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GENERIC DRUG NAME AND COMPOUND NUMBER: Methylnaltrexone/PF-05236803

PROTOCOL NO.: 3200K1-4000-WW (B2541005)

PROTOCOL TITLE:

A Randomized, Double-Blind, Placebo-Controlled Study of a Fixed Dose of Subcutaneous Methylnaltrexone in Adults With Advanced Illness and Opioid-Induced Constipation: Efficacy, Safety, and Additional Health Outcomes

EudraCT Number: 2007-000854-30

Study Centers:

A total of 87 study centers in 14 countries took part in the study and enrolled subjects. The study centers in these countries were as Australia (6), Belgium (3), Brazil (2), Canada (9), Finland (2), France (11), Germany (6), Italy (5), Mexico (1), Portugal (2), Spain (4), Sweden (2), the United Knigdom (6), and the United States (28).

Study Initiation Date and Final Completion Date:

06 June 2008 and 02 December 2010

Phase of Development:

Phase 4

Study Objective:

Primary Objective: To evaluate the efficacy and safety of a fixed dose of subcutaneous (SC) methylnaltrexone in inducing laxation over a 7 day period in subjects with advanced illness and opioid-induced constipation (OIC).

Secondary Objective: To assess the effect of SC methylnaltrexone on subject reported constipation symptoms and constipation-related quality of life and to assess the efficacy of SC methylnaltrexone beyond 7 days in individuals with advanced illness and OIC.

METHODS

Study Design:

This was a multicenter, randomized (1:1 ratio), double-blind, placebo-controlled, parallel group study in subjects with advanced illness and OIC, in acute care, long-term care, skilled nursing facility, assisted living, or home hospice subjects. This study was completed in

approximately 30 months which included approximately 29 months of enrollment, a 2-week treatment course, and a 15 to 21 day follow-up period.

Number of Subjects (Planned and Analyzed):

A total of 500 subject were planned for screening in this study. A total of 170 subjects were enrolled treated and analyzed.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male or female subjects aged ≥18 years with a diagnosis of advanced disease and receiving opioids for 2 weeks with a stable regimen for ≥3 days, who had OIC with no clinically notable laxation in the 24 hours before laxation, life expectancy of ≥1 months with stable vital signs and electrocardiogram record, not surgically sterile or postmenopausal or sexually abstinent for the duration of the study were included.

Main Exclusion Criteria: Subjects received treatment with methylnaltrexone at any time during the 7 days before the first dose of test article, those with known or suspected mechanical gastrointestinal obstruction, or those with any potential nonopiod cause of bowel obstruction that in the opinion of the Investigator might be a major contributor to the constipation were excluded from the study.

Study Treatment:

Subjects weighing 38 kg to <62 kg were administered 0.4 mL SC methylnaltrexone (8 mg) or placebo and subjects weighing ≥62 kg were administered 0.6 mL SC methylnaltrexone (12 mg) or placebo during the study.

Efficacy Endpoints:

The proportion of subjects with a rescue-free laxation response within 4 hours after atleast 2of the first 4 doses (the first week of treatment).

The secondary efficacy endpoints are the following:

- Time to first rescue-free laxation
- Proportion of subjects with rescue-free laxation within 4 hours after the first dose of study drug
- Proportion of subjects with rescue-free laxation within 4 or 24 hours after each dose.
- Proportion of subjects with rescue-free laxation within 4 hours after at least 4 of the maximum 7 doses
- Numbers of laxations per week
- Numbers of rescue-free laxations per week
- Time to first rescue-free laxation within 4 hours
- Time to first rescue-free laxation within 24 hours
- Time to first rescue-free laxation after each dose

- Proportion of subjects using rescue laxatives during the double-blind period
- Proportion of subjects using enemas during the double-blind period

Safety Evaluations:

Safety was evaluated by monitoring of adverse events (AEs), clinical laboratory results, and periodic measurements of vital signs and physical examinations. The change in pain scores obtained before and after test article administration was also evaluated.

Health Outcomes:

Health outcomes were measured using self-administered assessments including the Patient Assessment of Constipation-Symptoms), the Patient Assessment of Constipation-Quality of Life, and the EuroQoL Questionnaire. Since this study was blinded, health outcomes were not summarized.

Statistical Methods:

All statistical analyses were performed using SAS® software release 9.1.3 under the Unix operating system.

Demographic characteristic variables and medical history as well as baseline values are summarized. For continuous variables, the descriptive statistics included n, mean, median, standard deviation, minimum, and maximum. For dichotomous variables, the descriptive statistics include the count and the percentage in each category, and the total number of observations.

All safety analyses are based on the all-subjects population which included all subjects who received at least 1 dose of study drug.

AEs are categorized using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs and treatment-emergent adverse events (TEAEs) are summarized. AEs are classified by system organ class and preferred term using MedDRA, and summaries of the number of subjects with events will be provided. Reports summarized by severity and by relationship to test article are provided. A listing of AEs is also provided.

RESULTS

Subjects Disposition and Demography:

A total of 170 subjects (86 males and 84 females) with age range 27-98 years (mean age 65.30 years) were enrolled in the study and 131 subjects completed the study. Ethnicity of the subjects were American Indian (1.2%), black (2.4%), white (95.9%) and others (0.6%). A total of 12 subjects discontinued the study due to : Investigator request (2, 1.2%), protocol violation (1, 0.6%), subject request (4, 2.4%), unsatisfactory response (2, 1.2%), and other reasons (3, 1.8%). The study subjects were diagnosed with advanced illness from cancer (64.7%), cardiovascular disease (9.4%), neurological disease (3.5%), and other (8.2%).

Efficacy Results:

Data not available.

Safety Results:

Serious Adverse Events: A total of 15.3% subjects experienced serious adverse events (SAEs). Most of the reported SAEs were disease progression (6.5%) and spinal compression (1.2%).

Adverse Events: One hundred and twenty two (122) (71.8%) subjects reported for treatment emergent adverse events (TEAEs), most of which were TEAEs (≥5% of subjects), abdominal pain (18.2%), nausea (11.8%), diarrhea (9.4%), back pain (6.5%), disease progression (6.5%), vomiting (6.5%), and confusional state (5.3%).

Deaths: Fourteen (14) subjects died during the study. No deaths were attributed to study drug.

Discontinuation due to Adverse Events: Fifteen (15) subjects were withdrawn from the study due to AEs, most of which were abdominal pain (2.4%) and disease progression (2.4%).

Laboratory Abnormalities: Data not available.

Health Outcomes: Data was not available.

CONCLUSION:

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