first dose, and (**C**) within 4 hours of ≥2 of the first 4 doses by patient subgroups. Intention-to-treat population.
Note: *P*-values based on chi-squared test.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; RFL, rescue-free laxation.

Patient Disposition

A total of 82/364 (22.5%) patients discontinued the studies. The most common reasons for discontinuation included adverse events (methylnaltrexone, 6.7%; placebo, 5.4%), death (methylnaltrexone, 6.7%; placebo, 8.1%), and patient withdrawal (methylnaltrexone, 2.8%; placebo, 4.3%). The vast majority (48/51) of the deaths in the 2 studies were

Table 2 Median Time to Rescue-Free Laxation Within 4 Hours and 24 Hours of First Dose (Intention-to-Treat Population)

Patient Subgroup		Time to RFL Within 4 Hours			Time to RFL Within 24 Hours		
		Placebo	Methylnaltrexone	*P*-value	Placebo	Methylnaltrexone	*P*-value
Age, years	<65	>4	0.83	0.0050	>24	0.83	<0.0001
	≥65	>4	2.00	0.0004	22.87	2.00	<0.0001
Cancer status	Cancer	>4	0.96	<0.0001	22.53	0.96	<0.0001
	Noncancer	>4	1.25	<0.0001	>24	1.25	0.0002
ECOG PS	ECOG PS ≤2	>4	0.87	<0.0001	17.79	0.87	<0.0001
	ECOG PS >2	>4	1.46	<0.0001	>24	1.46	<0.0001
OED, mg/dL	<80	>4	3.31	0.0107	>24	3.31	0.0002
	80–150	>4	0.92	0.0725	17.21	0.92	0.0007
	≥150	>4	0.92	0.0007	23.96	0.92	<0.0001
Laxative type	Stimulant	>4	1.13	<0.0001	23.08	1.13	<0.0001
	Osmotic agent	>4	0.75	<0.0001	21.34	0.75	<0.0001
	Stool softener	>4	1.33	<0.0001	>24	1.33	<0.0001

Note: Log rank test to compare methylnaltrexone group with placebo for time to first laxation censored at 4 hours and 24 hours.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; OED, opioid equivalent dose.

Table 3 Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Placebo and Methylnaltrexone Treatment Groups (Safety Population)

TEAEs	Placebo (n = 185)	Methylnaltrexone (n = 179)
Patients with ≥1 TEAE	141 (76.2)	147 (82.1)
Abdominal pain	19 (10.3)	39 (21.8)
Nausea	23 (12.4)	20 (11.2)
Flatulence	10 (5.4)	16 (8.9)
Back pain	3 (1.6)	12 (6.7)
Peripheral edema	12 (6.5)	12 (6.7)
Abdominal pain, not otherwise specified	9 (4.9)	11 (6.1)
Disease progression	17 (9.2)	10 (5.6)
Fall	11 (5.9)	10 (5.6)
Diarrhea	15 (8.1)	9 (5.0)
Confusional state	11 (5.9)	9 (5.0)
Asthenia	10 (5.4)	7 (3.9)
Malignant neoplasm progression	13 (7.0)	7 (3.9)
Abdominal distension	11 (5.9)	6 (3.4)
Vomiting	10 (5.4)	5 (2.8)

Abbreviation: TEAE, treatment-emergent adverse event.

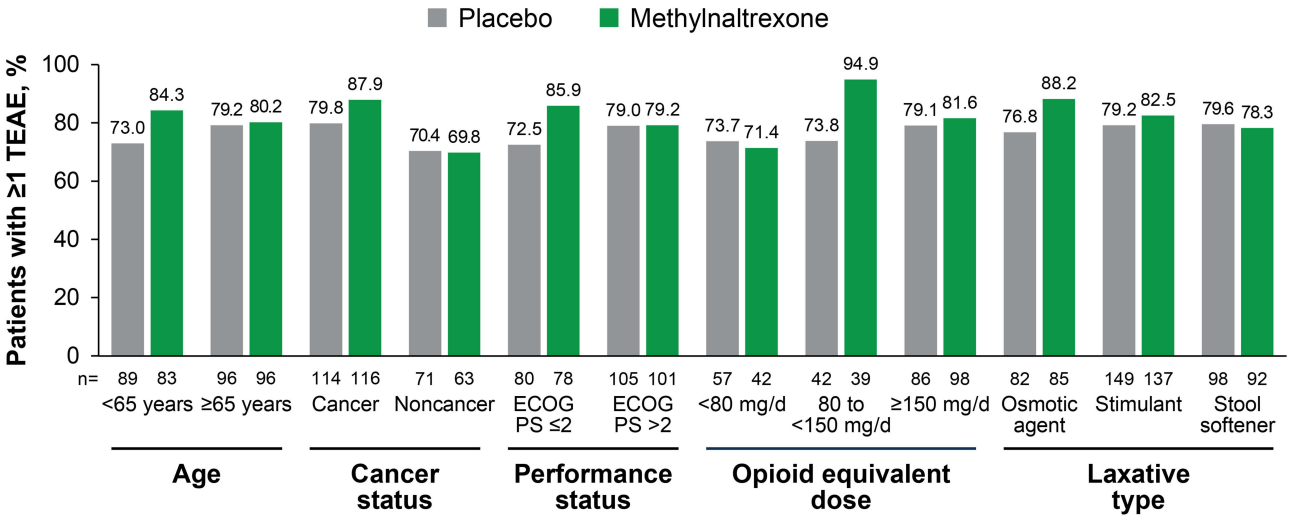

Figure 3 Overall incidence of TEAEs by patient subgroups. Safety population.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; TEAE, treatment-emergent adverse event.

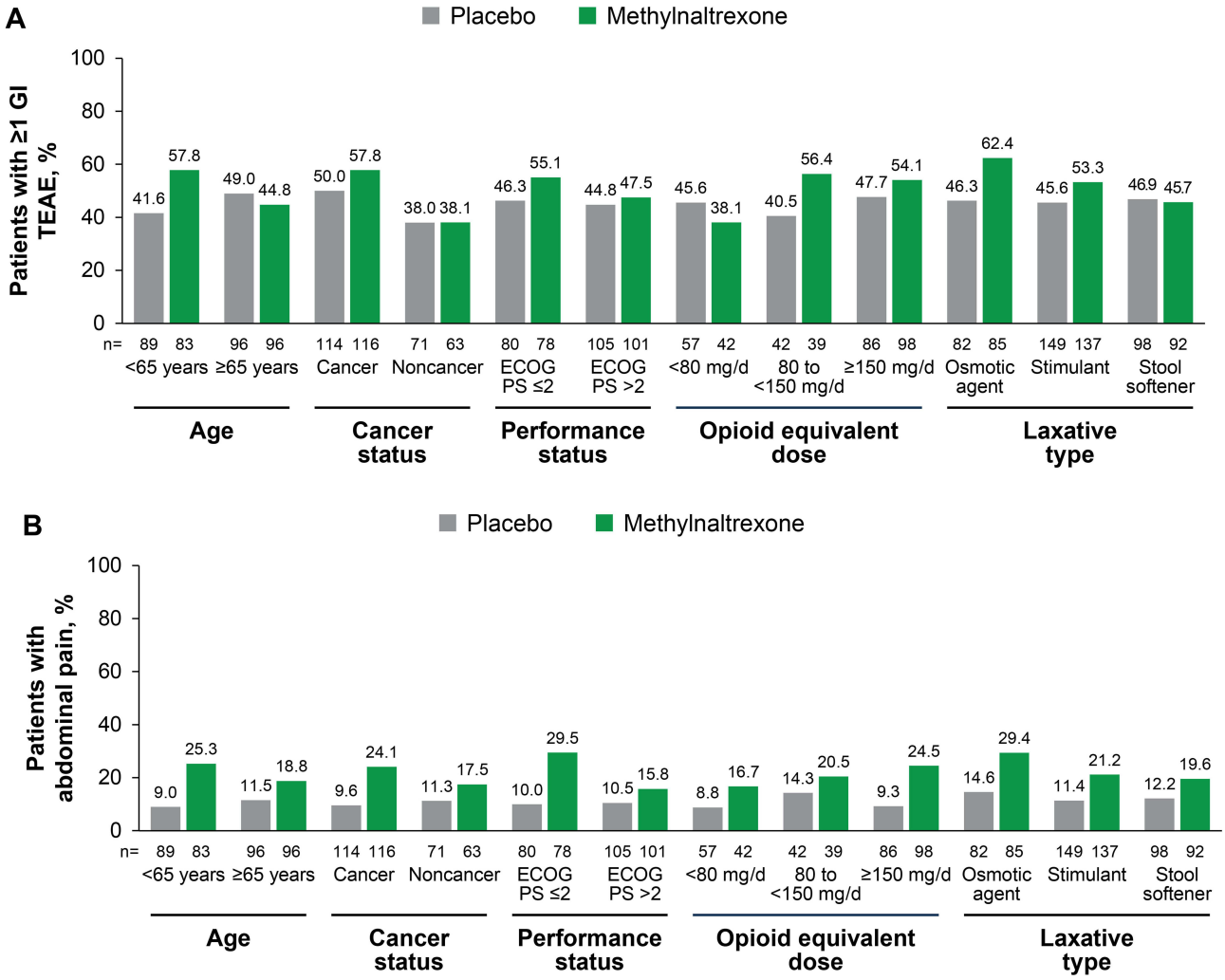

Figure 4 Incidence of (**A**) GI TEAEs and (**B**) TEAEs of abdominal pain by patient subgroups. Safety population.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; TEAE, treatment-emergent adverse event.

attributed to underlying illness (previously described).[9,10] Some variation in patient disposition was seen when stratified by patient baseline characteristic subgroups, including age, cancer status, ECOG performance status, opioid requirement, and laxative type (Table 4). Discontinuations tended to be higher in patients who were aged <65 years (vs ≥65 years), in patients with cancer (vs without cancer), and in patients with higher opioid equivalent doses (OEDs; vs lower doses).

Discussion

To our knowledge, this is the first evaluation to demonstrate the safety and efficacy of methylnaltrexone for the treatment of OIC in patients with advanced illness who are receiving palliative care across patient characteristics, including age, cancer status, ECOG performance status, opioid requirement, and concurrent laxative use. Methylnaltrexone was significantly more effective than placebo in achieving rescue-free laxation within 4 and 24 hours of the first dose and within 4 hours of ≥2 of the first 4 doses, irrespective of baseline patient characteristics. Time to rescue-free laxation was also significantly faster with methylnaltrexone compared to placebo and was generally similar across subgroups. Methylnaltrexone was generally well tolerated, with the most common TEAEs being gastrointestinal, which may be a consequence of restored laxation. The safety profile was similar to that in prior studies of methylnaltrexone.[8–10,12] Rates of abdominal pain were higher with methylnaltrexone versus placebo across all subgroups. Abdominal pain associated with methylnaltrexone treatment has previously been reported to typically be mild to moderate in severity and to correspond with a laxation response to treatment.[13] The incidence of abdominal pain usually decreases with subsequent methylnaltrexone dosing.[13]

The elderly are more prone to constipation due to a variety of factors, such as use of opioids for chronic pain and having a sedentary lifestyle, and are at greater risk of developing complications from constipation.[14] Our study showed that age did not affect the efficacy of methylnaltrexone. The overall rates of TEAEs were also similar between age categories (<65 years versus ≥65 years). Likewise, there has been no observed difference in the effectiveness or safety of the PAMORA naloxegol between older and younger patients.[15] Rates of discontinuations were somewhat higher in younger patients. This finding is not uncommon, and it has been postulated that this is due to greater disease severity and greater awareness of their health status in older patients.[16]

Opioid analgesics are often prescribed for the management of moderate-to-severe pain in patients with cancer.[17,18] Other approaches to treat constipation, such as lifestyle modification and some types of laxatives, are often not practical for patients with cancer with OIC.[19] Additionally, these approaches may be less effective because the underlying opioid receptor–mediated mechanism remains untargeted.[18,20,21] This is exemplified by the fact that patients in these studies met eligibility criteria despite the use of multiple laxatives. However, constipation in patients with cancer is often multifactorial and may arise from several sources in addition to opioid use.[19] Thus, patients with cancer may respond to PAMORA treatment differently than those with noncancer pain. As has been described previously, rates of rescue-free laxation were similar in patients with and without cancer who were receiving methylnaltrexone.[22] This analysis also showed that rates of rescue-free laxation with methylnaltrexone were similar between patients with lower (better) and higher (worse) ECOG performance status scores, although there was a slight numerical trend toward higher response rates in patients with lower scores. Overall, rates of TEAEs and rates of gastrointestinal TEAEs were somewhat higher in patients with cancer than those without but similar between patients treated with methylnaltrexone and placebo. Unexpectedly, patients with ECOG performance status scores ≤2 receiving methylnaltrexone also tended to have higher rates of overall TEAEs, gastrointestinal TEAEs, and abdominal pain than those receiving placebo and those with ECOG performance status scores >2. It is unclear why this may be.

The efficacy of methylnaltrexone did not appear to vary with baseline treatment. Significant treatment differences in the achievement of rescue-free laxation in favor of methylnaltrexone versus placebo were observed across all baseline opioid dose ranges, although there was a trend toward increased rates of rescue-free laxation with increasing OED. Rates of TEAEs were mostly similar between methylnaltrexone and placebo groups across dose ranges. However, patients in the methylnaltrexone 80 to <150 mg/day category showed slightly higher rates of overall TEAEs and gastrointestinal TEAEs than those in the same dose category receiving placebo. Achievement of rescue-free laxation was highly consistent across types of laxatives used at baseline. Slightly higher incidences of overall TEAEs and gastrointestinal

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Table 4 Patient Disposition Stratified by Baseline Parameters (Safety Population)

Parameter	Baseline OED <80 mg		Baseline OED 80 to 150 mg/d		Baseline OED ≥150 mg/d		Osmotic Agent		Stimulant		Stool Softener	
	PBO (n = 57) n (%)	MNTX (n = 42) n (%)	PBO (n = 42) n (%)	MNTX (n = 39) n (%)	PBO (n = 86) n (%)	MNTX (n = 98) n (%)	PBO (n = 82) n (%)	MNTX (n = 85) n (%)	PBO (n = 149) n (%)	MNTX (n = 137) n (%)	PBO (n = 98) n (%)	MNTX (n = 92) n (%)
Patients treated	57 (100)	42 (100)	42 (100)	39 (100)	86 (100)	98 (100)	82 (100)	85 (100)	149 (100)	137 (100)	98 (100)	92 (100)
Patients who completed treatment	48 (84.2)	34 (81.0)	33 (78.6)	31 (79.5)	61 (70.9)	75 (76.5)	58 (70.7)	61 (71.8)	113 (75.8)	105 (76.6)	75 (76.5)	73 (79.3)
Patients who discontinued treatment	9 (15.8)	8 (19.0)	9 (21.4)	8 (20.5)	25 (29.1)	23 (23.5)	24 (29.3)	24 (28.2)	36 (24.2)	32 (23.4)	23 (23.5)	19 (20.7)
Administrative/investigator decision	0	2 (4.8)	2 (4.8)	0	1 (1.2)	1 (1.0)	0	1 (1.2)	2 (1.3)	1 (0.7)	1 (1.0)	2 (2.2)
Adverse event	2 (3.5)	3 (7.1)	3 (7.1)	1 (2.6)	5 (5.8)	8 (8.2)	6 (7.3)	6 (7.1)	9 (6.0)	11 (8.0)	4 (4.1)	6 (6.5)
Death	3 (5.3)	2 (4.8)	3 (7.1)	4 (10.3)	9 (10.5)	6 (6.1)	9 (11.0)	9 (10.6)	12 (8.1)	11 (8.0)	10 (10.2)	6 (6.5)
Lack of efficacy	0	0	0	0	1 (1.2)	2 (2.0)	1 (1.2)	2 (2.4)	1 (0.7)	2 (1.5)	1 (1.0)	0
Lost to follow-up	0	0	0	0	1 (1.2)	0	0	0	1 (0.7)	0	0	0
Protocol violation	0	0	1 (2.4)	2 (5.1)	1 (1.2)	0	2 (2.4)	0	1 (0.7)	1 (0.7)	0	1 (1.1)
Withdrawal by subject	2 (3.5)	1 (2.4)	0	1 (2.6)	6 (7.0)	3 (3.1)	4 (4.9)	3 (3.5)	8 (5.4)	4 (2.9)	5 (5.1)	4 (4.3)
Other	2 (3.5)	0	0	0	1 (1.2)	2 (2.0)	2 (2.4)	2 (2.4)	2 (1.3)	2 (1.5)	2 (2.0)	0
Missing	0	0	0	0	0	1 (1.0)	0	1 (1.2)	0	0	0	0
Parameter	**Cancer**		**No Cancer**		**ECOG PS ≤2**		**ECOG PS >2**		**Age <65**		**Age ≥65**	
	PBO (n = 114) n (%)	MNTX (n = 116) n (%)	PBO (n = 71) n (%)	MNTX (n = 63) n (%)	PBO (n = 80) n (%)	MNTX (n = 78) n (%)	PBO (n = 105) n (%)	MNTX (n = 101) n (%)	PBO (n = 89) n (%)	MNTX (n = 83) n (%)	PBO (n = 96) n (%)	MNTX (n = 96) n (%)
Patients treated	114 (100)	116 (100)	71 (100)	63 (100)	80 (100)	78 (100)	105 (100)	101 (100)	89 (100)	83 (100)	96 (100)	96 (100)
Patients who completed treatment	79 (69.3)	87 (75.0)	63 (88.7)	53 (84.1)	62 (77.5)	64 (82.1)	80 (76.2)	76 (75.2)	64 (71.9)	59 (71.1)	78 (81.3)	81 (84.4)
Patients who discontinued treatment	35 (30.7)	29 (25.0)	8 (11.3)	10 (15.9)	18 (22.5)	14 (17.9)	25 (23.8)	25 (24.8)	25 (28.1)	24 (28.9)	18 (18.8)	15 (15.6)
Administrative/investigator decision	1 (0.9)	1 (0.9)	2 (2.8)	2 (3.2)	2 (2.5)	1 (1.3)	1 (1.0)	2 (2.0)	3 (3.4)	2 (2.4)	0	1 (1.0)

Adverse event	8 (7.0)	10 (8.6)	2 (2.8)	2 (3.2)	4 (5.0)	6 (7.7)	6 (5.7)	6 (5.9)	4 (4.5)	9 (10.8)	6 (6.3)	3 (3.1)
Death	13 (11.4)	10 (8.6)	2 (2.8)	2 (3.2)	5 (6.3)	3 (3.8)	10 (9.5)	9 (8.9)	5 (5.6)	6 (7.2)	10 (10.4)	6 (6.3)
Lack of efficacy	1 (0.9)	2 (1.7)	0	0	1 (1.3)	1 (1.3)	0	1 (1.0)	1 (1.1)	2 (2.4)	0	0
Lost to follow-up	1 (0.9)	0	0	0	1 (1.3)	0	0	0	1 (1.1)	0	0	0
Protocol violation	1 (0.9)	1 (0.9)	1 (1.4)	1 (1.6)	1 (1.3)	1 (1.3)	1 (1.0)	1 (1.0)	1 (1.1)	0	1 (1.0)	2 (2.1)
Withdrawal by subject	7 (6.1)	4 (3.4)	1 (1.4)	1 (1.6)	2 (2.5)	1 (1.3)	6 (5.7)	4 (4.0)	7 (7.9)	3 (3.6)	1 (1.0)	2 (2.1)
Other	3 (2.6)	0	0	2 (3.2)	2 (2.5)	1 (1.3)	1 (1.0)	1 (1.0)	3 (3.4)	1 (1.2)	0	1 (1.0)
Missing	0	1 (0.9)	0	0	0	0	0	1 (1.0)	0	1 (1.2)	0	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MNTX, methylnaltrexone; OED, opioid equivalent dose; PBO, placebo.

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TEAEs were seen in patients using osmotic laxatives who received methylnaltrexone versus placebo, but rates of TEAEs were consistent between treatment groups for patients using stimulants and stool softeners.

Taken together, these results can help inform the decision to treat patients with methylnaltrexone. The findings of this study support the use of methylnaltrexone to manage OIC even in patients with factors that can complicate treatment such as greater age and cancer. This study also indicates that the efficacy of methylnaltrexone is not impacted by the type of laxative previously used. Based on these findings, methylnaltrexone can be used in a wide variety of patient populations, and factors of age, cancer status, opioid dose, and prior type of laxative used are not expected to affect the efficacy or safety of methylnaltrexone.

There are several limitations to this analysis due to its post hoc nature. Importantly, the two studies pooled in this analysis were not initially designed to compare outcomes for these subgroups of patients stratified by baseline characteristics and statistical comparisons were not made. In addition, the trials were of short duration; however, this was a necessity due to the nature of the patients' advanced illness. Given that this was a patient population with advanced illness, the underlying disease may have significantly affected the occurrence of TEAEs.

Conclusion

Overall, methylnaltrexone treatment was superior to placebo for achievement of rescue-free laxation, irrespective of patients' cancer status, baseline ECOG performance status, or baseline opioid or laxative use. Methylnaltrexone remained consistently safe across different baseline clinical and demographic characteristics with abdominal discomfort being the most likely adverse event. These findings demonstrate that methylnaltrexone provides effective, tolerable, and safe relief of OIC in patients with advanced illness regardless of baseline demographic or clinical characteristics, therefore supporting methylnaltrexone as a valuable treatment in patients with OIC.

Abbreviations

ECOG, Eastern Cooperative Oncology Group; OED, opioid equivalent dose; OIC, opioid-induced constipation; PAMORA, peripherally acting μ-opioid receptor antagonists; QOD, every other day; TEAE, treatment-emergent adverse event.

Study 302

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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.

Ethics Approval and Informed Consent

Patients or their legally acceptable representatives provided written informed consent to participate before any study specific procedures were conducted. The specific ethical review boards that provided approval and oversight are listed above for study 302 and study 4000.

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Author Contributions

1. Made a significant contribution to the work reported: conception, study design, execution, acquisition of data, analysis, and interpretation. All authors
2. Have drafted or written, or substantially revised or critically reviewed the article. All authors
3. Have agreed on the journal to which the article will be submitted. All authors
4. Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors
5. Agree to take responsibility and be accountable for the contents of the article. All authors

Disclosure

NM: Salix Pharmaceuticals – advisory boards. NES: Salix Pharmaceuticals – employee. RJI: Bausch Health US, LLC – employee. NS: Progenics Pharmaceuticals, Inc. – employee; Lantheus Holdings, Inc. – shareholder. EDS: Ardelyx, Mahana, Bausch Health/Salix, GI Supply/Laborie, Sanofi, Mylan – personal fees; Takeda and Neuraxis – non-financial supports, outside the submitted work.

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