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Efficacy Variables in Cancer Versus Noncancer Patients Treated With Methylnaltrexone or Placebo: An Analysis of Two Placebo-Controlled Studies

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OBJECTIVE

- To investigate differences in baseline characteristics and various efficacy endpoints between patients with and without active cancer and between those treated with methylnaltrexone (MNTX) or placebo in 2 similarly designed multidose MNTX studies and their open-label extensions (studies 302 and 4000)

INTRODUCTION

- Constipation in individuals with cancer is multifactorial and may be a consequence of cancer-related physiologic dysfunction, drugs, dehydration, immobility, diet, metabolic causes, among others[1]
  - Long-term opioid therapy increases the likelihood of opioid-induced constipation (OIC)[2-4]
- The development of OIC may limit opioid use, thereby compromising effective analgesia in patients with cancer pain[4,5]
- OIC predominantly occurs as a result of opioid binding to peripheral μ-opioid receptors in the gastrointestinal tract[6-8]
- MNTX (Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) is a selective, peripherally acting μ-receptor antagonist that improves gastrointestinal transit in opioid-treated patients without affecting the central analgesic effects[8-12]
  - MNTX tablets and subcutaneous (SC) injection are approved for the treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation[13]
  - MNTX SC injection is also 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[13]
- Preclinical data have shown that the μ-opioid receptor has been implicated in cancer progression and shorter overall survival[14-16]; epidemiologic data have shown that greater use of opioids is associated with shorter overall survival in patients with advanced cancer[17]
- To minimize confounding factors and anticipate the potential burden of side effects, it is important to understand if MNTX has similar gastrointestinal effects in cancer and noncancer patients, especially as constipation may itself be a factor in survival[18]

METHODS

Key Inclusion Criteria

- Aged ≥18 years
- Diagnosis of advanced illness (ie, terminal illnesses such as incurable cancer, end-stage diseases) with a life expectancy of ≥1 month
- Receiving opioids routinely for discomfort or pain management for ≥2 weeks (excluding as needed or rescue doses) and taking a stable (defined as no reduction in dose of ≥50%; increases in dose were permitted) regimen for at least 3 days before the first dose
- OIC defined as either of the following:
  - <3 bowel movements during the previous week and no clinically significant laxation in the 24 hours before first dose of study drug
  - No clinically significant laxation within 48 hours before first dose of study drug
- For patients taking laxatives (eg, stool softener and senna or equivalent), the regimen was to be stable for ≥3 days prior to the first dose of study drug and was permitted to continue throughout the study

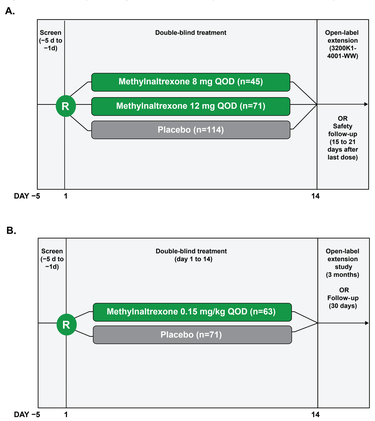
Key Exclusion Criteria

- History of MNTX treatment
- Any disease process suggestive of mechanical bowel obstruction
- Evidence of fecal impaction
- Any potential nonopioid cause of bowel dysfunction, in the opinion of the investigator that might have been primarily responsible for constipation
- History of fecal ostomy

Study Design

- This post hoc analysis included 2 multicenter, double-blind, randomized, placebo-controlled studies and the first 2 weeks of open-label extension data in adult patients with advanced illness and OIC
- In study 4000, patients were randomized to receive SC injections of 0.4 mL MNTX (8 mg) or equal volume of placebo for patients weighing 38 kg to <62 kg and 0.6 mL MNTX (12 mg) or equal volume of placebo for those weighing ≥62 kg every other day for a maximum of 7 doses for 14 days (Figure 1A)
- In study 302, following a 5-day screening period, patients were randomized to receive SC injections of MNTX 0.15 mg/kg or placebo every other day for 2 weeks (Figure 1B; dosage escalation to 0.30 mg/kg was possible starting on day 9 at the discretion of the investigator)
- All patients who completed the studies were eligible to enroll in an open-label extension study
  - Patients received the same doses of MNTX as needed during the first 2 weeks of open-label extensions

Figure 1. Study Design for (A) Study 4000 and (B) Study 302



QOD = every other day; R = randomization.

Assessments

- Patients were stratified by those with active cancer and those without cancer, and analyzed by baseline characteristics and the following efficacy endpoints:
  - The proportion of patients with rescue-free laxation within 4 hours after ≥2 of first 4 doses
  - The proportion of patients with rescue-free laxation within 4 hours after the first dose
  - Time to first rescue-free laxation assessed at 4 hours and 24 hours
  - Number of laxations within 24 hours after dosing per week
    - Weekly number of laxations were set to missing for the week where bowel movement assessment was missing for more than 3 days
  - The proportion of patients using rescue laxatives
  - Pain scores
    - Current and worst pain evaluated after the first dose of study medication and on day 7
    - Graded on a scale of 0 (none) to 10 (worst possible pain)
- For those electing to enter the open-label extensions, results of the 2-week double-blind treatment (MNTX or placebo) were combined with the first 2 weeks of open-label treatment (MNTX) to create 2 cohorts (placebo/MNTX and MNTX/MNTX)
  - Responders were defined as those patients with ≤3 RFBMs per week at baseline having ≥3 RFBMs/week with an increase over baseline of ≥1 RFBM per week

Statistical Analyses

- Data were pooled from both studies and patients were stratified 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 at least 1 dose of study drug
- Data was analyzed using chi-square tests for rescue-free laxation response and use of rescue laxatives; log-rank tests for time to first rescue-free laxation response censored at 48 hours or the time of the next dose of study medication; and Wilcoxon rank-sum tests for weekly number of laxations
- The nominal level of significance was 0.05, with no adjustment for multiplicity

RESULTS

Patients

- After the patients were pooled, there were 114/185 patients (61.6%) in the placebo group with cancer and 116/178 patients (65.2%) in the MNTX group with cancer
  - In the open-label extensions, 103 patients received placebo/MNTX and 108 patients received MNTX/MNTX
- Baseline characteristics stratified by cancer status are shown in Table 1
  - Men were slightly over-represented in the cancer group, but under-represented in the noncancer group
  - Patients with cancer were taking higher baseline doses of opioid analgesics compared with those without cancer
  - Despite higher dosage of baseline opioid use in the cancer group, there was similar use of laxatives to relieve constipation in patients with cancer and without cancer
  - There were no notable differences in baseline current and worst pain scores between study populations

Table 1. Baseline Characteristics Stratified by Cancer Status (Pooled ITT Population)

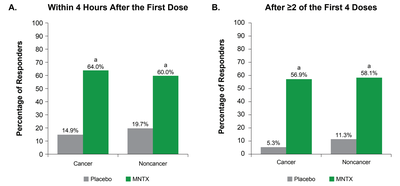
	Cancer Patients		Noncancer Patients	
Characteristic	Placebo (n=114)	MNTX (n=116)	Placebo (n=71)	MNTX (n=62)
Age, years				
Mean (range)	64.21 (32.00–90.00)	63.41 (27.00–91.00)	69.11 (40.00–98.00)	72.16 (34.00–101.00)
Gender, n (%)				
Male	60 (52.6)	62 (53.4)	29 (40.8)	25 (40.3)
Female	54 (47.4)	54 (46.6)	42 (59.2)	37 (59.7)
Race or ethnic group, n (%)				
American Indian or Alaskan Native	–	–	1 (1.4)	1 (1.6)
Asian	0	1 (0.9)	–	–
Black or African American	6 (5.3)	4 (3.4)	2 (2.8)	2 (3.2)
Hispanic or Latino	9 (7.9)	10 (8.6)	2 (2.8)	1 (1.6)
White	105 (92.1)	109 (94.0)	68 (95.8)	59 (95.2)
Other	3 (2.6)	2 (1.7)	–	–
Weight, kg				
Mean (range)	71.09 (40.90–138.00)	70.90 (38.10–135.80)	74.92 (33.50–225.90)	71.81 (38.10–158.80)
Daily dose opioid morphine equivalents, mg/day				
Median (range)	187.85 (0.00–10160.00)	180.00 (0.00–4160.00)	80.00 (0.00–633.20)	120.00 (0.00–4427.00)
Number of laxatives concurrently being used, n (%)				
0	1 (0.9)	2 (1.7)	1 (1.4)	1 (1.6)
1	31 (27.2)	40 (34.5)	17 (23.9)	16 (25.8)
2	40 (35.1)	40 (34.5)	29 (40.8)	25 (40.3)
3	23 (20.2)	17 (14.7)	17 (23.9)	10 (16.1)
4	14 (12.3)	14 (12.1)	4 (5.6)	4 (6.5)
≥5	5 (4.4)	3 (2.6)	3 (4.2)	6 (9.7)
Current pain score, mean (SD)	3.5 (2.49)	3.6 (2.53)	4.0 (3.14)	4.4 (2.82)
Worst pain score, mean (SD)	5.2 (2.89)	5.1 (2.73)	5.4 (2.93)	5.6 (2.70)

ITT = intent to treat; MNTX = methylnaltrexone; SD = standard deviation.

Laxation Response

- A significantly (*P*<0.0001) greater proportion of patients with cancer and without cancer treated with MNTX had a laxation response within 4 hours of treatment compared with patients receiving placebo when measured after the first dose of study drug or after ≥2 of the first 4 doses of study drug (Figure 2)

Figure 2. Percentage of Responders With Laxation (Pooled ITT Population)

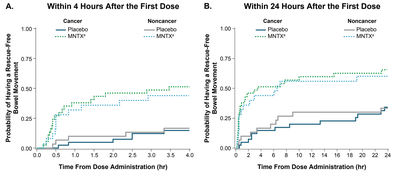


ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=114 for placebo; n=116 for MNTX.
Among patients without cancer, n=71 for placebo; n=62 for MNTX.
[a]P<0.0001 vs placebo.

Time to First Rescue-Free Laxation

- The time to laxation was significantly shorter in the MNTX group in both cancer and noncancer patients compared with patients receiving placebo within 4 and 24 hours after the first dose of study medication (Figure 3)

Figure 3. Time to Rescue-Free Laxation (Pooled ITT Population)

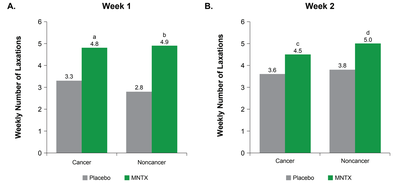


hr = hour; ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=114 for placebo; n=116 for MNTX.
Among patients without cancer, n=71 for placebo; n=62 for MNTX.
[a]P<0.001.

Weekly Number of Laxations

- The number of laxations within 24 hours after dosing per week were similar in patients treated with MNTX with and without cancer at week 1 and week 2 of the study (Figure 4)

Figure 4. Mean Weekly Number of Laxations Within 24 Hours After Dosing (Pooled ITT Population)

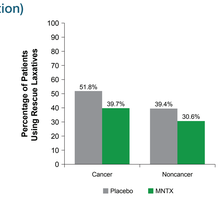


ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=114 for placebo; n=116 for MNTX.
Among patients without cancer, n=71 for placebo; n=62 for MNTX.
[a]P<0.0002; [b]P<0.0001, [c]P=0.0642, [d]P=0.0012.

Use of Rescue Laxatives

- Fewer patients in the cancer and noncancer groups treated with MNTX required the use of rescue laxatives than patients receiving placebo in the cancer and noncancer groups (Figure 5)
  - Overall use of rescue laxatives was higher in the cancer than noncancer groups

Figure 5. Proportion of Patients Using Rescue Laxatives (Pooled ITT Population)

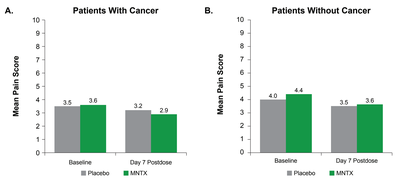


ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=114 for placebo; n=116 for MNTX.
Among patients without cancer, n=71 for placebo; n=62 for MNTX.

Pain Intensity

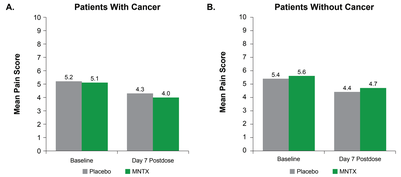
- There were no significant changes from baseline to day 7 postdose in current pain scores among patients treated with MNTX or placebo with or without cancer (Figure 6)
- Similarly, there were no significant changes from baseline to day 7 postdose in worst pain scores in patients treated with MNTX compared with those receiving placebo with or without cancer (Figure 7)

Figure 6. Current Pain Scores Stratified by (A) Patients With Cancer (B) Patients Without Cancer



MNTX = methylnaltrexone.

Figure 7. Worst Pain Scores Stratified by (A) Patients With Cancer (B) Patients Without Cancer



ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=114 for placebo; n=116 for MNTX.
Among patients without cancer, n=71 for placebo; n=62 for MNTX.

Open-Label Extensions Analysis

- In the 4-week analysis that included the 2 double-blind and 2 open-label extension weeks, 73.1% (79/108) of patients who received MNTX/MNTX responded to treatment vs 46.6% (48/103) of patients who received placebo/MNTX (Table 2)

Table 2. Percentage of Responders in the Pooled 4-Week Analysis of Double-Blind and Open-Label Extensions

	Placebo/MNTX n=103	MNTX/MNTX n=108
Responders, n (%)	48 (46.6)	79 (73.1)
Percent difference (95% CI)	–	26.5 (13.8, 39.3)
P value (vs placebo)[b]	–	<0.001

[a]Responders included all patients who had ≥3 RFBMs/week and an increase of ≥1 RFBM/week in ≥3 of 4 weeks.
[b]Based on chi-square test.
CI, confidence interval; DB, double-blind; MNTX, methylnaltrexone; RFBM, rescue-free bowel movement.

Adverse Events

- Overall, MNTX was well tolerated in patients with and without cancer (Table 3)
  - The most frequently occurring treatment-emergent adverse events (TEAEs) in cancer and noncancer patients in the MNTX group included abdominal pain (24.1% and 17.5%, respectively), nausea (14.7% and 4.8%, respectively), and flatulence (10.3% and 6.3%, respectively)
- Serious adverse events were reported more commonly in patients with cancer with disease progression and malignant neoplasm progression as the most common events in this population (Table 4)

Table 3. Treatment-Emergent Adverse Events (Pooled ITT Population)

	Cancer Patients Using Placebo (n=114) n (%)	Cancer Patients Using MNTX (n=116) n (%)	Noncancer Patients Using Placebo (n=71) n (%)	Noncancer Patients Using MNTX (n=63) 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)
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)
Diarrhea	9 (7.9)	6 (5.2)	6 (8.5)	3 (4.8)
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)
Headache	2 (1.8)	3 (2.6)	1 (1.4)	3 (4.8)
Body temperature increase	1 (0.9)	3 (2.6)	2 (2.8)	2 (3.2)
Hyperhidrosis	1 (0.9)	3 (2.6)	1 (1.4)	2 (3.2)

ITT = intent to treat; MNTX = methylnaltrexone.

Table 4. Treatment-Emergent Serious Adverse Events (Pooled ITT Population)

	Cancer Patients Using Placebo (n=114) n (%)	Cancer Patients Using MNTX (n=116) n (%)	Noncancer Patients Using Placebo (n=71) n (%)	Noncancer Patients Using MNTX (n=63) n (%)
Disease progression	13 (11.4)	9 (7.8)	1 (1.4)	0
Malignant neoplasm progression	12 (10.5)	6 (5.2)	0	1 (1.6)
Concomitant disease progression	0	0	1 (1.4)	2 (3.2)
Gastric ulcer perforation	0	1 (0.9)	0	0
Intestinal obstruction	0	1 (0.9)	0	0

ITT = intent to treat; MNTX = methylnaltrexone.

CONCLUSIONS

- **Treatment with MNTX improved the percentage of patients with a laxation response and reduced the need for rescue laxatives in both patients with and without cancer**
- **Treatment with MNTX reduced the time to an RFBM in patients with advanced illness with and without active cancer, despite the use of higher baseline opioid doses in patients with cancer at baseline**
- **MNTX therapy allowed patients to continue their opioid treatment without experiencing increases in pain scores while reducing their symptoms of constipation**
- **RFBM response rates for the MNTX/MNTX-treated group (vs placebo/MNTX) continued to improve into the first 2 weeks of the open-label extensions**

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DISCLOSURES

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