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Reductions in All-Cause Mortality Associated With the Use of Methylnaltrexone for Opioid-Induced Bowel Disorders: A Pooled Analysis

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INTRODUCTION

- Opioids are often associated with the development of delays in gastrointestinal motility and associated conditions
- Recent preclinical and clinical studies have suggested that activation of the μ-opioid receptor may reduce overall survival and increase the risk for all-cause mortality in patients with cancer and noncancer pain syndromes[1-4]
  - In patients with newly diagnosed advanced cancer, higher μ-opioid receptor expression and greater opioid requirements were associated with reductions in overall survival (OS) and shorter progression-free survival[5]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, Bridgewater, NJ, USA), a selective peripherally acting μ-opioid receptor antagonist, is approved for[6]
  - The treatment of opioid-induced constipation (OIC) in adults with chronic noncancer pain, including patients with chronic pain related to cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation
  - The treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care
- A post hoc analysis of 2 placebo-controlled studies of MNTX treatment of patients with advanced illness and OIC found that patients with advanced cancer who received MNTX had significantly improved OS compared with those receiving placebo
  - The improvement in OS was even more pronounced among MNTX-treated patients who had responded to MNTX (ie, those who had a laxative response within 4 hours of at least 2 of the first 4 doses)[1]
- To further evaluate whether MNTX treatment for opioid-induced bowel disorders affects mortality risk, we conducted a post hoc pooled analysis of 12 clinical trials evaluating all-cause mortality

METHODS

Study Design

- Retrospective analysis of pooled data from 12 phase 2 to 4 randomized, double-blind, placebo-controlled studies of MNTX for opioid-induced bowel disorders (**Table 1**)
- Patients had advanced illness or noncancer pain who received subcutaneous, intravenous or oral MNTX or placebo
- Data were pooled to evaluate
  - The overall population and the cohort of patients who died (mortality cohort)
  - Subgroups stratified by cancer vs noncancer, aged <60 years vs ≥60 years, men vs women, and acute diagnosis vs chronic diagnosis

Table 1. Randomized, Double-blind, Placebo-controlled Studies of Methylnaltrexone Included in Pooled Analysis

Study	Phase	Patient Population	Group Ns[a] MNTX	PBO	MNTX Dosage
MNTX 2101[7]	2	Acute OIC after orthopedic surgery	18	15	12 mg SC MNTX once daily for 4–7 days
MOA-728 0200	2	OIBD and chronic noncancer pain	192	44	10, 50, 150, 300, or 450 mg oral MNTX once daily for 4 weeks
MOA-728 2201	2	OIBD and chronic noncancer pain	89	33	150, 300, 450, or 600 mg oral MNTX once daily for 4 weeks
MOA-728 2202	2	OIBD and chronic noncancer pain	99	29	150, 300, 450, or 600 mg oral MNTX once daily for 4 weeks
MOA-728 300[8b]	3	Postoperative ileus	357	176	12 or 24 mg IV MNTX every 6 hours for up to 10 days
MNTX 3301[8b]	3	Postoperative ileus	344	171	12 or 24 mg IV MNTX every 6 hours for up to 10 days
MOA-728 301	3	Postoperative ileus	249	124	12 or 24 mg IV MNTX every 6 hours for up to 10 days
MNTX 301[9]	3	OIC and advanced illness	102	52	Single dose 0.15 or 0.30 mg/kg SC MNTX
MNTX 302[10]	3	OIC and advanced illness	62	71	0.15 mg/kg SC MNTX every other day for 2 weeks (optional increase to 0.30 mg/kg for week 2)
MNTX 3356[11]	3	OIC and chronic noncancer pain	298	162	12 mg SC MNTX once daily or every other day for 4 weeks
MNTX 3201[12]	3	OIC and chronic noncancer pain	602	201	150, 300, or 450 mg oral MNTX once daily for 12 weeks
MNTX 4000[13]	4	OIC and advanced illness	116	114	8 or 12 mg SC MNTX every other day for 14 days

[a]Intent-to-treat population.
[b]Studies MOA-728 300 and MNTX 3301 were phase 3 studies of identical design, described in a single publication.[8]
IV = intravenous; MNTX = methylnaltrexone; OIBD = opioid-induced bowel dysfunction (defined as <3 spontaneous bowel movements per week and hard or lumpy stools, a sensation of incomplete evacuation and/or straining, in ≥ 25% of bowel movements); OIC = opioid-induced constipation; PBO = placebo; SC = subcutaneous.

Assessments

- Demographics and baseline characteristics were described descriptively for age, gender, body mass index, daily opioid consumption based on oral morphine equivalents, and the presence of cardiovascular risk factors
- All-cause mortality was defined for this analysis as the number of patients who died ≤30 days after the final dose of study medication during the double-blind phase of each study
- Person-years of exposure (PYE) was calculated as
  - For those who died: (sum of exposure days before death/365.25) × 100
  - For those who survived: (sum of exposure days before last study visit/365.25) × 100
- The duration of mortality follow-up ranged from approximately 1 to 3 months, depending on the study
- Mortality risk for each treatment group was calculated for the overall population and for subgroups stratified by cancer vs noncancer, aged <60 years vs ≥60 years, men vs women, and acute diagnosis vs chronic diagnosis

Statistical Analysis

- The mortality risks (*P*-values, hazard ratios and 95% confidence intervals [CIs]) for patients receiving MNTX or placebo were compared using a Cox proportional hazards regression model with only treatment effect in the model, not adjusting for other factors
- *P*-values had a nominal 2-sided significance level of 0.05 without adjustment for multiplicity
- The pattern of deaths over time among patients in the MNTX and placebo groups was evaluated by Kaplan-Meier analysis

RESULTS

Disposition

- Baseline disposition for the overall population and by subgroup are presented in **Table 2**
- In the overall population, 2526 patients received MNTX of which 33 died and 1192 patients received placebo of which 35 died

Table 2. Baseline Disposition for the Overall Population and by Subgroup

	Overall Population MNTX (n = 2526)	PBO (n = 1192)	Mortality Cohort MNTX (n = 33)	PBO (n = 35)
Subgroups, n (%)				
Cancer	537 (21.3)	324 (27.2)	22 (66.7)	27 (77.1)
Noncancer	1989 (78.7)	868 (72.8)	11 (33.3)	8 (22.9)
Aged <60 years	1631 (64.6)	701 (58.8)	6 (18.2)	11 (31.4)
Aged ≥60 years	895 (35.4)	491 (41.2)	27 (81.8)	24 (68.6)
Men	1152 (45.6)	549 (46.1)	18 (54.5)	16 (45.7)
Women	1374 (54.4)	643 (53.9)	15 (45.5)	19 (54.3)
Acute diagnosis (postoperative ileus)	966 (38.2)	486 (40.8)	9 (27.3)	4 (11.4)
Chronic diagnosis (advanced illness and chronic noncancer pain)	1560 (61.8)	706 (59.2)	24 (72.7)	31 (88.6)

MNTX = methylnaltrexone; PBO = placebo.

Demographics

- Baseline demographics and cardiovascular risk factors for the overall and mortality populations are summarized in **Table 3**

Table 3. Demographics and Baseline Characteristics and Cardiovascular Risk Factors for the Pooled Analysis Population

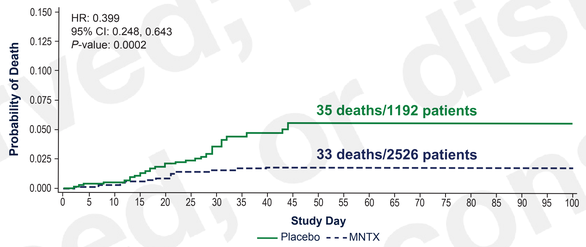
Characteristic	Overall Population MNTX (n = 2526)	PBO (n = 1192)	Mortality Cohort MNTX (n = 33)	PBO (n = 35)
Age, years, mean (range)	55.0 (18, 101)	57.1 (19, 100)	69.6 (27, 93)	66.2 (39, 87)
Body mass index, kg/m², n (%)				
<30	1552 (61.4)	769 (64.5)	28 (84.8)	28 (80.0)
≥30	967 (38.3)	418 (35.1)	5 (15.2)	7 (20.0)
Missing	7 (0.3)	5 (0.4)	0	0
Cardiovascular risk factors, n (%)[a,b]				
Hypertension	1094 (43.3)	509 (42.7)	6 (18.2)	2 (5.7)
Hyperlipidemia/hypercholesterolemia	1033 (40.9)	527 (44.2)	19 (57.6)	18 (51.4)
Diabetes mellitus	695 (27.5)	398 (33.4)	19 (57.6)	19 (54.3)
Myocardial infarction	380 (15.0)	247 (20.7)	12 (36.4)	15 (42.9)
Stroke	393 (15.6)	256 (21.5)	11 (33.3)	17 (48.6)
Angina	278 (11.0)	150 (12.6)	2 (6.1)	2 (5.7)
Daily opioid consumption (OME), mg, median (range)[c]	174.0 (4.5, 33,120)	134.8 (8.0, 10,160)	125.0 (12.0, 4071)	200.0 (33.5, 10,160)

[a]Some patients had multiple cardiovascular risk factors.
[b]Risk factors affecting ≥10% of patients in either group.
[c]Calculated for studies MNTX301, MNTX302, and MNTX4000 only.
MNTX = methylnaltrexone; OME = oral morphine equivalents; PBO = placebo.

Mortality Risk for the Overall Population

- There were 33 deaths among 2526 patients who received MNTX and 35 deaths among 1192 patients who received placebo, resulting in a significant 60% reduction in all-cause mortality risk among patients treated with MNTX compared with placebo (HR: 0.399, 95% CI: 0.248, 0.643, *P* = 0.0002)
  - The mortality rate was 17.8 and 49.5 deaths/100 PYE for MNTX and placebo, respectively
  - A Kaplan-Meier analysis showed a temporal pattern of deaths for patients receiving MNTX and placebo diverge early, with between-group differences emerging around day 15 before flattening due to the limited duration of studies and follow-up periods (**Figure 1**)

Figure 1. Kaplan-Meier Analysis and Plot of All-cause Mortality Over Time in the Pooled Methylnaltrexone and Placebo Groups from Phase 2 to Phase 4 Randomized, Double-blind, Placebo-controlled Studies

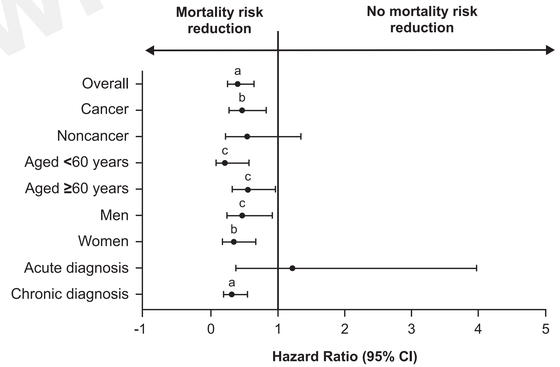


CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone.

Mortality Risk by Subgroup Stratification

- Mortality risk comparing hazard ratios (95% CI) for the overall population and the stratified cohorts (cancer vs noncancer, aged <60 years vs aged ≥60 years, men vs women, acute diagnosis vs chronic diagnosis) (**Figure 2**)
  - In the stratified subgroups, each cohort except patients without cancer or those with an acute diagnosis had a significant mortality risk reduction when receiving MNTX

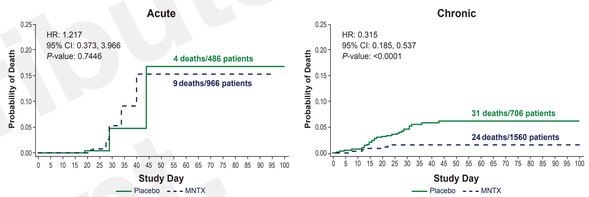
Figure 2. Comparison of Mortality Risk Based on Hazard Ratios (95% CI) for the Overall Population and for Each Subgroup



[a]*P* < 0.001.
[b]*P* < 0.01.
[c]*P* < 0.05.
CI = confidence interval.

- For patients with an acute diagnosis (postoperative ileus), there was no treatment effect on mortality risk (HR: 1.217, 95% CI: 0.373, 3.966, *P* = 0.7446). However, among those patients with a chronic diagnosis, which included patients with cancer and chronic noncancer pain, those receiving MNTX had a 68.5% reduction in mortality risk relative to those receiving placebo (HR: 0.315, 95% CI: 0.185, 0.537, *P* < 0.0001, **Figure 3**).

Figure 3. Kaplan-Meier Analysis of Mortality Risk by Diagnosis



CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone.

CONCLUSIONS

- **All-cause mortality was significantly reduced among patients receiving MNTX**
  - **This effect was consistent regardless of age and gender and observed in patients with cancer or chronic illness**
  - **The lack of effect observed for those with an acute diagnosis implies benefits among patients with chronic diagnoses**
- **MNTX μ-opioid receptor antagonism may provide protective benefit against the additional mortality risk associated with opioid treatment in patients with chronic illnesses**

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DISCLOSURES

Dr. Webster is a consultant or advisor for Bonti, BDSI, Charleston Labs, Daiichi Sankyo, Ensyse Biosciences, Elysium Therapeutics, Insys Therapeutics, Mallinckrodt Pharmaceuticals, Merck, Neurana, Pain Therapeutics, Pernix, Pfizer, Salix, Shionogi, Teva, and Trevena. Dr. Brenner is a consultant, advisor, and speaker for Salix Pharmaceuticals. Dr. Israel is an employee of Bausch Health US, LLC. Dr. Stambler is a full-time employee and shareholder of Progenics Pharmaceuticals. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US, LLC.

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