SYNOPSIS

Sponsor:
Lung Rx, LLC
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Silver Springs, MD 20910
United States

Individual Study Table Referring to Part of the Dossier

(For National Authority Use only)

Name of Finished Product:
Beraprost Sodium Modified Release

Volume:

Name of Active Ingredient:
Beraprost Sodium

Page:

Study Title:

A Multi-Center, Open-Label, Multiple Dose, Dose-Finding Study Exploring the Safety and Tolerability of Beraprost Sodium Modified Release (BPS-MR) in Pulmonary Arterial Hypertension (PAH) Patients

Investigators and Study Centers:

Six study centers:

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- Prof. Marion Delcroix; Gastuisberg University Hospital, Leuven, Belgium
- Prof. Sean Gaine; Mater Misericordiae University Hospital Ltd., Dublin, Ireland
- Prof. Robert Naeije; University Libre de Bruxelles-Hospital Erasme, Bruxelles, Belgium
- Ronald Oudiz, MD; Harbor-UCLA Medical Center, Los Angeles, CA, US
- Fernando Torres, MD; University of Texas Southwestern Medical Center, Dallas, TX, US

Publication (reference): None at this time

Study Period:

10 February 2009 (first patient enrolled) to 03 September 2009 (last patient completed)

Study Phase: Phase 2

Objectives:

Primary Objective**:**
To determine the maximum tolerated dose (MTD) of BPS-MR following chronic, twice-daily administration to PAH patients

Secondary Objectives:
To assess the effect of BPS-MR on:

- Safety [adverse events (AEs), physical exam, vital signs, tolerability, clinical laboratory parameters, electrocardiogram findings], and
- Patient pharmacokinetic (PK) parameters at MTD

Methodology: An open-label, multi-center, Phase II, multi-dose, dose-finding study designed to investigate the safety, tolerability, and PK characteristics of BPS-MR tablets in male and female patients with PAH. All subjects continued background therapy with either a phosphodiesterase type-5 inhibitor (PDE-5i), an endothelin receptor antagonist (ERA), or a combination of the two.

Eligible subjects began the Treatment Phase on an outpatient basis at a Baseline Visit (V1) and took one 60 µg BPS-MR tablet twice daily (BID) for a total daily dose of 120 µg for one week. The dose was escalated by one tablet BID each week, for up to 10 weeks, or until the subject reached their MTD (i.e., 120 µg BID/240 µg total daily dose for Week 2 up to 600 µg BID/1200 µg total daily dose for week 10). A second visit (V2) occurred at Week 5. Subjects had an End of Treatment visit upon reaching their MTD and were given the option of discontinuing treatment or continuing to receive BPS-MR at the MTD dose in an open-label extension study. Subjects who opted to discontinue treatment were to down-titrate their daily doses by one tablet BID each week.

Number of Patients (Planned and Analyzed):

Planned: up to 20
Enrolled: 19
Analyzed for safety: 19
Analyzed for tolerability (MTD): 18
Analyzed for PK variables: 9

Test Product, Dose and Mode of Administration, Lot Number:

Product: BPS-MR tablets, 60 µg
Dose: 60, 120; 180, 240, 300, 360, 420, 480, 540, 600 µg BID
Administration: Oral
Lot Number: A602L

Diagnosis and Main Criteria for Inclusion: Eligible subjects were clinically stable male or female PAH patients between the ages of 18 and 75 years of age, inclusive, diagnosed with either idiopathic or familial PAH, PAH associated with collagen vascular disease, or PAH induced by anorexigens who had previously undergone a cardiac catheterization with results consistent with PAH. Other eligibility criteria included treatment with an ERA or a PDE-5i (or a combination of the two) for at least 90 days prior to the Baseline visit and an unencouraged six-minute walk distance (6MWD) between 300 and 600 meters at the Screening visit.

Subjects were ineligible if they had received prostanoid therapy, another investigational medicine or had changed or discontinued any PAH medication within 30-days prior to the Baseline visit. They were also ineligible if they had a diagnosis of pulmonary venous hypertension, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, severe chronic obstructive pulmonary disease, pulmonary hypertension related to congenital heart disease, chronic thromboembolic pulmonary hypertension, hemorrhagic conditions, or any preexisting disease known to cause pulmonary hypertension. Women who were pregnant or lactating were excluded.

Duration of Treatment: Up to 10 weeks for the Treatment Phase and up to 9 weeks for the Down-Titration Phase.

Reference Therapy, Dose and Mode of Administration, Lot Number: None

Criteria for Evaluation

Efficacy: None

Tolerability: The primary endpoint was tolerability, i.e., determination of the MTD of BPS-MR in PAH patients following twice-daily administration, with weekly up-titration for up to 10 weeks. Subjects reaching an intolerable dose were instructed to continue treatment at the previous dose, which was considered their individual MTD. If subjects tolerated the full 10 weeks of BPS-MR dosing, the individual MTD was considered 600 µg BID. Evaluable subjects were those who achieved their MTD and had an End of Treatment visit.

Optional Pharmacokinetic Assessment: Subjects were offered the opportunity to participate in an optional pharmacokinetic assessment. For those subjects who agreed to participate, PK endpoints were determined from individual subject plasma concentration profiles of total BPS and the active enantiomer BPS-314*d* 3 to 5 days after reaching the subject's MTD. Blood samples (10 mL each, 100 mL total) were collected by venipuncture from each subject for PK analysis at pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours after study drug administration. A noncompartmental PK analysis was conducted using individual subject plasma concentration versus time data.

Safety: Safety was assessed for all subjects receiving at least one dose of study medication by determining the frequency of treatment-emergent AEs (TEAEs) and the frequency of clinically notable abnormal vital signs and laboratory values, including 12-lead electrocardiogram (ECG) data.

Statistical Methods

No hypothesis testing or sample size calculations were performed.

Quantitative parameters were summarized by descriptive statistics including the population size, the mean and standard deviation (SD), and the median with minimum and maximum values. Categorical parameters were

summarized as numbers and percentages of the corresponding population. For parameters measured at baseline (e.g., ECG, vital signs), the analyses of interest were the changes from baseline in these variables.

Efficacy: Not assessed

T**olerability:** The MTD dose for patients was summarized for all evaluable patients.

PK Analysis: Noncompartmental PK data for BPS and BPS-314*d*, including peak plasma concentration (C_{MAX}), time to peak plasma concentration (T_{MAX}), average plasma concentration (C_{AVG}), minimum plasma concentration (C_{MIN}), Fluctuation (C_{MAX}-C_{MIN})/$C_{AVG,}$ area under the curve over the 12-hr dosing interval (AUC_{τ}), and plasma clearance divided by absolute bioavailability (CL/F), were summarized for each subject and the relationship of C_{MAX} and AUC to dose was determined.

Safety: TEAEs were summarized by total number of events and total number of patients with events. AEs were considered treatment emergent if they were newly occurring or worsening from the start of dosing at baseline.

Summary of Results

The mean age of the 19 enrolled subjects (15 women and 4 men) was 47.6±12.9 years. The majority of subjects were white (16/19, 84%) with a diagnosis of familial or idiopathic PAH (16/19, 84%). The mean distance for the 6-minute walk test performed at the Screening Visit was 420.6±71.2 meters and mean Borg dyspnea score was 3.6±2.5. Subjects' medical and surgical histories were generally representative of a PAH patient population. One (1) subject withdrew in the first week of the study due to worsening symptoms of Stills disease. Background therapy for enrolled subjects was either a PDE-5i alone (N=7), an ERA alone (N=2), or combination of both (N=10).

Efficacy: Not assessed

Tolerability: The MTD of BPS-MR by each dose group for all evaluable subjects is summarized below. In 11 subjects, an AE or multiple AEs resulted in a dose reduction to the next lowest dose and defined the subject's MTD. The remaining 7 subjects (38.9%) tolerated the maximum allowable dose of 600 µg BID.

MTD (µg BID)	Number of Subjects (%) N=18
120	2 (11.1)
180	2 (11.1)
240	3 (16.7)
300	2 (11.1)
420	1 (5.6)
540	1 (5.6)
600	7 (38.9)

Pharmacokinetics : Nine (9) subjects elected to participate in the PK assessment: 1 subject each at an MTD of 120, 180, 240 and 420 µg BID, 2 subjects at an MTD of 300 µg BID, and 3 subjects at an MTD of 600 µg BID. Three (3) to 5 days after reaching the MTD or 600 µg BID dose, individual subject plasma BPS and BPS-314*d* concentrations were at steady state, dose-related, and comparable to those observed in a previous single-dose PK study of BPS-MR in healthy volunteers. BPS C_{MAX} and C_{MIN} increased with dose, with C_{MAX} values ranging from 142 to 694 pg/mL and C_{MIN} from 56.4 to 306 pg/mL over the dose range of 120 to 600 µg. T_{MAX} values for BPS were variable and ranged from 1 to 8 hours; possibly a result of 2 peaks observed in some patients. AUCτ values increased with increase in dose ranging from 1340 to 6085 h*pg/mL. C_{avg}, calculated as the ratio of AUCτ/τ ranged from 111.7 to 507 pg/mL. Clearance (CL/F) was independent of dose and variable, averaging 1.51 L/h/kg with CV% of 34.4%. Secondary BPS peaks and the 12-hr dosing interval precluded the accurate determination of the drug half-life ($t_{½}$).

C_{MAX} for BPS-314*d* ranged from 30.3 to 145 pg/mL and also increased in proportion to the administered dose. The ratio of C_{MAX} for BPS-314*d* /BPS averaged 0.20 and ranged from 0.19 to 0.22. AUCτ values increased with increase in dose for BPS-314*d,* ranging from 1340 to 6085 h*ng/mL. The ratio of AUC for BPS-314*d*/BPS averaged 0.17 and ranged from 0.14 to 0.20. C_{AVG}, ranged from 20.0 to 79.3 for BPS-314*d*. CL/F was also high for BPS-314*d*, averaging 2.17 L/h/kg with a 34.3% CV%.

Safety: A total of 121 TEAEs were observed in 19 subjects. The most common TEAEs were those typically associated with prostacyclin therapy including headache (23 events in 14/19 subjects, 73.7%), diarrhea (11/19, 57.9%), flushing (7/19 subjects, 36.8%), extremity pain and jaw pain (7/19, 36.8% for each), nausea (6/19, 31.6%) and general pain (5/19, 26.3%). The majority (87%) of AEs were mild (70/121, 58%) or moderate (35/121, 29%) in intensity. Sixteen (16) events in 6 subjects were listed as severe and included headache (8 events in 6 subjects), diarrhea (2 events in 2 subjects), pain (2 events in 2 subjects), and single events in 1 subject each of jaw pain, neck pain, nausea, and cold sweats. Adverse events were generally managed by dose reductions and no AE resulted in subject withdrawal from the study. No SAEs were reported and no deaths occurred during the study. There were no clinically relevant trends observed with respect to laboratory, vital sign, ECG, or physical examination results after BPS-MR administration.

Conclusions

This is the first study to assess the MTD of BPS-MR in patients with PAH. PAH patients on various background therapies initiated BPS-MR dosing at 60 µg BID and tolerated doses ranging from 120 to 600 µg BID following up-titration at weekly intervals. BPS-MR had an acceptable safety profile and AEs were consistent with those observed with administration of prostacyclin analogues to patients with PAH. Adverse events were generally managed by dose reductions of BPS-MR. Steady state plasma concentrations of BPS and BPS-314*d* were dose-related and support the twice-daily dosing regimen of BPS-MR in PAH patients.

Final Date: 14 September 2011