P1130
(S0493)

Subcutaneous Methylnaltrexone in Cancer and Noncancer Patients for Rapid Relief of Opioid-Induced Constipation

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INTRODUCTION

- Rapid relief of opioid-induced constipation (OIC) is often necessary in acute care settings for patients with cancer and chronic noncancer pain
  - OIC affects approximately 60% of patients who use opioids for cancer-related pain[1]
- Methylnaltrexone (MNTX, Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) inhibits OIC by binding to peripheral μ-opioid receptors without impacting central opioid receptor mediated analgesia[2]
- MNTX is the only FDA approved peripherally acting μ-opioid receptor antagonist with a subcutaneous (SC) formulation for OIC
- SC MNTX is 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 opioid dosage escalation[3]
  - The treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[3]
- We report findings from 2 individual studies[4,5] to evaluate the ability of SC MNTX to achieve early rescue-free laxation (RFL) in advanced-illness OIC patients with and without cancer

METHODS

Key Inclusion Criteria

- Aged ≥18 years
- Diagnosis of advanced illness with a life expectancy of ≥1 month
- Receiving opioids for discomfort or pain management for ≥2 weeks and taking a stable regimen for at least 3 days before the first dose
- OIC definition
  - <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, the regimen was to be stable for ≥3 days before the first dose of study drug and was permitted to continue throughout the study

Key Exclusion Criteria

- History of MNTX treatment
- Mechanical bowel obstruction, fecal impaction, or history of fecal ostomy
- Any potential nonopioid cause of bowel dysfunction, in the opinion of the investigator that might have been primarily responsible for constipation

Study Design

- Two multicenter, double-blind, randomized, placebo-controlled studies (302 [NCT00402038] and 4000 [NCT00672477]) were conducted in adult patients with advanced illness and OIC (>95% of whom were laxative refractory)
- Each study was approved by individual site institutional review boards; all patients provided written informed consent
- In study 302, patients from 27 sites (26 US; 1 Canada) were randomized 1:1 to receive SC MNTX 0.15 mg/kg or placebo every other day for 2 weeks
- In study 4000, patients from 48 US and international sites were randomized 1:1 to receive SC MNTX based on body weight (8 or 12 mg) or placebo for a maximum of 7 doses for 14 days

Assessments

- Patients were stratified by cancer status (active cancer versus noncancer)
- Endpoints included
  - The proportion of patients achieving RFL within 4 hours after the first dose (coprimary endpoint for study 302; secondary endpoint for study 4000)
  - The proportion of patients achieving RFL within 24 hours after the first dose
  - The proportion of patients with RFL within 4 hours for ≥2 of the first 4 doses (coprimary endpoint for study 302; primary endpoint for study 4000)
  - Time to RFL
  - Mean changes from baseline in pain scores
  - Safety assessed by treatment-emergent adverse events (TEAEs) and serious AEs

Statistical Analysis

- Efficacy analyses were performed on the intent-to-treat analysis, defined as patients who received at least 1 dose of study medication
- In both studies, RFL response data were analyzed by chi-square tests
- The nominal significance level was 0.05, with no multiplicity adjustment
- Time to RFL within 4 and 24 hours was determined using Kaplan-Meier methods

RESULTS

Patients

- Study 302 included 78 cancer patients (MNTX n = 37; placebo n = 41) and 56 noncancer patients (MNTX n = 26; placebo n = 30)
- Study 4000 included 152 cancer patients (MNTX n = 79; placebo n= 73) and 78 noncancer patients (MNTX n = 37; placebo n = 41)
- Baseline demographics are described in Table 1

Table 1. Baseline Demographics Stratified by Cancer Status in Study 302 and Study 4000 (Pooled Intent-to-Treat Analysis)

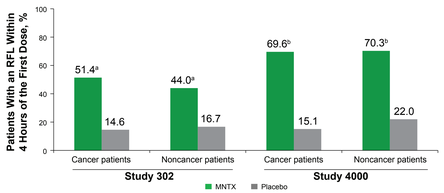
	Study 302				Study 4000			
	Patients With Cancer		Patients Without Cancer		Patients With Cancer		Patients Without Cancer	
	MNTX (n = 37)	Placebo (n = 41)	MNTX (n = 25)	Placebo (n = 30)	MNTX (n = 79)	Placebo (n= 73)	MNTX (n = 37)	Placebo (n = 41)
Age, mean (range)	62.8 (34–91)	64.4 (39–90)	77.2 (47–93)	70.0 (40–98)	63.7 (27–87)	64.1 (32–89)	69.8 (34–101)	68.5 (49–98)
Women, n (%)	20 (54.1)	23 (56.1)	15 (60.0)	17 (56.7)	34 (43.0)	31 (42.5)	22 (59.5)	25 (61.0)
Race/Ethnicity, n (%)								
White	35 (94.6)	37 (90.2)	25 (100)	28 (93.3)	74 (93.7)	68 (93.2)	34 (91.9)	40 (97.6)
Black or African American	1 (2.7)	3 (7.3)	0	2 (6.7)	3 (3.8)	3 (4.1)	2 (5.4)	0
Other	1 (2.7)	1 (2.4)	0	0	2 (2.5)	2 (2.7)	1 (2.7)	1 (2.4)
Weight, mean (SD)	71.0 (13.3)	71.7 (19.2)	67.1 (22.5)	70.7 (29.6)	70.9 (17.8)	70.7 (14.9)	75.0 (26.1)	78.0 (34.8)
Daily dose opioid morphine equivalent, mean (mg/d) Range	543.5 20–4160	509.4 15–10,160	234.4 9–2170	105.7 10–560	352.4 0–4071	515.5 0–7229	356.2 0–4427	177.6 0–633
Current pain score, mean (SD)	3.2 (2.4)	3.0 (2.3)	4.1 (3.1)	4.0 (3.1)	3.7 (2.6)	3.9 (2.5)	4.7 (2.7)	4.1 (3.2)
Worst pain score, mean (SD)	4.9 (2.6)	5.5 (2.7)	5.3 (2.8)	5.2 (2.9)	5.2 (2.8)	5.0 (3.0)	5.8 (2.7)	5.7 (3.0)
Number of laxatives used at baseline,[a] n (%)								
0	0	0	1 (4.0)	1 (3.3)	2 (2.5)	1 (1.4)	0	0
1	12 (32.4)	11 (26.8)	5 (20.0)	5 (16.7)	28 (35.4)	20 (27.4)	11 (29.7)	12 (29.3)
2	12 (32.4)	10 (24.4)	9 (36.0)	8 (26.7)	28 (35.4)	30 (41.1)	16 (43.2)	21 (51.2)
3	5 (13.5)	9 (22.0)	4 (16.0)	11 (36.7)	12 (15.2)	14 (19.2)	6 (16.2)	6 (14.6)
4	6 (16.2)	6 (14.6)	1 (4.0)	3 (10.0)	8 (10.1)	8 (11.0)	3 (8.1)	1 (2.4)
5	2 (5.4)	2 (4.9)	3 (12.0)	2 (6.7)	1 (1.3)	0	1 (2.7)	1 (2.4)
6	0	2 (4.9)	2 (8.0)	0	0	0	0	0
7	0	1 (2.4)	0	0	0	0	0	0

[a]Defined as those reported either as ongoing prior medications or as concomitant medications first used on the same day as the first dose of study drug.

Laxation Efficacy

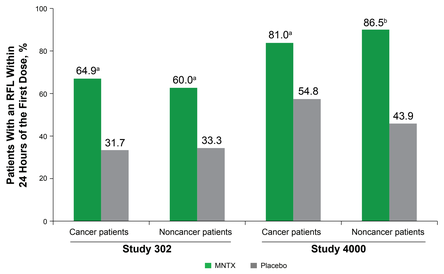
- In both studies, significantly greater proportions of patients treated with MNTX versus placebo achieved RFL within 4 hours after the first dose among both cancer and noncancer patients (Figure 1)
- The significant difference in RFL response between treatment groups was maintained at 24 hours in both cohorts in both studies (Figure 2)

Figure 1. Patients Achieving a Rescue-Free Laxation Response Within 4 and 24 Hours After the First Dose of Study Treatment (ITT Population)



[a]MNTX vs placebo, $P<0.05$; [b]MNTX vs placebo, $P<0.0001$.
MNTX = methylnaltrexone; RFL = rescue-free laxation.

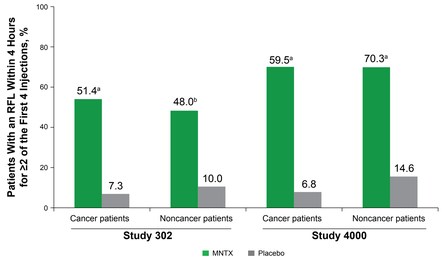
Figure 2. Patients Achieving Rescue-free Laxation Within 24 Hours of the First Dose



[a]MNTX vs placebo, $P<0.05$; [b]MNTX vs placebo, $P<0.0001$.
MNTX = methylnaltrexone; RFL = rescue-free laxation.

- Repeat dosing with SC MNTX also maintained bowel symptom response within 4 hours in both cohorts (Figure 3)

Figure 3. Repeat Dosing With SC MNTX (RFL Within 4 Hours for ≥2 of the First 4 Injections) Maintained Bowel Symptom Response in Cancer and Noncancer Patients (ITT Population)



[a]MNTX vs placebo, $P<0.0001$; [b]MNTX vs placebo, $P = 0.0016$.
MNTX = methylnaltrexone; RFL = rescue-free laxation.

- The time to RFL at 4 and 24 hours was less for MNTX than for placebo (Table 2)

Table 2. Time to Rescue-Free Laxation Response at 4 and 24 Hours After the Study Dose

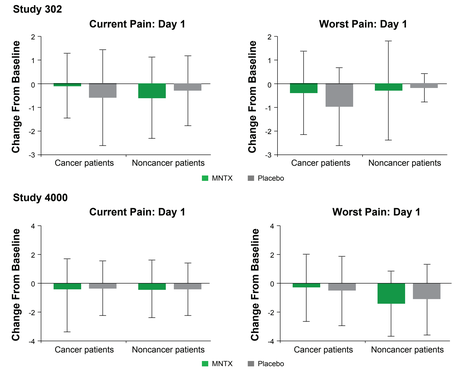
		Study 302		Study 4000	
	Treatment	Median Time to RFL (h)	Log-rank *P*-value	Median Time to RFL (h)	Log-rank *P*-value
4-hour Interval					
Cancer patients	MNTX	3.47	0.0002	0.75	<0.0001
	Placebo	>4		>4	
Noncancer patients	MNTX	>4	0.0201	0.92	<0.0001
	Placebo	>4		>4	
24-hour Interval					
Cancer patients	MNTX	3.47	0.0007	0.75	<0.0001
	Placebo	>24		18.00	
Noncancer patients	MNTX	6.52	0.0250	0.92	<0.0001
	Placebo	>24		23.80	

MNTX = methylnaltrexone; RFL = rescue-free laxation.

Safety

- No significant differences in pain scores were observed between treatment groups in either study (Figure 4)

Figure 4. Mean Change From Baseline to Day 1 in Pain Intensity for Study 302 and Study 4000.[a]



[a]Error bars represent the standard deviation.

- The most common AEs across all groups were generally gastrointestinal in nature (Table 3)
- Serious AEs were reported
  - In study 302, among patients with cancer, 12 (29.3%) patients who received placebo and 6 (16.2%) patients who received MNTX reported malignant neoplasm progression. No patients without cancer reported this serious AE
  - In study 4000, among patients with cancer, 13 (17.8%) of patients who received placebo and 9 (11.4%) of patients who received MNTX reported disease progression. No patients without cancer reported this serious AE

Table 3. Treatment-Emergent Adverse Events in >10% of MNTX Patients in Study 302 and Study 4000

Study 302

	Patients With Cancer		Patients Without Cancer	
TEAE, n (%)	MNTX (n = 37)	Placebo (n = 41)	MNTX (n = 26)	Placebo (n = 30)
Abdominal pain	9 (24.3)	6 (14.6)	2 (7.7)	3 (10.0)
Diarrhea	4 (10.8)	2 (4.9)	0	0
Flatulence	6 (16.2)	3 (7.3)	2 (7.7)	2 (6.7)
Nausea	6 (16.2)	4 (9.8)	0	0
Vomiting	7 (18.9)	7 (17.1)	0	0
Lethargy	4 (10.8)	4 (9.8)	0	0
Peripheral edema	4 (10.8)	7 (17.1)	0	0
Malignant neoplasm progression	6 (16.2)	13 (31.7)	0	0
Dizziness	4 (10.8)	2 (4.9)	0	0

Study 4000

	Patients With Cancer		Patients Without Cancer	
TEAE, n (%)	MNTX (n = 79)	Placebo (n = 73)	MNTX (n = 37)	Placebo (n = 41)
Abdominal pain	28 (35.4)	11 (15.1)	11 (29.7)	8 (19.5)
Diarrhea	6 (7.6)	9 (12.3)	3 (8.1)	6 (14.6)
Nausea	11 (13.9)	12 (16.4)	2 (5.4)	6 (14.6)
Vomiting	5 (6.3)	8 (11.0)	0	0
Disease progression	10 (12.7)	16 (21.9)	0	0
Confusional state	8 (10.1)	3 (4.1)	0	0

MNTX = methylnaltrexone; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- **In 2 multicenter, randomized studies, treatment with SC MNTX effectively reduced OIC in both cancer and noncancer patients**
  - **Relative to placebo, the effect of SC MNTX treatment on RFL was pronounced at both 4 and 24 hours after the first study dose**
  - **Bowel symptom response was maintained with repeat dosing**
  - **The time to RFL was significantly shorter with MNTX treatments in both studies and in both cohorts**
- **Central opioid receptor mediated analgesia was not affected by SC MNTX use**
- **SC MNTX was safe to use with AEs reflective of those that often occur during effective laxation**

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DISCLOSURES

Dr. Shah has nothing to disclose. Dr. Chamberlain has nothing to disclose. Dr. Rhiner has received a grant from Wyeth Pharmaceuticals for the 302 study mentioned in this poster. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US, LLC. Dr. Stambler is an employee of Progenics Pharmaceuticals, Inc. Dr. Israel is an employee of Bausch Health US, LLC.

ACKNOWLEDGMENTS

These studies were funded by Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA, which has licensed the rights to develop and commercialize Relistor® from Progenics Pharmaceuticals, Inc., New York, NY, USA. Technical editorial and medical writing assistance was provided under the direction of the authors by Dana A. Franznick, PharmD, Echelon Brand Communications, LLC, an OPEN Health company, Parsippany, NJ, USA. Funding for this assistance was provided by Salix Pharmaceuticals.

Research funded by: Salix Pharmaceuticals