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

PROTOCOL NO.: 3200K1-4006-WW (B2541007)

PROTOCOL TITLE:

A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Subcutaneous Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Subjects With Cancer-Related Pain

EUDRACT NUMBER: 2008-005692-10

Study Centers:

An unknown number of centers in Argentina, Canada, Egypt, France, Saudi Arabia, Spain, the United Sates and Venezuela were planned to take part in the study and enroll subjects.

Study Initiation and Final Completion Dates:

28 April 2009 to 10 August 2009
The study was terminated prematurely on 13 August 2009 due to business/operational issues not related to safety and prior to dosing any subjects.

Phase of Development:

Phase 4

Study Objective:

To evaluate the efficacy and safety of subcutaneous (SC) methylnaltrexone in relieving opioid-induced constipation (OIC) in subjects with cancer-related pain.

METHODS

Study Design:

This was multinational, multicenter, randomized (1:1 ratio), double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of methylnaltrexone versus placebo for the treatment of OIC in subjects with cancer-related. Eligible subjects entered a 7 to 14 days screening period to assess constipation. Subjects who remained eligible at the End of the Screening period were randomly assigned to receive SC methylnaltrexone or an equal volume of placebo solution in a 1:1 allocation ratio. Subjects would then receive treatment every other day (QOD) for 2 weeks. Subjects were required to record date and time of bowel movements and opioid and laxative usage in an electronic diary. A follow-up visit was planned 15 to 21 days after the last dose of study drug. The

maximum duration of study participation was 8 weeks, including up to 2 weeks in a screening period, 2 weeks of treatment, and a follow-up period of up to 3 weeks in duration.

Number of Subjects (Planned and Analyzed):

No data available on the planned number of subjects. No subjects were enrolled in this study. However, 3 subjects (1 subject in the United States and 2 subjects in Spain) were evaluated during the screening period and considered screen failures. The study was terminated prematurely prior to dosing any subjects.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male or female subjects aged ≥18 years with cancer (active or in remission) and cancer-related pain, body weight ≥38 kg, who had received opioids for at least 2 weeks prior to starting study treatment and diagnosis of OIC, willing to follow study-specific laxative use requirements, with life expectancy ≥6 months were eligible.

Main Exclusion Criteria: Subjects with a history of chronic constipation before starting opioids, with renal disease receiving dialysis, ostomy for stools and pregnant or breastfeeding woman were excluded.

Study Treatment:

Subjects were randomized to receive either SC methylnaltrexone or placebo, QOD for 2 weeks. Subjects randomly assigned to methylnaltrexone were to receive 12 mg (0.6 mL) if their glomerular filtration rate (GFR) was ≥30 mL/min/1.73 m^2 or a dose of 8 mg (0.4 mL) if their GFR was <30 mL/min/1.73 m^2.

Efficacy Endpoints:

The efficacy assessments for this study included the recording of daily laxation information (date and time, Bristol Stool Scale, Straining Scale, and sense of complete evacuation, for each bowel movement). An analysis of efficacy was not conducted because this study was terminated prior to dosing any subjects.

Safety Evaluations:

Safety evaluation was based on monitoring of adverse events (AEs), serious AEs, physical examinations, vital sign measurements and clinical laboratory determinations. An analysis of safety was not conducted due to termination of study prior to dosing of any subjects.

Statistical Methods:

Due to study termination no efficacy analyses of subjects were conducted.

RESULTS

Subject Disposition and Demography:

A total of 3 subjects were evaluated during the screening period. No subjects were enrolled in this study. The study was terminated prematurely prior to dosing any subjects.

Efficacy Results:

Not applicable. The study was terminated prematurely.

Safety Results:

No subjects died during the screening period; no AEs, serious AEs were reported, and no subjects were discontinued from the screening period due to AEs.

CONCLUSIONS:

The objective of this study was to evaluate the efficacy and safety of SC methylnaltrexone in relieving OIC in subjects with cancer-related pain. No subjects were enrolled in this study; however, 3 subjects were evaluated during the screening period to assess constipation. None of these subjects met all of the qualifying criteria for continuing in the study, and all 3 were considered screen failures. No subjects died during the screening period; no serious AEs were reported, and no subjects were discontinued from the screening period because of an AE. None of the subjects experienced an AE. This study was terminated early by the Sponsor for business reasons not related to safety.