SYNOPSIS

SPONSOR:
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INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER

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NAME OF FINISHED PRODUCT:
Beraprost Sodium Modified Release 60 µg (BPS-MR) Tablets

VOLUME:

NAME OF ACTIVE INGREDIENT:
Beraprost Sodium

PAGE:

STUDY TITLE:
A 12-week, double-blind, international, multicenter, dose-response study of the safety and efficacy of Beraprost Sodium Modified Release (BPS-MR) in patients with pulmonary arterial hypertension (PAH)

INVESTIGATORS AND STUDY CENTERS:
Multicenter

PUBLICATION (REFERENCE):
None at this time

STUDIED PERIOD:
01 February 2010 (first patient enrolled) to
13 September 2011 (last patient completed)

STUDY PHASE:
2

OBJECTIVES:
The primary objective of this study was to determine the effect of twice daily administration of BPS-MR on the change from Baseline in hemodynamic parameters at Week 12.

The secondary objectives of this study were to assess the effect of an individual Maximum Titrated Dose (iMTD) and two Fixed Dose (FD 60 µg and FD 240 µg) levels of BPS-MR, administered twice daily, on:

- Exercise capacity 2 to 3 hours after dosing (peak), at Weeks 6 and 12;
- Exercise capacity at the end of the dosing interval (trough), at Week 12;
- Borg Dyspnea Score 2 to 3 hours after dosing (at Weeks 6 and 12) and at the end of the dosing interval (at Week 12);
- World Health Organization (WHO) Functional Class, at Weeks 6 and 12;
- Pro-B-Type Natriuretic Peptide (pro-BNP) plasma concentrations, at Weeks 6 and 12;
- Safety (adverse events, clinical laboratory parameters, electrocardiogram (ECG) findings, physical examination, and vital signs); and
- BPS and BPS-314*d* plasma concentrations, at Week 12.

METHODOLOGY:
This was a 12-week, international, multicenter, double-blind, parallel group, dose-response study to assess the safety and efficacy of BPS-MR in patients with PAH. Eligible patients were previously diagnosed with PAH and were on a stable course of an Endothelin Receptor Antagonist (ERA) and/or Phosphodiesterase Type 5 Inhibitor (PDE-5 inhibitor) for at least 60 days prior to Baseline.

A total of 36 patients were randomized to 1 of 3 treatment groups in a 1:1:1 ratio and were stratified by PAH background therapy (ERA, PDE-5 inhibitor, and both). The treatment groups consisted of one iMTD and two FD

groups (FD 60 µg and FD 240 µg). Following randomization, patients began taking active drug (60 µg) orally twice daily (BID). Patients visited their clinical site at Week 6 and Week 12 for study evaluations. Between visits, clinical site staff contacted patients by phone each week to assess tolerability, provide instructions for a change in dosage, record changes in concomitant medications, and record adverse events. Patients who completed the study were offered the opportunity to continue taking study medication in a separate open-label continuation protocol (BPS-MR-PAH-204). Patients who withdrew early from the study or who otherwise did not elect to enroll into the open-label continuation protocol were down-titrated off of BPS-MR at the discretion of the Investigator, at a maximum decrement that did not exceed one tablet (60 µg) BID per day and a minimum decrement of one tablet (60 µg) BID per week.

Patients in the iMTD treatment group dose escalated weekly by 60 µg BID until they reached the maximum dose of 600 µg BID or they reached an intolerable dose which required them to down-titrate by 60 µg BID. In these instances, and at the Investigator's discretion, further attempts at dose escalation were allowed.

The FD treatment groups consisted of a low dose group receiving 60 µg BID and a high dose group receiving 240 µg BID. Patients in the high dose group dose escalated weekly by 60 µg BID until they reached the fixed dose of 240 µg BID. Once patients in these treatment groups reached their assigned maximum dose of active drug, weekly increases in the number of placebo tablets administered continued in order to maintain the blind.

Patients were requested to maintain a daily diary of symptoms and study drug administration for evaluation by clinical site staff. Also, patients were given the option to contribute blood for pharmacokinetic assessment of BPS and BPS-314*d* plasma concentrations at the Week 12 visit.

NUMBER OF PATIENTS (Planned and Analyzed):
36 patients were planned and were randomized; 36 patients were analyzed for safety; 33 patients were analyzed for efficacy.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
The patient population consisted of adult male and female patients with PAH (idiopathic or familial, collagen vascular disease associated, induced by anorexigens, or associated with repaired congenital systemic-to-pulmonary shunts [repaired ≥5 years]), aged 18 to 75 years, presently on a stable course of ERA and/or PDE-5 inhibitor background therapy.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER:
The investigational drug in this study was BPS-MR 60 µg tablets for oral administration. The batches/lots of BPS-MR utilized in the study were TA01 and TA04.

To preserve study blinding of the treatment group, placebo tablets were used to supplement the active medication within the Dose-Pak® wallets. The placebo tablets were identical in size, shape, color, and appearance to the BPS-MR tablets. The batch/lot of placebo tablets utilized in the study was PJ04.

DURATION OF TREATMENT:
12 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER:
None

CRITERIA FOR EVALUATION:
Efficacy:
The primary objective of the study was to determine the effect of twice daily administration of BPS-MR on hemodynamic parameters in patients with PAH. The primary efficacy endpoint was the change from baseline in hemodynamic parameters at Week 12 of the study and was based on right heart catheterization (RHC) measures, including mean pulmonary arterial pressure (PAPm), cardiac output (CO) and pulmonary vascular resistance (PVR). The secondary efficacy variables included six-minute walk distance (6MWD) at Weeks 6 and 12 measured at 2 to 3 hours after dosing (peak), 6MWD at Week 12 measured at the end of the dosing interval (trough), Borg Dyspnea Score at Weeks 6 and 12 measured at 2 to 3 hours after dosing (peak), Borg Dyspnea Score at Week 12 measured at

the end of the dosing interval (trough), WHO functional class measured at Weeks 6 and 12 and pro-BNP plasma concentrations measured at Weeks 6 and 12.

Pharmacokinetic:
Patients were offered the opportunity to participate in an optional pharmacokinetic (PK) assessment. Patients who elected to participate in the PK assessment provided blood samples for measurement of BPS and BPS-314*d* plasma concentrations at the Week 12 visit. A total of 10 blood samples (10 mL each, 100 mL total) were collected by venipuncture from each participating patient for PK analysis. Blood samples were collected pre-dose (within 10 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after the study drug administration. The 12 hour PK blood sample was collected prior to the evening dose. The exact time of collection was recorded in the eCRF and on the plasma storage vial that was shipped to the analytical laboratory. Plasma concentrations of BPS and BPS-314*d* were measured using liquid chromatography, tandem mass spectrometry (LC-MS/MS) methods. The assay was developed and validated by Alta Analytical Laboratory who also analyzed the collected samples. The lower limit of quantification (LLOQ) of BPS and BPS-314*d* in plasma was 5.0 pg/mL.

Safety:
Adverse events were collected throughout the study. Patients were contacted by telephone each week to record any changes in concomitant medications and possible adverse events. Laboratory parameters (hematology, serum chemistry and coagulation) and ECG were assessed at Screening, Week 6 and Week 12. Vital signs were recorded and physical examinations were performed at all visits.

STATISTICAL METHODS:
Planned analyses of all efficacy and safety data were pre-specified in a statistical analysis plan, which was finalized prior to unblinding. The following analysis populations were defined for this study:

- Full Analysis: All patients randomized into the study (per intended treatment assignment).
- Per-Protocol: All patients randomized into the study (per actual treatment assignment) who have completed the study and have received the required protocol processing for the study, i.e., no major protocol deviations.
- Pharmacokinetic: All patients who consented to the PK study, received their administration of BPS-MR, and had adequate plasma concentrations to estimate pharmacokinetic parameters of BPS and/or BPS-314*d*.
- Safety: All patients randomized into the study (per actual treatment assignment) who have received at least one dose of study drug.

As prospectively defined in the statistical analysis plan, all efficacy analyses were based on the Per-Protocol analysis population, with analyses conducted using the Full Analysis population as supportive. Dropouts were not replaced during the study, but were included in the data analysis to the extent that data was available and per the analysis population. In the event that any data points were missing, no imputation was used for data analysis. Only the data observed during the study were used. No interim analyses were conducted. As recruitment by clinical site was expected to produce too few patients to allow for the inclusion of the covariate of clinical site in efficacy analyses, a pooling algorithm was not used. Patients on background therapy of ERA and/or PDE-5 inhibitor were combined for all analyses. No adjustments were made for multiplicity among parameters analyzed.

Efficacy:
The change from baseline in hemodynamic measures at Week 12 was analyzed using an ordinary least squares (LS) analysis of covariance (ANCOVA) model. Adjusted baseline and treatment group were included in the model as covariates. Separate ANCOVA analyses were conducted for each dependent variable. LS means and their 95% confidence intervals were computed for each treatment group. LS mean differences between the treatment groups with 95% confidence intervals for the pairwise differences were also displayed, together with the p-values corresponding to testing the hypotheses of no difference between treatment groups.

With the exception of WHO functional class, the analysis of secondary efficacy endpoints were conducted on the change from baseline measures for each of the continuous secondary efficacy variables. Analyses of these continuous secondary measures were made similarly to the analyses of the primary measures. Secondary efficacy analyses were made separately for each secondary efficacy variable and by visit. For pro-BNP levels, transition tables from Baseline to Week 6 and Week 12, separately, were created to present the number and percentage of patients by treatment group and overall.

The categorical secondary measures of the WHO functional class measured at Weeks 6 and 12 were presented descriptively. The number of patients in each WHO functional class was presented by treatment group and visit (Baseline, Week 6 and Week 12) and transition tables from Baseline to Week 6 and Week 12, separately, was created to present the number and percentage of patients by treatment group and overall.

Pharmacokinetic:
Pharmacokinetic parameters were derived using noncompartmental methods employing WinNonlin® Professional version 5.2.1 (Pharsight Corp, Mountain View, CA). Plasma beraprost and BPS-314*d* concentrations were summarized using descriptive statistics (including N, mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum) for each treatment. The PK parameters of C_{max}, T_{max}, C_{min} , AUC_{τ}, C_{avg}, λ_z, $t½$, V_z/F and CLss/F were estimated from plasma samples. Actual elapsed times from dosing were used to estimate all individual PK parameters.

For pharmacokinetic analysis, beraprost and BPS-314*d* concentrations that were below the limit of quantification (BLQ) were assigned a value of zero when they were preceded by quantifiable samples in the initial portion of the profile. Following C_{max}, BLQ values embedded between two quantifiable data points were treated as missing when calculating area under the curve. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) were treated as missing data. When consecutive BLQ concentrations were followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values were excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile. Concentrations assigned a value of missing were omitted from the calculation of descriptive statistics.

Efficacy parameters used for efficacy assessment were used for PD and PK-PD assessments. Change from Baseline for PVR, 6MWD and Borg Dypnea Score were related to the BPS-MR dose and plasma BPS concentrations assuming a direct relationship between effect and dose or concentration.

Safety:
The safety of BPS-MR was evaluated by adverse events for BPS-MR overall and by comparisons across dosing groups. The primary assessment of safety was based on the frequency of treatment-emergent AEs, and on the frequency of clinically notable abnormal vital signs and laboratory values. Changes in laboratory parameters, vital signs and ECGs were summarized and assessed.

SUMMARY OF RESULTS:
All 36 patients were included in the Full Analysis population, to the extent that data were available, per the treatment group randomized at the Baseline visit. Three patients discontinued the study prematurely and were excluded from the Per-Protocol analysis population. In addition, one patient was randomized to iMTD treatment but was incorrectly provided the wrong study drug kit at the Baseline visit, thus the patient is presented in the FD 60 µg treatment for both the Per-Protocol and Safety analysis populations. All 36 patients received BPS-MR and were included in the Safety analysis population. There were no notable baseline differences between the treatment groups.

Doses of BPS-MR ranged from 60-600 µg BID. All patients in the FD 60 µg treatment group achieved 60 µg, 91.7% of the FD 240 µg treatment group achieved 240 µg and the iMTD group patients achieved between 300 µg to 600 µg.

Efficacy:
The study was designed to assess the effect of BPS-MR on hemodynamic parameters in patients with PAH, as measured at Baseline and after 12 weeks of dosing. The Per-Protocol population was the primary population that was analyzed to assess the effect. Point estimates gave no indication of an improvement in hemodynamic parameters at Week 12, as compared to Baseline, for the overall study population or for any of the individual treatment groups, and all 95% confidence intervals contained 0, indicating that none of the estimates were statistically significant. In addition, pair-wise comparisons were made between the three treatment groups to obtain an indication of potential differences in treatment effect among the doses. The pair-wise difference scores and their 95% confidence intervals and p-values did not indicate differences in treatment effect as assessed by hemodynamic parameters among any of the three treatment groups.

Secondary efficacy variables included 6MWD, Borg Dyspnea Score, WHO functional class, and pro-BNP levels. Measurements were made at baseline and at Weeks 6 and 12. 6MWD and Borg Dyspnea Score were measured at peak plasma concentrations at Week 6 and both peak and trough plasma concentrations at Week 12. Analyses were performed to assess improvements from baseline to Weeks 6 and 12. The only secondary variable found to show improvement from Baseline in the overall study population or in any of the individual treatment groups was that the 6MWD, which showed improvements from Baseline to Week 6 peak, Week 12 peak and Week 12 trough in the overall study population and in each of the individual treatment groups. The 6MWD Week 6 peak showed increased improvement with increased doses, suggesting a dose-response effect; however, the 95% confidence intervals about the treatment group means include 0 so the observed mean increases would not be statistically significant. The improvements in 6MWD at Week 12 peak and Week 12 trough did not suggest a clear dose response effect. While the improvements for the FD 60 µg and the FD 240 µg treatment groups for the Week 12 peak and trough were statistically significant, the improvement in the iMTD group was not.

Pharmacokinetic:
A total of 18 (50%) of the 36 patients randomized into the study consented to the optional PK study, the percentage of patients in each treatment group who consented to participate was: 69.2% (9/13) in FD 60 µg, 33.3% (4/12) in FD 240 µg and 45.5% (5/11) in iMTD. All 18 of the patients who consented to the optional pharmacokinetic study had adequate concentration-time data to permit complete pharmacokinetic analysis. BPS-MR doses ranged from 60 to 480 µg among the 18 patients. Noncompartmental PK analysis of plasma BPS and BPS-314*d* concentration-time data was conducted using a steady-state concentration data over the 12-hour dosing interval. The plasma concentration time profiles showed that BPS and BPS-314*d* were relatively slowly absorbed, as anticipated for the modified-release formulation. The T_{max} was variable ranging between 30 minutes and 3 hours for most patients and in several patients a visible secondary peak was present at 4 to 6 hours after dosing. The BPS-314*d* concentration time profiles were very similar to those of BPS but plasma concentrations were approximately one-fourth of the BPS concentrations. Mean C_{max} and AUC_{τ} values were shown to increase with dose, but were not fully dose proportional. There appeared to be higher variability in plasma concentrations in this study compared to results in previous studies. C_{max} and AUC_{τ} did not demonstrate an association with efficacy parameters at 12 weeks. However, the number of patients at the higher doses was few and may have affected the results.

Safety:
A total of 334 treatment emergent adverse events (TEAEs) were observed in 35 (97.2%) patients. There were 91 TEAEs in 13 (100%) patients in the FD 60 µg treatment group, 63 TEAEs in 11 (91.7%) patients in the FD 240 µg treatment group and 180 TEAEs in 11 (100%) patients in the iMTD treatment group. The most common treatment emergent adverse events (occurring in >20% of patients overall) were headache (66.7%), nausea (44.4%), diarrhea (27.8%) and dizziness (22.2%). Patient reports of the more common TEAEs, e.g., headache, nausea and diarrhea, appear to occur more frequently in the iMTD treatment group than the FD treatment groups, as would be expected with a prostanoid therapy dosed to tolerance. The majority (89.5%) of AEs were mild or moderate in intensity. Three patients withdrew from the study due to multiple adverse events. Five SAEs were reported in four patients (right heart failure, headache, pneumonia, coronary artery stenosis and cardiac arrest) and no deaths occurred during the study. No clinically significant changes indicating a treatment effect were observed in clinical laboratory parameters, vital signs, ECGs or physical examinations.

CONCLUSIONS:
Efficacy Conclusions:
In summary, in this small study there was no overall improvement and no clearly identifiable differences among the treatment groups. However, conclusions are limited due to the absence of a placebo treatment group. There was an indication of effectiveness in exercise capacity as patients exhibited improved 6MWD consistently across 12 weeks of treatment with BPS-MR. However, these findings are not robust as no discernible dose response was demonstrated. Overall, the efficacy results are inconclusive for many reasons, mainly due to the limitations in trial design. The study was not adequately powered for hypothesis testing and, in fact, the observed variability for primary endpoints was larger than predicted. Also, by design, was the limitation that the study did not include a placebo-control group to reference observed changes against. It is unknown what would have been observed in patients not dosed with BPS-MR, i.e., were the increases in 6MWD due to BPS-MR or involvement in a clinical study, disease characteristics, etc. Finally, all patients were on a stable course of ERA and/or PDE-5 inhibitor background therapy but further examination of subgroups effects could not be performed due to very small sample sizes in some subgroups. Further study is needed to make a final determination of efficacy for BPS-MR.

Pharmacokinetic Conclusions:
Steady state plasma concentrations of BPS and BPS-314*d* were shown to increase with dose, but were not fully dose proportional. There appeared to be higher variability in plasma concentrations in this study compared to results in previous studies. C_{max} and AUC_{τ} did not demonstrate an association with efficacy parameters at 12 weeks. However, the number of patients at the higher doses was few and may have affected the results.

Safety Conclusions:
BPS-MR was well tolerated and the safety profile was consistent with the experience to date with administration of BPS-IR, BPS-MR and other prostacyclin analogues in patients with PAH. Adverse events were generally those typically encountered with prostanoid therapy, and were generally managed by reductions in the dose of study medication.

FINAL DATE: 06 September 2012