SYNOPSIS

SPONSOR:
Lung Biotechnology Inc.

INDIVIDUAL STUDY TABLE REFERRING TO PARTOF THE DOSSIER:

(FOR NATIONAL AUTHORITY USE ONLY):

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

VOLUME:

NAME OF ACTIVE INGREDIENT:
Beraprost Sodium

PAGE:

STUDY TITLE:
An Open-Label Extension of BPS-MR-PAH-201 in Pulmonary Arterial Hypertension (PAH) Patients

INVESTIGATORS AND STUDY CENTERS:
Multicenter

PUBLICATION (REFERENCE):
Armstrong, D.J., Benza, R.L., Delcroix, M., Gaine, S.P., Naeije, R., Torres, F., Sullivan, E.J., Armstrong, III, D.W. (2010). Clinical pharmacology and safety of beraprost sodium modified release (BPS-MR), an oral twice daily prostacyclin analogue – A phase II study. Am J Respir Crit Care Med., 181, A3360

Oudiz, R.J., Benza, R.L., Delcroix, M., Gaine, S.P., Naeije, R., Torres, F., Sullivan, E.J., Armstrong, III, D.W. (2011). Long-term follow-up in patients dosed with beraprost sodium modified release (BPS-MR) tablets, an oral twice daily prostacyclin analogue. Am J Respir Crit Care Med., 183, A5905

STUDIED PERIOD:
11 March 2009 (first subject enrolled)
26 November 2013 (last subject completed)

STUDY PHASE: 2

OBJECTIVES:
The primary objective of this study was to assess the safety of long-term treatment with BPS-MR tablets in eligible subjects who participated in the BPS-MR-PAH-201 study.

The secondary objectives were to describe the efficacy of BPS-MR tablets on an unencouraged 6-Minute Walk Test (6MWT), the Borg Dyspnea Scale, and Clinical Worsening in eligible subjects who participated in the BPS-MR-PAH-201 study.

METHODOLOGY:
This was an open-label study for subjects who had participated in the BPS-MR-PAH-201 study and volunteered to continue treatment for PAH with BPS-MR tablets. Following enrollment in the study, each subject returned to the clinic 3, 6, and 12 months, and annually thereafter for assessment. Subjects also returned to the study site for a Closeout visit within two weeks of discontinuation/study termination.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):
Eighteen subjects who completed treatment in the BPS-MR-PAH-201 study were enrolled into the study. Eighteen subjects were analyzed for safety, and 18 subjects were analyzed for efficacy.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Subjects who remained on study drug and completed all assessments during the Treatment Phase of Study BPS-MR-PAH-201 were eligible for the BPS-MR-PAH-202 study.

Female subjects had to continue to be physiologically incapable of childbearing or be practicing an acceptable method of birth control (e.g., surgical sterilization, approved hormonal contraceptives, barrier methods [such as condom or diaphragm] used with a spermicide, or an intrauterine device).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER:
BPS-MR 60µg tablets for oral administration. The batches/lots of BPS-MR utilized in the study were A602L, TA01, TA04 and TA06.

DURATION OF TREATMENT:
11 March 2009 to 26 November 2013

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

CRITERIA FOR EVALUATION:
Efficacy:
Efficacy was assessed by measuring the distance walked during an unencouraged 6MWT, the score on the Borg Dyspnea Scale, and Clinical Worsening. While not specified in the protocol, efficacy measurements also included assessment of WHO Functional Class.

Safety:
Safety was assessed by AEs, physical examination, collection of vital signs, tolerability to BPS-MR, clinical laboratory parameters, and electrocardiogram (ECG) findings.

STATISTICAL METHODS:
The safety, tolerability and efficacy data collected in this study were presented descriptively in listings and tables. No inferential statistical analyses were conducted.

Subject characteristics (demographic and other baseline characteristics), medication information and safety data were summarized overall and by study completion status (subjects who withdrew before the Sponsor terminated the study vs. subjects discontinued when the Sponsor terminated the study).

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage of available data for each class of the parameter were presented. Unless otherwise specified, percentages were based on the available data. Quantitative parameters were summarized by the population size (N for sample size and n for available data), the mean, the standard deviation (SD), the median, the minimum and maximum values. Data transformation might have been applied to meet the necessary statistical assumptions for analysis (i.e., normality).

For parameters measured at baseline, the variables of interest were the change from baseline of the original measurements. Unless otherwise specified, all changes from baseline (for all variables where this is applicable) were calculated as follows:

Change from baseline = Post baseline – baseline

SUMMARY OF RESULTS:
Efficacy:
All efficacy results were descriptive; no statistical analysis was conducted.

An evaluation of change from Baseline (initiation of BPS-MR treatment in the BPS-MR-PAH-201 study) to the end of participation in the BPS-MR-PAH-202 study revealed that while a majority of subjects declined and discontinued prematurely, there was a trend towards sustained improvement in 6MWD in a post hoc analysis of a subset of subjects who were ongoing until study termination. Due to an inherent selection bias, this should be interpreted with caution and only be considered in the context of hypothesis generation for future research. The overall observed Borg Dyspnea scores were variable and did not fit any consistent pattern. These results suggest that while there was no discernable trend for improvement in Borg score, there was no significant deterioration observed either. Seven (38.9%) subjects experienced clinical worsening in the study, all of whom discontinued participation before Sponsor's termination of the study. The clinical events comprised of 1 death and initiation of new PAH treatment by 6 subjects, all potentially indicative of disease progression. Given the uncontrolled study design, the small sample size and the variable dosing in this study, it is difficult to assess the impact of the study drug on disease progression. These limitations require further study in a randomized, placebo-controlled trial.

Safety:

- Subjects were exposed to BPS-MR treatment across the BPS-MR-PAH-201 and -202 studies for an average of 1,032.4 days, with subjects terminating prematurely and subjects who were ongoing until study termination exposed for 680.5 and 1472.4 days, respectively.

- During the BPS-MR-PAH-202 study period, all 18 subjects (100%) had at least one TEAE.
- The most common TEAEs (occurring in > 20% of subjects) were upper respiratory tract infection, headache, diarrhea, dizziness, dyspnea, flushing, palpitations, and worsening PAH.
- The TEAEs that were considered certainly, probably, and possibly related to the study drug clustered in gastrointestinal disorders (44.4% subjects), musculoskeletal and connective tissue disorders (44.4%), and nervous system disorders (38.9%).
- Seven subjects (38.9%) experienced 14 SAEs and one subject died of worsening PAH.
- Four subjects (22.2%) discontinued study participation because of AEs.
- Four subjects had hypokalemia and one had anemia that were documented as TEAEs.
- The vital sign and physical examination findings were consistent with the PAH disease condition and did not reveal apparent trends of abnormalities associated with the study drug.
- Eleven (61.1%) subjects had at least one clinically significant ECG abnormality. The findings were not unexpected in PAH subjects.

CONCLUSIONS:

Efficacy Conclusions:

An evaluation of change from Baseline (initiation of BPS-MR treatment in the BPS-MR-PAH-201 study) to the end of participation in the BPS-MR-PAH-202 study revealed that while a majority of subjects declined and discontinued prematurely, there was a trend towards sustained improvement in 6MWD in a post hoc analysis of a subset of subjects who were ongoing until study termination. Due to an inherent selection bias, this should be interpreted with caution and only be considered in the context of hypothesis generation for future research.

A majority of subjects (10/18) prematurely terminated their participation in this study, mostly due to disease progression. Based on the descriptive efficacy results, the overall study population showed an inconsistent pattern of improvement from baseline. However, there was a trend towards sustained improvement in 6MWD in a post hoc analysis of a subset of subjects who were ongoing until study termination. This potential trend towards sustained improvement in 6MWD for a subset of subjects who were ongoing until study termination needs to be verified by further studies in a larger controlled trial.

Safety Conclusions:

BPS-MR was reasonably 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 subjects with PAH. From the initiation of treatment in study BPS-MR-PAH-201 to the end of participation in study BPS-MR-PAH-202, the mean drug exposure of BPS-MR was 1032 days. The most common TEAEs were consistent with those related to prostacyclin class and disease progression and no unknown drug-related safety signals emerged in this study.

FINAL DATE:

25 November 2014