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GENERIC DRUG NAME / COMPOUND NUMBER: Methylnaltrexone / S-728

PROTOCOL NO.: 3200K1-4001-WW (B2541006)

PROTOCOL TITLE:

Open-Label Extension Study to Assess the Safety of a Fixed Dose of Subcutaneous Methylnaltrexone in Subjects With Advanced Illness and Opioid-Induced Constipation

Study Centers:

A total of 8 centers in the United States took part in the study.

Study Initiation and Final Completion Dates:

31 July 2009 to 15 November 2010

Phase of Development:

Phase 4

Study Objective:

To obtain additional safety data on subcutaneous (SC) methylnaltrexone administered as needed (PRN; but not more than once daily) to subjects with advanced illness in a realistic end-of-life health care situation.

METHODS

Study Design:

This was an open-label, multicenter study. Subjects received fixed doses of SC methylnaltrexone PRN with no >1 dose administered in a 24-hour period. Subjects were divided into 2 treatment groups. The entire duration of participation for subjects in this study was up to 12 weeks (2 weeks in study NCT00672477 and 10 weeks in this extension study).

Number of Subjects (Planned and Analyzed):

A total of 168 subjects were planned to be enrolled in this study. One hundred five (105) subjects who had advanced illness and opioid-induced constipation (OIC) were enrolled in this study.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male or female subjects of White race between the ages of 34 and 98 years receiving opioids for pain on a regular schedule, who had stable vital signs, and continued treatment for OIC

during study were included in this study. The subjects should have completed study NCT00672477.

Main Exclusion Criteria: Subjects were excluded from the study if they had suspected mechanical gastrointestinal obstruction, fecal impaction, or clinically important active diverticular disease, using an opioid antagonist or partial antagonist and had any other clinically important abnormalities.

Study Treatment:

Subjects weighing 38 kg to <62 kg received 0.4 mL SC methylnaltrexone (8 mg) and weighing ≥62 kg received 0.6 mL SC methylnaltrexone (12 mg). If the subjects' weights fell <38 kg during the study, subsequent doses were weight-based (0.15 mg/kg). If a subject's glomerular filtration rate was <30 mL/min per 1.73 m^2, the dose was reduced to 0.075 mg/kg for subjects weighing <62 kg and 8 mg/kg for those weighing ≥62 kg. The duration of the study for each subject was 10 weeks in this extension study.

Efficacy Evaluations:

Efficacy evaluation were not performed for this study.

Safety Evaluations:

Safety was evaluated based on the monitoring of adverse events (AEs), serious AEs, physical examinations, vital sign measurements, and clinical laboratory determinations.

Statistical Methods:

The analyses were descriptive in nature such as mean, median, standard deviations, minimum, and maximum were used to summarize demographic characteristic variables, medical history and baseline values. For dichotomous variables, the descriptive statistics included the count and the percentage in each category, and the total number of observations.

RESULTS

Subject Disposition and Demography:

A total of 105 subjects with ages between 34 to 98 years were enrolled in the study. Of these, 43 (41.0%) subjects completed the study and 49 (46.7%) subjects were withdrawn from the study. A total of 34 (32.4%) subjects were in the 38 to <62 kg weight group and 71 (67.6%) subjects were in the ≥62 kg weight group. Forty-nine (49) subjects discontinued from the study with the most common reasons for discontinuation being disease progression resulting in death (27 subjects) and subject request (10 subjects).

Efficacy Results:

Efficacy evaluation were not performed for this study.

Safety Results:

Serious Adverse Events (SAEs)/Deaths: SAEs were reported in 38 (36.2%) subjects. SAEs reported by >1 subject included disease progression in 26 (24.8%) subjects, anemia in

4 (3.8%), pneumonia in 4 (3.8%), congestive cardiac failure in 2 (1.9%), and dyspnea in 2 (1.9%) subjects, respectively. No SAEs were attributed to the study drug. Twenty-nine (29) subjects died in the study, but none of the deaths were attributed to the study drug.

Treatment-Emergent Adverse Events (TEAEs): Overall, 81/105 (77.1%) subjects reported TEAEs. Of these, the most common were abdominal pain in 20 (19.0%) subjects, edema peripheral in 14 (13.3%) subjects, diarrhea in 13 (12.4%) subjects, fall in 13 (12.4%) subjects, and nausea in 13 (12.4%) subjects.

Discontinuations due to Adverse Events: Overall, 4 subjects were withdrawn from the study due to AEs, of which 2 subjects discontinued due to disease progression, 1 subject due to asthenia, and 1 subject due to worsening of a pre-existing wound in the right leg. No AEs leading to discontinuation have been attributed to the study drug.

CONCLUSION:

The AE profile as described in these interim safety results is consistent with the known safety profile reported in current approved labeling for use in subjects with advanced illness.