

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008;358:2332-43.

On-Line Table 1. Inclusion and Exclusion Criteria for Open-Label Extension Study

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| <ul style="list-style-type: none">• Patients must have been enrolled in the study and provided signed informed consent within 28 days after the end-of-study visit in the randomized study and ≥ 14 days after receiving the first dose of study drug in the randomized study• Patients (or legal representative) had to provide written informed consent• Women of childbearing age had to be using effective birth control and have a negative pregnancy test at screening• Stable vital signs | <ul style="list-style-type: none">• Women who were pregnant or nursing• Participation in any other studies involving investigational products, other than methylnaltrexone, within 30 days before screening• Any disease process suggestive of mechanical gastrointestinal obstruction (eg, tumor adhesion)• Clinically significant active diverticular disease• Evidence of fecal impaction• Surgically acute abdomen |

On-Line Table 2. Effect of Baseline Characteristics on Laxation Response Within 4 Hours of the First Double-Blind Dose: Responders vs Nonresponders in Methylnaltrexone-Treated Patients

| Variable | Responder n/N (%) | Nonresponder n/N (%) | Adjusted Odds Ratio (95% CI) | p-Value |
|------------------------|------------------------------|---------------------------------|---|----------------|
| WHO Performance Status | | | | |
| 1 and 2 | 9/17 (52.9) | 8/17 (47.1) | 0.714 (0.211, 2.420) | 0.5885 |
| 3 and 4 | 21/45 (46.7) | 24/45 (53.3) | | |
| Cancer | | | | |
| No | 7/15 (46.7) | 8/15 (53.3) | 1.278 (0.318, 5.139) | 0.7300 |
| Yes | 23/47 (48.9) | 24/47 (51.1) | | |
| Age | | | 1.013 (0.971, 1.056)* | 0.5583 |
| Opioid Usage | | | 1.000 (0.999, 1.000)† | 0.5117 |

*Per 1-year increment.

†Per 1-mg/day increment.

On-Line Table 3. Global Clinical Impression of Change (GCIC) ratings (analysis set: ITT)

| Statistics | Placebo (N=71) | | MNTX (N= 62) | |
|---------------|-------------------|------------|-----------------|------------|
| | Patient | Clinician | Patient | Clinician |
| Day 7 | | | | |
| N* | 57 | 57 | 49 | 49 |
| Better† | 20 (35.1%) | 20 (35.1%) | 36 (73.5%) | 34 (69.4%) |
| No Change | 34 (59.6%) | 35 (61.4%) | 12 (24.5%) | 15 (30.6%) |
| Worse | 2 (3.5%) | 2 (3.5%) | 0 (0%) | 0 (0%) |
| Day 14 | | | | |
| N* | 56 | 56 | 53 | 53 |
| Better† | 25 (44.6%) | 28 (50.0%) | 36 (67.9%) | 36 (67.9%) |
| No Change | 27 (48.2%) | 25 (44.6%) | 14 (26.4%) | 16 (30.2%) |
| Worse | 2 (3.6%) | 3 (5.4%) | 2 (3.8%) | 1 (1.9%) |

*N=number with patient rating, clinician rating, or both; percents are based on these numbers. The patient rating was not done by 1 patient in each treatment group on Day 7 and by 2 patients in the placebo group and 1 patient in the MNTX group on Day 14. Patients with no patient or clinician ratings for either day were not included in this table.

†Better: Includes responses of Much Better, Somewhat Better and Slightly Better. Worse: Includes responses of Much Worse, Somewhat Worse and Slightly Worse.

On-Line Table 4. Patients with Serious Adverse Events

| Adverse Event | Placebo (n=71) N (%) | Methylalntrexone (n=63) N (%) |
|---|---------------------------------|--|
| Patients with ≥ 1 serious adverse event | 20 (28.2) | 11 (17.5) |
| Cardiac disorders | | |
| Congestive heart failure aggravated | 1 (1.4) | 1 (1.6) |
| Coronary artery disease aggravated | 0 (0.0) | 1 (1.6) |
| Cyanosis | 1 (1.4) | 0 (0.0) |
| Myocardial ischemia | 0 (0.0) | 1 (1.6) |
| Gastrointestinal disorders | | |
| Abdominal pain | 1 (1.4) | 0 (0.0) |
| Constipation | 1 (1.4) | 0 (0.0) |
| General disorders/administration site conditions | | |
| Asthenia | 1 (1.4) | 0 (0.0) |
| Concomitant disease progression | 1 (1.4) | 2 (3.2) |
| Pain exacerbated | 1 (1.4) | 0 (0.0) |
| Infections/infestations | | |
| Pneumonia | 1 (1.4) | 0 (0.0) |
| Investigations | | |
| International normalized ratio increased | 1 (1.4) | 0 (0.0) |
| Metabolism and nutrition disorders | | |
| Dehydration | 2 (2.8) | 0 (0.0) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | | |
| Malignant neoplasm progression | 12 (16.9) | 7 (11.1) |
| Nervous system disorders | | |
| Coma | 1 (1.4) | 0 (0.0) |
| Convulsions | 1 (1.4) | 0 (0.0) |
| Progressive multiple sclerosis | 1 (1.4) | 0 (0.0) |
| Psychiatric disorders | | |
| Aggression | 0 (0.0) | 1 (1.6) |
| Suicidal ideation | 0 (0.0) | 1 (1.6) |
| Renal and urinary disorders | | |
| Renal failure | 1 (1.4) | 0 (0.0) |
| Respiratory, thoracic, and mediastinal disorders | | |
| Chronic obstructive airways disease exacerbated | 1 (1.4) | 0 (0.0) |
| Dyspnea | 2 (2.8) | 0 (0.0) |
| Dyspnea exacerbated | 0 (0.0) | 1 (1.6) |
| Pulmonary congestion | 1 (1.4) | 0 (0.0) |
| Pulmonary embolism | 1 (1.4) | 0 (0.0) |

| | | |
|--------------------|---------|---------|
| Respiratory arrest | 0 (0.0) | 1 (1.6) |
| Tracheal stenosis | 1 (1.4) | 0 (0.0) |
| Vascular disorders | | |
| Aneurysm ruptured | 0 (0.0) | 1 (1.6) |
| Gangrene | 1 (1.4) | 0 (0.0) |
| Hypotension | 1 (1.4) | 0 (0.0) |

N=Number of patients who received at least one dose of study drug. Patients were counted only once for each body system and once for each preferred term.