Clinical Trial Protocol: BPS-314*d*-MR-PAH-302

Study Title:	A multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the efficacy and safety of oral BPS-314*d*-MR added-on to treprostinil, inhaled (Tyvaso®) in subjects with pulmonary arterial hypertension
Study Number:	BPS-314*d*-MR-PAH-302
Study Phase:	3
Product Name:	Beraprost Sodium 314*d* Modified Release
IND Number:	111,729
Indication:	Treatment of Pulmonary Arterial Hypertension
Investigators:	Multicenter
Sponsor:	Lung Biotechnology Inc.
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	16 April 2013
Amendment 1:	17 December 2013
Amendment 2	15 October 2014

GCP Statement: This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

LIST OF CONTACTS

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Medical Monitor:	[redacted]
SAE Reporting:	[redacted]

SYNOPSIS

Sponsor: Lung Biotechnology Inc.

Name of Investigational Product: Beraprost Sodium 314*d* Modified Release

Name of Active Ingredient: Beraprost Sodium 314*d* (BPS-314*d*)

Study Title:
A multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the efficacy and safety of oral BPS-314*d*-MR added-on to treprostinil, inhaled (Tyvaso®) in subjects with pulmonary arterial hypertension

Study Number: BPS-314*d*-MR-PAH-302

Study Phase: 3

Primary Objective:
The primary objective of this study is to compare the effect of BPS-314*d*-MR versus placebo added to treprostinil, inhaled (Tyvaso®) on the composite endpoint of time-to-clinical-worsening (TtCW), defined as the time from randomization to the first of any of the following clinical worsening events:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure and requiring intensification of treatment; or
  - Lung or heart / lung transplantation; or
  - Atrial septostomy
- Initiation of a parenteral (infusion or sub-cutaneous) prostacyclin, directly related to worsening PAH (transient use [≤ 7 days] for non-PAH related illness allowable)
- Disease progression (all criteria required):
  - A decrease in six minute walk distance (6MWD) of at least 15% from Baseline (defined as the average of the two 6MWTs performed on sequential days of the Baseline Visit), or being too ill to walk as a consequence of PAH progression, confirmed by six-minute walk tests (6MWT) performed at 2 consecutive visits
  - Worsening of PAH symptoms, which must include either:
    - An increase in WHO Functional Class or
    - Worsening symptoms of right heart failure
- Unsatisfactory long-term clinical response (all criteria below required):
  - Receiving randomized treatment for at least 24 weeks
  - A decrease of at least 15% from Baseline (defined as the average of the two Baseline Visit 6MWTs) in 6MWD, or too ill to walk, directly related to PAH progression, at Week 24 and beyond; at 2 consecutive visits, and
  - Sustained WHO Functional Class III or IV symptoms for at least 24 weeks.

Secondary Objectives:

- To compare the effect of BPS-314*d*-MR versus placebo added to treprostinil, inhaled (Tyvaso®) on the composite endpoint of time-to-clinical-failure (TtCF), defined as the time from randomization to the first of any of the following events:
  - Meets primary endpoint definition of clinical worsening, as confirmed by EAC; or
  - Receiving randomized treatment for at least 24 weeks and has:
    - Lack of sustained improvement from Baseline WHO Functional Class: defined by two consecutive visits of no sustained improvement from Baseline WHO FC, visits may be scheduled or unscheduled; and
    - Lack of sustained improvement from Baseline 6MWD (average at Baseline): defined by two consecutive visits of no sustained improvement from Baseline 6MWD ($\leq$ 0 meters or too ill to walk, directly related to PAH), visits may be scheduled or unscheduled.
- To compare the effects of BPS-314*d*-MR to placebo on changes from baseline to each scheduled study visit, as applicable, for the following measures:
  - 6MWD
  - Borg Dyspnea Score
  - WHO Functional Class
  - NT-pro-BNP levels
- To evaluate the safety of BPS-314*d*-MR based on adverse events, clinical laboratory parameters, electrocardiogram (ECG) findings, physical examination and vital signs.

Exploratory Objectives:

- [redacted]

Study Design:
A multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the efficacy and safety of oral BPS-314*d*-MR added-on to treprostinil, inhaled (Tyvaso®) in subjects with pulmonary arterial hypertension.

Patients who consent to the study will be assessed at the Screening and Baseline Visits to determine eligibility for the study. After the Screening Visit, subjects who consent to the study and are determined to be eligible but are not currently taking inhaled treprostinil will enter a run-in period on inhaled treprostinil to achieve 90 days of experience to ensure drug tolerability before being randomized. During the run-in period, subjects will be prescribed inhaled treprostinil by the Investigator and will receive the Tyvaso® inhalation device and inhaled treprostinil, and training in accordance with specialty pharmacy and the standard procedures of the clinical site. Subjects who consent to the study and are currently taking inhaled treprostinil at the Screening Visit should be randomized into the study as soon as eligibility criteria have been met. Subjects who meet eligibility criteria and who have been treated with inhaled treprostinil for at least 90 days, with 30 or more of the 90 days at a stable dose, at the time of the Baseline Visit

will be randomized into the study using a centralized randomization system, stratified by use of inhaled treprostinil, to either active or placebo study drug. Subjects who are initially ineligible for this study may be reassessed for eligibility following consultation with the Sponsor. Following randomization, the subject, study site staff, the Sponsor and the Event Adjudication Committee (EAC) will all be blinded to the treatment group assignment.

Following the Baseline Visit, subjects will return to the study site at Week 4, Week 8, Week 12 (first Quarterly Visit) and for Quarterly Visits thereafter. During these study visits, subjects will undergo all scheduled efficacy and safety assessments as defined by the protocol and the Schedule of Events (Appendix 1). Between scheduled study visits, the subject will be contacted by phone to assess for possible clinical worsening events and to record any newly occurring or changes to adverse events or concomitant medications. Phone contact should be made weekly (except during study visit weeks) between Baseline and Week 12 (first Quarterly Visit), then monthly between Quarterly Visits through the end of study participation.

An optional hemodynamic assessment will be offered to subjects at selected study sites providing those sites agree to participate in the hemodynamic study and are approved by the Sponsor. Hemodynamic measurements which will be measured/calculated are heart rate, pulmonary arterial pressure (systolic, diastolic and mean), systemic arterial pressure (systolic, diastolic and mean), right atrial pressure, pulmonary capillary wedge pressure, mixed venous oxygen saturation, system arterial oxygen saturation, cardiac output via the Fick or thermodilution methods, will be assessed by Right Heart Catheterization (RHC). For those subjects who consent to this assessment, the RHC procedure will be performed at the Baseline Visit (or within 0-21 days prior) and at the Month 6 Quarterly Visit (or within 7 days before or after).

An optional plasma concentration assessment will also be offered to subjects at study sites that are capable of collecting, processing and storing samples, are approved by the Sponsor and agree to participate. For subjects electing to participate, a trough (15 minutes pre-dose, ± 5 minutes) blood sample will be collected at the Week 4 Visit and four blood samples will be collected during Week 12 (first Quarterly Visit) around the second daily dose of study drug (15 minutes pre-dose, and 15 minutes, 1 hour and 2.5 hours post-dose; ± 5 minutes). If feasible, a sample should be collected for SAEs. Unwillingness to participate in the hemodynamic and/or the plasma concentration assessment sub-studies will not affect the subject's or site's participation in the main study.

Subjects will continue participation in the study until it is formally concluded by the Sponsor. When the Sponsor concludes the study the subjects will return to the study site for an End of Study visit to undergo all scheduled assessments. Subjects who are participating in the study at its conclusion may be offered the opportunity to enroll in a long-term open-label extension study.

In the event that a subject withdraws consent for participation in the study or the Investigator terminates the subject prior to formal study conclusion, the subject will be weaned from study drug and return to the study site for an End of Study Visit to undergo all scheduled assessments.

Study Population: 240 subjects are planned across sites in the U.S. and Israel.

Test Product, Dose, and Mode of Administration:
Beraprost sodium 314*d* Modified Release (BPS-314*d*-MR) tablets, 15 µg for oral, four times daily (QID) administration. Subjects will begin treatment at a dose of 15 µg QID. The dose will be increased by 15 µg QID for a maximum dose of 30 µg QID, 120 µg total daily dose (TDD) as tolerated.

Duration of Treatment:
The maximum duration of treatment for an individual subject is expected to be 3 years. The anticipated date for last subject, last study visit in mid-2016.

Efficacy Assessments:
Efficacy parameters for this study include: clinical worsening, clinical failure, exercise capacity measured by a 6MWT, Borg Dyspnea Score, WHO Functional Class and NT-pro-BNP.

Safety Assessments:
Safety assessments will include the recording of adverse events (AE), clinical laboratory evaluations, ECG findings, physical examination, and vital signs.

Statistical Methods:
The primary efficacy endpoint is clinical worsening confirmed by an independent EAC. The primary efficacy endpoint analysis will evaluate clinical worsening as the time to first clinical worsening (TtCW) event.

Based on the assumptions specified in Section 10.2, a one-year rate of clinical worsening of 45% in the placebo (inhaled treprostinil alone) group, 25% in the BPS-314*d*-MR group (a 20% reduction from treprostinil, inhaled (Tyvaso®) therapy alone), proportional hazards over time, an accrual period of 1.5 years, a 0.01 two-sided significance level, and a total follow-up time of 2.5 years, an exponential maximum likelihood test of equality of survival curves would require 113 events and 116 subjects per treatment group to detect treatment difference at a power of 90% at a 0.01 two-sided significance level (or 97% power at a 0.05 two-sided significance level or approximately 90% power at a 0.05 two-sided significance level to detect a 13% reduction from an inhaled treprostinil rate as low as 30%). Therefore, this study will randomize approximately 240 subjects. Sample size calculations were performed using nQuery Advisor 7.0 using sample size methods for the log-rank statistic based on Lakatos & Lan (1992).

The Sponsor will continuously monitor the overall (pooled) event and drop-out rates during the course of the study. Sample size may be increased during the trial to maintain the planned power at between 80% and 90% and the intended trial duration. Only pooled blinded data will be used to increase sample size.

Date of Original Approved Protocol: 16 April 2013

Amendment 1: 17 December 2013

Amendment 2: 15 October 2014

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse Event
ALB	Albumin
ALT	Alanine Aminotransferase
ALK-P	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BID	Twice Daily
BPS	Beraprost Sodium
BPS-IR	Beraprost Sodium-Immediate Release
BPS-MR	Beraprost Sodium-Modified Release
BPS-314*d*	Beraprost Sodium 314*d*
BPS-314*d*-MR	Beraprost Sodium 314*d*-Modified Release
BUN	Blood Urea Nitrogen
Ca	Calcium
CD4	Cluster of Differentiation 4
CFR	Code of Federal Regulations
CI	Cardiac Index
CL	Chloride
CO_2	Carbon Dioxide
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
ECG	Electocardiogram
ERA	Endothelin Receptor Antagonist
FC	Functional Class
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume at one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HCG	Human Chorionic Gonadotropin
Hct	Hematocrit
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPAH	Idiopathic Pulmonary Arterial Hypertension
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent To Treat
IV	Intravenous
LDH	Lactate Dehydrogenase
LVEDP	Left Ventricular End-Diastolic Pressure
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MR	Modified Release
Na	Sodium
NT-pro-BNP	N-terminal pro-Brain Natriuretic Peptide

OTC	Over the Counter
PAH	Pulmonary Arterial Hypertension
PAPm	Mean Pulmonary Artery Pressure
PP	Per Protocol
PCWP	Pulmonary Capillary Wedge Pressure
PGI2	Prostacyclin
PDE-5i	Phosphodiesterase Type 5 Inhibitor
PK	Pharmacokinetics
PPH	Primary Pulmonary Hypertension
PT	Prothrombin Time
PTT	Activated partial thromboplastin time
PVR	Pulmonary Vascular Resistance
QID	Four Times Daily
RBC	Red Blood Cell (count)
RHC	Right Heart Catheterization
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SQ	Sub-cutaneous
TEAE	Treatment-Emergent Adverse Event
TDD	Total Daily Dose
TLC	Total Lung Capacity
TtCF	Time to Clinical Failure
TtCW	Time to Clinical Worsening
UAE	Unexpected Adverse Event
UPI	Unique Patient Identification
US	United States
USP	United States Pharmacopeia
WBC	White Blood Cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 Pulmonary Arterial Hypertension Overview and Treatment

Pulmonary arterial hypertension (PAH), defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance, is a severe hemodynamic abnormality common to a variety of diseases and syndromes. Elevation in pulmonary arterial pressure causes an increase in right ventricular afterload, impairing right ventricular function and ultimately leading to heart failure and death.

The diagnosis of PAH requires confirmation with a right heart catheterization (RHC). The current hemodynamic definition of PAH is mean pulmonary artery pressure (PAPm) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units (McLaughlin et al, 2009).

Subjects most commonly present in their third and fourth decade; however, PAH may occur at any age. Women are more likely than men to be diagnosed with idiopathic PAH (McLaughin et al, 2009) (Rich et al, 2001). The prognosis of PAH is poor, with an approximately 15% mortality in the first year after diagnosis when treated with modern therapies (Thenappan et al, 2007).

The typical etiologies of PAH include idiopathic, heritable or associated with collagen vascular/connective tissue disease, portal hypertension, infection with the human immunodeficiency virus (HIV), history of cocaine inhalation and exposure to appetite suppressant drugs. An estimated annual incidence of approximately 2 cases per million has been reported for idiopathic PAH (Rich, 1987; Rubin 1997).

There are three major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis. There are a number of metabolic pathways which contribute to these changes that involve vasoactive mediators such as the vasodilators nitric oxide and prostacyclin, and the vasoconstrictor endothelin-1. These substances affect both vascular tone and remodeling leading to their use as pharmacologic targets (Farber, 2004).

Approval of current PAH-specific pharmacotherapies has traditionally been based upon the 6 minute walk test (6MWT). The 6MWT is an assessment of exercise capacity and remains a standard measure of efficacy for trials of investigational medicines in subjects with PAH. However, recent literature has challenged the continued use of 6MWT as a primary endpoint to assess the efficacy of treatments for PAH. Although the 6MWT is still viewed as a valuable tool for measuring clinical efficacy of PAH therapies, a composite endpoint to evaluate the 'time to clinical worsening' is emerging as an alternative, to allow better assessment of long-term efficacy (McLaughlin, 2009).

1.2 Investigational Drug: Beraprost Sodium, BPS-314*d*-MR and Dosing

1.2.1 Beraprost Sodium

Beraprost sodium (BPS) is an orally bioavailable prostacyclin (PGI_2) analogue that was synthesized at the Basic Research Laboratories, Toray Industries, Inc. in 1979. BPS consists of equal amounts of four optical isomers: two diastereomers, each containing a racemic mixture of two optical isomers (BPS-314*d* and BPS-314*l*, and BPS-315*d* and BPS-315*l*). Of these isomers, nonclinical studies have identified BPS-314*d* as the primary pharmacologically active isomer in BPS.

Two formulations of BPS have been developed and studied prior to BPS-314*d*-MR: an immediate release (BPS-IR) formulation and a modified release (BPS-MR) formulation. Marketing approval for BPS-IR was obtained in Japan in 1992 with an indication for improvement of ulcer, pain, and feeling cold accompanying chronic arterial occlusion. In 1999, marketing approval was obtained in Japan to treat primary pulmonary hypertension (PPH). BPS-MR contains the same active substance as BPS-IR (i.e., the racemic mixture of four optical isomers) and obtained marketing approval for the treatment of PAH in Japan in 2007.

The safety and efficacy of BPS has been evaluated in multiple Phase 2 and Phase 3 studies, including a Japanese study of patients with primary pulmonary hypertension or pulmonary hypertension related to collagen vascular disease (Kurumatani, 2009; Kunieda et al, 1997). In this study, the mean change from baseline 6 minute walk distance (6MWD) at Week-12 was 33.4 meters. In addition to this statistically significant improvement in 6MWD, improvements were also noted in several hemodynamic parameters. In a randomized, placebo-controlled European-based study (ALPHABET), the primary endpoint of 6MWD was significantly improved at Week 12 (+25.1 meters) in the BPS treatment group (Galie et al, 2002). However, in a US-based randomized, controlled study, the primary (composite) endpoint of disease progression was not significantly improved at month 12 (Barst et al, 2003). While this study did not achieve statistical significance for the primary analysis, there were strong trends favoring BPS treatment in disease progression as well as 6MWD across all study time points.

1.2.2 BPS-314*d*-MR

As previously noted, BPS consists of four optical isomers, one of which (BPS-314*d*) is primarily responsible for the pharmacologic properties. BPS-314*d* exerts its pharmacologic actions by specifically binding to PGI_2 receptors on smooth muscle, vascular endothelium, and platelets (Nishio, et.al, 1997). This results in vasodilatation, inhibition of platelet aggregation, and antiproliferation (Kurumatani, 2009; Melian & Goa, 2002; Demolis, Robert, Mouren, Funck-Brentano, & Jaillon, 1993). The presence of three optical isomers that carry little or no desired pharmacologic activity is not a requisite feature of BPS drug substance. For this reason, a modified release product containing only the physiologically active BPS-314*d* stereoisomer has been developed.

1.2.3 Dosing

Earlier multiple-dose studies with BPS demonstrated steady state pharmacokinetics (PK) with twice daily (BID) administration, though with considerable fluctuation in the peak and trough plasma concentrations of BPS-314*d*. PK modeling of BPS simulating four times daily (QID) dosing suggests reduction in peak-to-trough fluctuation and more consistent plasma concentrations maintained over a 24-hour period compared to BID dosing. Accordingly, it is postulated that four times daily dosing may enhance daily BPS-314*d* exposure, improving tolerability and potentially therapeutic benefit through mimicking continuous dosing, compared to twice daily dosing.

BPS-314*d* four times daily (QID) dosing has been evaluated in study BPS-314*d*-PAH-MR-101 in healthy volunteers. Consistent peak values were seen between 1.5 to 2 hours after dosing along with an increase in overall BPS-314*d* exposure time.

1.3 Study Rationale

Intravenous prostacyclin therapy prolongs survival in patients with PAH (Barst 1996), and it is considered by many clinicians as the “gold standard” of care. As more therapies have emerged for PAH treatment, prostacyclin therapy has evolved, now with inhaled formulations available and oral formulations under development.

Parenteral prostacyclins are typically reserved until later in the course of disease due to risks and challenges associated with this route of administration.

The rationale for the use of BPS-314*d*-MR as an add-on oral therapy to inhaled treprostinil in subjects with PAH is based upon the quantitative differences observed in their mechanism of action and more specifically their complementary pharmacokinetic profiles.

Inhaled treprostinil and oral BPS exhibit independent pharmacokinetics. Inhaled treprostinil is characterized by rapid absorption and a relatively short half-life, whereas BPS-314*d*-MR demonstrates lower peak plasma concentrations, slower absorption, and a more protracted elimination from the circulation.

Pharmacokinetic modeling of their respective profiles, suggested that the proposed combination of inhaled treprostinil and BPS-314*d*-MR given together, might provide a less invasive, tolerable and clinically beneficial approach to achieving sustained prostacyclin exposure, approximating the desired profile observed with continuous intravenous delivery. Pharmacokinetic modeling used actual PK data for BPS-314*d* from Study BPS-314*d*-MR-PAH-101, evaluating 15 µg and 30 µg dose, QID along with predicted PK data for combination administration with inhaled treprostinil to gain an understanding of the concentration-time profiles and how they might influence the safety and efficacy of both drugs.

1.3.1 Treprostinil, Inhaled (Tyvaso®) Background

Inhaled delivery of treprostinil for the treatment of pulmonary arterial hypertension was developed to deliver selective vasodilatory effects to the lung vasculature while minimizing systemic side effects. Inhaled treprostinil was FDA approved (Tyvaso®) in July 2009 (Tyvaso® US Package Insert) and approved in Israel in 2010.

During the development of inhaled treprostinil, a series of acute and chronic Investigator initiated clinical studies were conducted with inhaled treprostinil sodium to optimize the formulation for inhalation, determine dose response, tolerability, and safety and also to evaluate safety and tolerability when combined with other PAH therapies (Voswinckel 2006; Channick 2006). In the acute dosing studies, administration of inhaled treprostinil sodium resulted in pulmonary vasodilation with excellent tolerability at relatively low doses inhaled in a few breaths. In the chronic studies, administration of inhaled treprostinil sodium resulted in sustained improvement of exercise capacity.

A randomized, double blind, placebo controlled, Phase 3 pivotal study (TRIUMPH-I) was conducted to assess the safety and efficacy of inhaled treprostinil. Two hundred thirty-five subjects who were clinically stable on approved background oral PAH therapy (either bosentan or sildenafil) were randomly allocated to receive either placebo or inhaled treprostinil for 12 weeks. The primary efficacy endpoint was change in exercise capacity at Week 12 as measured by 6 minute walk distance (6MWD). At Week 12, patients receiving inhaled treprostinil had a median improvement of +21.6 meters in 6MWD and patients in the placebo group had a median improvement of +3.0 meters. The Hodges-Lehmann placebo corrected median change from baseline in peak 6MWD was +20.0 meters (p=0.00044). This result was supported by secondary measures related to 6MWD, including similar Week 6 results and maintenance of effect on 6MWD improvement at Week 12 trough, which was measured at least 4 hours after the last dose. The most common adverse events in the treprostinil group were cough (54%), headache (41%), and nausea (19%). There were no remarkable treatment related changes in vital signs, physical examination findings, chest x-rays, pulmonary function tests, or clinical laboratory parameters (McLaughlin 2010).

1.4 Clinical Hypothesis

Treprostinil, inhaled (Tyvaso®) is a registered treatment for PAH with an acceptable safety profile. Oral BPS-314*d*-MR is under development as a prostacyclin for the treatment of PAH. This study is designed to leverage the complimentary mechanistic and pharmacokinetic differences between locally acting inhaled treprostinil and the systemic delivery of BPS-314*d*-MR, creating an effect that more closely approximates parenteral therapy than using either therapy alone. This study will test the hypothesis that combining these therapies will achieve a more effective and longer lasting therapeutic effect, delaying time to clinical worsening.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the effect of BPS-314*d*-MR versus placebo added to treprostinil, inhaled (Tyvaso®) on the composite endpoint of time-to-clinical-worsening (TtCW), defined as the time from randomization to the first of any of the following clinical worsening events:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure and requiring intensification of treatment; or
  - Lung or heart / lung transplantation; or
  - Atrial septostomy
- Initiation of a parenteral (infusion or sub-cutaneous) prostacyclin, directly related to worsening PAH (transient use [≤ 7 days] for non-PAH related illness allowable)
- Disease progression (all criteria required):
  - A decrease in six minute walk distance (6MWD) of at least 15% from Baseline (defined as the average of the two 6MWTs performed on sequential days of the Baseline Visit), or being too ill to walk as a consequence of PAH progression, confirmed by six-minute walk tests (6MWT) performed at 2 consecutive visits
  - Worsening of PAH symptoms, which must include either:
    - An increase in WHO Functional Class or
    - Worsening symptoms of right heart failure
- Unsatisfactory long-term clinical response (all criteria below required):
  - Receiving randomized treatment for at least 24 weeks
  - A decrease of at least 15% from Baseline (defined as the average of the two Baseline Visit 6MWTs) in 6MWD, or too ill to walk, directly related to PAH progression, at Week 24 and beyond; at 2 consecutive visits, and
  - Sustained WHO Functional Class III or IV symptoms for at least 24 weeks.

The Investigator will initially judge whether a suspected clinical worsening event has occurred based on the definition provided above. An Event Adjudication Committee (EAC) will review all suspected clinical worsening events and make a final determination. The EAC will be composed of medical experts in the PAH field, will be independent from the Sponsor, and will assess each event in a blinded fashion. Specific details regarding the Committee's membership, processes and procedures will be outlined in the EAC charter.

Subjects will continue participation in the study until it is formally concluded by the Sponsor. Subjects are expected to remain on study drug throughout their participation in the study unless/until IV or SQ prostanoid therapy is added or in the event of lung transplantation. If a subject discontinues the study for any reason prior to the formal conclusion of the study by the Sponsor, the subject will be asked to return to the clinical for an End of Study (Early Termination) Visit.

Vital status will be assessed for all randomized subjects at the formal conclusion of the study. For randomized subjects who terminate early, vital status will be assessed three months following discontinuation unless the formal conclusion of the study occurs within the three month time period.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the effect of BPS-314*d*-MR versus placebo added to treprostinil, inhaled (Tyvaso®) on the composite endpoint of time-to-clinical-failure (TtCF), defined as the time from randomization to the first of any of the following events:
  - Meets primary endpoint definition of clinical worsening, as confirmed by EAC, or
  - Receiving randomized treatment for at least 24 weeks and has:
    - Lack of sustained improvement from Baseline WHO Functional Class: defined by two consecutive visits of no sustained improvement from Baseline WHO FC, visits may be scheduled or unscheduled; and
    - Lack of sustained improvement from Baseline 6MWD (average at Baseline): defined by two consecutive visits of no sustained improvement from Baseline 6MWD (≤ 0 meters or too ill to walk, directly related to PAH), visits may be scheduled or unscheduled.
- To compare the effects of BPS-314*d*-MR to placebo added to inhaled treprostinil on changes from baseline to each scheduled study visit, as applicable, for the following measures:
  - 6MWD
  - Borg Dyspnea Score
  - WHO Functional Class
  - NT-pro-BNP levels
- To evaluate the safety of BPS-314*d*-MR based on adverse events, clinical laboratory parameters, electrocardiogram (ECG) findings, physical examination and vital signs.

2.3 Exploratory Objectives

[redacted]

3 EXPECTED RISKS/BENEFITS

The risks of BPS-MR and BPS-314*d*-MR appear to be associated with the known risks of the prostanoid class of medication and no new or unique safety concerns have been identified. BPS-MR and BPS-314*d*-MR has been administered to approximately 100 healthy volunteers and to over 50 patients with PAH through Lung Biotechnology Inc. sponsored studies. Total daily doses of BPS 314*d* (calculated as one fourth of the racemic BPS MR dose) ranged from 30 to 570 µg with more than two years of clinical observations in most patients. Data from these studies indicate that BPS is well tolerated and has an acceptable safety profile in the treatment of PAH via the oral route. The most frequently reported treatment emergent adverse reactions (≥ 10%) are headache, nausea, diarrhea, flushing, jaw pain, dizziness, pain in extremity, palpitations, pain, fatigue, vomiting, and hot flush. For more information please refer to the Investigators' Brochure.

The theoretical benefits of BPS-314*d*-MR are based on several factors, including the current understanding of the pathophysiology of the disease, the established pharmacodynamic activities of beraprost (e.g. vasodilation, anti-proliferation, and anti-platelet activity) and the beneficial effects that have been established for other members of the prostanoid class (epoprostenol, treprostinil, and iloprost). Notably, these other routes of administration are associated with certain inherent risks, such as bloodstream infections and local site reactions, which have not been observed and would not be expected with oral administration of BPS-314*d*-MR. In addition to these factors, prior clinical studies conducted by Lung Biotechnology Inc, Toray Industries and others have suggested beneficial effects of BPS-IR and BPS-MR in the treatment of patients with PAH, Section 1.0. In addition, as described in Section 1.3, it is hypothesized that the proposed combination of BPS-314*d*-MR with inhaled treprostinil might provide a less invasive, more tolerable and clinically beneficial approach to achieving sustained prostacyclin exposure, approximating the desired profile observed with continuous intravenous delivery.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This study is designed to evaluate the efficacy and safety of BPS-314*d*-MR in subjects with PAH who are also treated with treprostinil, inhaled (Tyvaso®).

Patients who consent to the study will be assessed at the Screening and Baseline Visits to determine eligibility for the study. After the Screening Visit, subjects who consent to the study and are determined to be eligible but are not currently taking inhaled treprostinil will enter a run-in period on inhaled treprostinil to achieve 90 days of experience to ensure drug tolerability before being randomized. During the run-in period, subjects will be prescribed inhaled treprostinil by the Investigator and will receive the Tyvaso® inhalation device and inhaled treprostinil, and training in accordance with specialty pharmacy and the standard procedures of the clinical site. Subjects who consent to the study and are currently taking inhaled treprostinil at the Screening Visit should be randomized into the study as soon as eligibility criteria have been met. Subjects who meet eligibility criteria and who have been treated with inhaled treprostinil for at least 90 days, with 30 or more days at a stable dose, at the time of the Baseline Visit will be

randomized into the study using a centralized randomization system, stratified by use of inhaled treprostinil, to either active or placebo study drug. See Appendix 2. Two baseline 6MW assessments will be done, one each on consecutive days after randomization has been completed. The mean value of these two assessments will establish the baseline value for later comparisons. Subjects, study site personnel, the Sponsor and the EAC will be blinded to the treatment group assignment.

Following the Baseline Visit, subjects will return to the study site for scheduled study visits at Week 4, Week 8, and Week 12 (first Quarterly Visit) and for scheduled Quarterly Visits thereafter. Subjects will undergo all scheduled efficacy and safety assessments as defined by the protocol and the Schedule of Events (Appendix 1). Between scheduled study visits, the subject will be contacted to assess for possible clinical worsening events and to record any newly occurring or changes to adverse events or concomitant medications. Subject contact should occur weekly for the first twelve weeks (except for study visit weeks) when subjects are becoming familiar with the study drug dosing (including up-titration to the fixed dose, as tolerated) and study procedures. Subjects should be contacted monthly between scheduled Quarterly Visits through the end of study participation.

Subjects will continue the study until it is formally concluded by the Sponsor. Following study conclusion the subject will return to the clinical site for an End of Study Visit to undergo all scheduled assessments. Subjects who are participating in the study at its conclusion may be offered the opportunity to enroll in a long-term open-label extension study.

In the event that a subject withdraws consent for participation in the study or the Investigator terminates the subject from the study the subject will be weaned from study drug and will return to the clinical site for an End of Study (Early Termination) Visit to undergo all scheduled assessments.

4.1.1 Initial Dosing and Safety Assessment

As this study is novel in the use of combined prostanoid therapy, the Sponsor intends to limit study site start-up and subject recruitment activities during the first six months. Study site selection during this period will be based on site experience with prostanoid therapy and the conduct of clinical studies. As such, a minimum number of subjects will initially be exposed to combined prostanoid therapy.

The independent Data Safety Monitoring Board (DSMB), in accordance with the charter, reviews unblinded study data during scheduled review meetings to ensure adequate subject safety to the combined exposure of BPS-314*d*-MR and inhaled treprostinil. No new safety signals have been detected thus far.

4.1.2 Optional Plasma Concentration Assessment

An optional plasma concentration assessment will be offered at study sites that are capable of collecting, processing and storing samples, are approved by the Sponsor and agree to participate. Subjects within those sites will decide if they wish to participate in the optional plasma concentration assessment. Subjects electing to participate will have blood drawn at the following time points: A trough sample (15 minutes pre-dose, ± 5 minutes) at the Week 4 Visit, and four

blood samples (around the second daily dose of study drug) during Week 12 (first Quarterly Visit) at 15 minutes pre-dose, and 15 minutes, 1 hour and 2.5 hours post-dose (± 5 minutes), and, if feasible, for SAEs for measurement of BPS-314*d* and treprostinil plasma concentrations. Dosing times should be documented in the subject's source documentation. Unwillingness to participate in the optional plasma concentration assessment will not affect the subject's or the site's participation in the study.

See Appendix 1 Study Events Table.

4.1.3 Optional Hemodynamic Assessment

An optional hemodynamic assessment will be offered at study sites capable of conducting hemodynamic procedures, are approved by the Sponsor and agree to participate. Subjects at selected research centers may elect to volunteer in the sub-study until the Sponsor closes enrollment. Hemodynamic measurements, such as mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance, will be assessed by right heart catheterization (RHC). For those subjects consenting to the RHC, the procedure will be performed at the Baseline Visit (within 0-21 days prior to the scheduled Baseline Visit) and at the Month 6 Quarterly Visit (or within 7 days before or after). During the Baseline assessment the RHC should be performed prior to study drug dosing. At the Month 6 Quarterly Visit the RHC should be performed at peak study drug blood levels (1-2 hours, ± 15 minutes, after the study drug is administered).

4.2 Rationale for Study Design and Control Group

This is a randomized, double-blind, placebo-controlled study with a parallel group design. Randomization will avoid potential bias in the assignment of subjects to treatment arms and will increase the likelihood that unknown and known subject characteristics (e.g., demographics and disease characteristics) are evenly balanced across the two arms. Double-blind treatment is used to reduce potential bias in dosing, therapeutic decisions, and data handling. The placebo control group allows all subjects to receive similar treatment paradigms and serves as a direct reference group for assessing the effect of study drug. The parallel (control)-group design allows the direct comparison of the two treatment groups with minimal confounding of time and reduces the potential that improvements in measures of efficacy from baseline are merely due to the fact that subjects are involved in a clinical intervention during the course of the study.

4.3 Study Duration and Dates

As the trial is intended to continue until the specified number of Clinical Worsening Events (113) has occurred, the duration of treatment for individual subjects will vary. The maximum duration of treatment for any individual subject is expected to be 3 years, with the anticipated date for last subject last study visit in Q2 2016.

5 STUDY POPULATION SELECTION

5.1 Study Population

The study population is comprised of males and females with PAH, age 18 to 80 years, inclusive, presently on a stable regimen of inhaled treprostinil.

5.2 Inclusion Criteria

The following are inclusion criteria to be enrolled in this study:

1. Male or female, age 18 to 80 years (inclusive).
2. Established diagnosis of pulmonary arterial hypertension that is either idiopathic or familial PAH, collagen vascular disease associated PAH, PAH associated with HIV infection, PAH induced by anorexigens/toxins, or PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥1 years).
3. If HIV positive, has a CD4 lymphocyte count ≥200 cells/mm3 within 30 days of Baseline Visit and is receiving current standard of care anti-retroviral or other effective medication.
4. At the Screening Visit, WHO functional class III or IV and who have declining or unsatisfactory clinical response to current PAH therapy.
5. At the Baseline Visit, WHO functional class III or IV and who have declining or unsatisfactory clinical response to inhaled treprostinil therapy.
6. Able to walk unassisted (oxygen use allowed).
7. A 6-Minute Walk distance (6MWD) of ≥ 100 meters at the Screening Visit.
8. Previous (within five years prior to the Baseline Visit) right heart cardiac catheterization (RHC) with findings consistent with PAH, specifically mean Pulmonary Arterial Pressure (PAPm) ≥25 mmHg (at rest), Pulmonary Capillary Wedge Pressure (PCWP) (or left ventricular end diastolic pressure) ≤15 mmHg, and Pulmonary Vascular Resistance (PVR) >3 mmHg/L/min.[1]
9. Echocardiography excluding any clinically significant left heart disease (e.g. left sided valve disease, wall motion abnormality suggesting of myocardial infarction, left ventricular hypertrophy, etc.).
10. Pulmonary function tests conducted within 12 months before or during the Screening period to confirm the following:
    a. Total lung capacity (TLC) is at least 60% (predicted value); and
    b. Forced expiratory volume at one second (FEV1) of at least 50% (predicted value).
11. Subjects receiving additional FDA approved PAH therapies must be stable on their current dose for at least 30 days prior to the Baseline Visit, apart from modification of anticoagulant or diuretic dosages.
12. Must have completed 90 days of uninterrupted inhaled treprostinil treatment and received a stable dose of inhaled treprostinil for at least 30 days prior to Baseline to be eligible for randomization into the study.
13. Women of child-bearing potential (defined as less than 1 year post-menopausal and not surgically sterile) must be practicing abstinence or using two highly effective methods of contraception (defined as a method of birth control that result in a low failure rate, i.e., less

[1] For conflicting RHCs, the most recent assessment is preferred if relevant in Investigator's judgment.

than 1% per year, such as approved hormonal contraceptives, barrier methods [such as a condom or diaphragm] used with a spermicide, or an intrauterine device). Subject must have a negative pregnancy test at the Screening and Baseline Visits.

14. Willing and able to comply with study requirements and restrictions.

5.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Pregnant or lactating.
2. Has previous experience with beraprost or BPS-314*d* (i.e., BPS-IR, BPS-MR or BPS-314*d*-MR).
3. PAH related to any condition not covered under inclusion criteria, including but not limited to pulmonary venous hypertension, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or chronic thromboembolic pulmonary hypertension.
4. History of interstitial lung disease, unless subject has collagen vascular disease and has had pulmonary function testing conducted within 12 months of the Baseline Visit demonstrating a total lung capacity ≥60% of predicted.
5. Has active hemorrhagic condition (e.g., upper digestive tract hemorrhage, hemoptysis, etc.), or has a pre-existing condition that, in the Investigator's judgment, may increase the risk for developing hemorrhage during the study (e.g., hemophilia). Transient hemorrhage (e.g., epistaxis, normal menstrual bleeding, gingival bleeding, hemorrhoidal bleeding, etc.) will not preclude enrollment.
6. Has received any investigational drug, device or therapy within 30 days prior to the Baseline Visit or is scheduled to receive another investigational drug, device or therapy during the course of the study.
7. Has any musculoskeletal disease or any other disease that would significantly limit ambulation.
8. Has any form of unrepaired or recently repaired (< 1 year) congenital systemic-to-pulmonary shunt other than patent foramen ovale.
9. Evidence of significant coronary arterial disease with symptoms, such as angina.
10. Left sided myocardial disease as evidenced by left ventricular ejection fraction < 40%, or shortening fraction <22%.[2]
11. Has creatinine clearance <30 (using the Crockroft-Gault formula) or requires hemodialysis.
12. Has Childs-Pugh class C liver cirrhosis.
13. Has had previous atrial septostomy.
14. Any other clinically significant illness or abnormal laboratory values (measured during the Screening period) that, in the opinion of the Investigator, might put the subject at risk of harm during the study or might adversely affect the interpretation of the study data.[3]
15. Anticipated survival less than 1 year due to concomitant disease.

[2] Note that subjects in whom abnormal left ventricular function is attributed entirely to impaired left ventricular filling due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) will not be excluded.

[3] Please see Appendix 9 for non-binding Sponsor guidance to be considered when determining a subject's appropriateness for this study.

The Sponsor recognizes that the pulmonary hypertension population is complex and diverse. In order to facilitate enrollment of appropriate subjects to this pivotal trial, Investigators are strongly encouraged to contact the medical director or study team to discuss potential study subjects who have comorbid conditions before enrollment into this study. See Appendix 9 for additional details.

No waivers to entry criteria are allowable in this study. Subjects who are initially ineligible for this study may be reassessed for eligibility after consultation with the Sponsor.

6 STUDY TREATMENT

6.1 Description of Treatment

6.1.1 Study Drug

The study drug is BPS-314*d*-MR, available as 15 µg tablets for oral, four times daily (QID) administration. BPS-314*d*-MR 15 µg tablets contain 15 µg of the drug substance BPS-314*d.*

BPS-314*d*-MR active and matching placebo tablets will be mounted in child resistant Dose Pak® wallet cards. Following randomization, each subject will receive a "starter kit" containing four weekly wallet cards to cover the first 4 weeks of the study. Subjects will then receive weekly bulk wallet cards for the remainder of the study. Each subject will be provided appropriate quantities of study drug at each study visit.

6.1.2 Placebo

To preserve study blinding, the placebo tablets are identical in size, shape, color, and appearance to the BPS-314*d*-MR tablets. The tablet packaging and configuration for placebo tablets are also identical to active tablets.

6.1.3 Treprostinil, Inhaled (Tyvaso®)

For subjects who are currently taking inhaled treprostinil at the Screening Visit and who meet study eligibility criteria, Tyvaso starter kits will be provided by the clinical site during the Baseline Visit. For subjects who are not currently taking inhaled treprostinil at the Screening Visit and continue to remain study eligible, these subjects will be contacted by the specialty pharmacy to schedule device training, supply the Tyvaso® inhalation device and inhaled treprostinil and initiate of Tyvaso® treatment. The specialty pharmacy will maintain regular contact with the study subject until the subject achieves 90 days of experience on inhaled treprostinil. These subjects, when study eligibility criteria are met, will be randomized into the study. Re-supply of Tyvaso will be managed through a specialty pharmacy throughout the duration of the study.

6.2 Treatments Administered

6.2.1 Drug Dosage, Administration and Schedule

After all Baseline assessments are completed and randomization occurs, subjects will be provided a study drug "starter kit" and will take the first dose (one tablet) of study drug. Study drug dosing should occur in conjunction with the treprostinil inhalation dose. All doses of study drug are to be administered in conjunction with inhaled treprostinil. The dosage for Tyvaso®, inhaled treprostinil, according to label, is a maximum of 9 breaths per treatment session QID. The number of breaths per treatment session should remain consistent throughout the subject's participation in the trial. Following the first dose of study drug, the subject should remain in the clinic for approximately 2 - 3 hours for periodic observation by study personnel.

The study drug "starter kit" will supply the subject with study drug for the first four weeks of the study to allow subject to become familiar with the study drug tablets, configuration, packaging, and dosing frequency.

For the first two weeks after randomization, the study drug dose will be one tablet QID. After two weeks on study drug, site personnel will contact the subject to monitor adverse events and, as appropriate, instruct the subject to increase the study drug dose to two tablets QID. At the Week 4 Visit, subjects will receive study drug in bulk dosing cards which will be the study drug packaging and configuration provided for the remainder of the study (see Section 6.9). Study drug will continue to be administered in conjunction with inhaled treprostinil throughout the study. If a subject is unable to tolerate the targeted two tablets QID dosing regimen, it is acceptable to continue in the study on one tablet QID dosing. At the Investigator's discretion, an observed re-challenge may be attempted using the target, two tablets QID dosing, at either the Week 4 or Week 8 Visit.

6.3 Method of Assigning Patients to Treatment Groups

Treatment groups consist of one active and one placebo group. Subjects will be randomly allocated in a 1:1 ratio to one of the two treatment groups. All subjects will be randomized using a centrally administered randomization stratified by use of inhaled treprostinil (specifically, current user at the time of the Screening Visit: yes or no). Randomization codes will be blocked. Block sizes will not be disclosed to Investigators to prevent inferences about possible treatment assignments for current or future subjects. Interactive Randomization Technology (IRT) will be utilized for the central randomization procedure. Once all entry criteria have been met at the Baseline Visit, the Investigator or designee will access the IRT (by phone or by web) to assign the subject a randomization number and the study drug corresponding to the assigned treatment group.

An independent biostatistician, designated by the Sponsor, will review and approve the randomization scheme.

Each screened subject will receive a Unique Patient Identification (UPI) number (a unique 7 character alpha-numeric identifier) consisting of a 3-digit clinical site number, a 3-digit patient number (i.e., subject number), and a hyphen separating these two numbers. The Sponsor will assign site numbers to each clinical site. The patient number will be assigned by the IRT system

as a 3-digit number to each subject in sequential order by clinical site at the time of the Screening Visit. For example: The first subject who is screened at Site 301 will be assigned the UPI of 301-001, the second, 301-002, etc.

The UPI will remain the same throughout the study to identify uniquely the subject's Case Report Forms (CRFs) and other documentation. The UPI of a subject who discontinues from the study for any reason after having been assigned a UPI will not be reassigned.

6.4 Blinding

The study is double-blind. The Investigator and study staff, the subjects, the monitors, the sponsor staff and the EAC will remain blinded to the treatment group allocation until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way to ensure study blinding.

At regular intervals an independent Data Safety Monitoring Board (DSMB) will review unblinded data to ensure subject safety and assess study conduct, as defined in the Charter. To ensure proper blinding of study personnel, an independent statistician will prepare data tables for the DSMB.

6.5 Unblinding Procedures

Study subjects, site medical staff, the Sponsor and the EAC will be blinded to which treatment is being administered to the subject.

Subjects who complete the study may be offered the opportunity to continue taking study drug in a separate open-label continuation protocol. Data will remain blinded until fully reviewed, cleaned and the database locked, at which time the randomization schedule may be formally unblinded by the Sponsor.

Only if a subject's medical condition warrants, such as a medical emergency for which treatment requires knowledge of what study drug was given, may the Investigator break the blind to determine if the subject received active drug or placebo. In most instances of medical emergency, the Medical Monitor must grant prior approval to break the code. However, the code can be broken on the Investigator's request in those cases where the subject's condition is so severe that time would not permit prior approval. In any case, the study monitor must be informed as soon as possible by telephone following the event and by letter explaining the details of the case with accompanying diagnostic reports, where appropriate.

6.6 Concomitant Therapy

All subjects randomized into this study and receiving study drug will be treated with inhaled treprostinil. Subjects must have received a stable dose of inhaled treprostinil for at least 30 days prior to the Baseline Visit. All subjects must have been stabilized on an optimal dosing regimen of conventional PAH therapies (e.g., oral vasodilator, digoxin, oxygen) for at least 30 days prior to the Baseline Visit.

No PAH therapies may be added, removed or dose adjusted during the study, unless a change is required by medical necessity. Initiation, discontinuation or dose changes of anticoagulants, diuretics and non-PAH medications are allowable.

6.7 Restrictions

6.7.1 Prior Therapy

Subjects must meet inclusion and exclusion criteria outlined in Sections 5.2 and 5.3. Prior experience with BPS is exclusionary. No further restrictions on prior or concomitant therapies are required.

6.7.2 Fluid and Food Intake

In general, subjects should follow their normal diet and fluid intake through the course of the study.

For subjects participating in the plasma concentration assessment portion of the study, caffeine or alcohol-containing beverages may not be consumed during the day of the scheduled study visit until the assessment is completed. There are no other restrictions during the day of the assessment.

6.7.3 Patient Activity Restrictions

Subjects should continue their normal activities of daily living during the study.

6.8 Treatment Compliance

Subjects should be reminded to return all unused study drug at each study visit, as well as the empty packages of study drug used. The study coordinator or designee will document the unused study drug and verify that the quantity is consistent with the intended dosing schedule. Based on drug accountability with regard to the subject's prescribed dosage regimen, throughout the study, if non-compliance is suspected, the clinical site personnel will re-educate the subject on the importance of proper adherence to the prescribed dosing. Continued non-compliance may lead to termination of the subject from the study after consultation between the Investigator and the Sponsor.

6.9 Packaging and Labeling

The Sponsor will supply study drug for the study. BPS-314*d*-MR (15 µg) tablets and matching placebo will be mounted in identical child resistant Dose-Pak® wallet cards. At the Baseline Visit following randomization, each subject in the study will be assigned a study drug "starter kit". The subject's "starter kit" will contain 4 weekly wallet cards, one for each of the first four weeks of the study. Each designated wallet card will provide the appropriate daily dosing for the assigned week based on weekly dose escalation (Weeks 1 and 2 dosing card will contain 4 tablets to be taken each day; Weeks 3 and 4 wallet card will contain 8 tablets per day, two for each of the four doses to be taken that day). The "starter kit" will allow the subject time to

become familiar and comfortable with the study drug (tablets, configuration, and packaging), dosing frequency, etc.

At the Week 4, Week 8, Week 12 (first Quarterly Visit) and at Quarterly Visits thereafter, the subject will be issued bulk dosing cards of study drug tablets to provide an adequate supply of study drug for continued use until the subject's next scheduled study visit.

Subjects will be trained by the site personnel on how to open the study drug packages and collect the proper quantity of tablets to make up the prescribed dose. The subject will be instructed on the importance of not damaging the tablets and educated on the importance of compliance with taking the study drug and attending study visits.

Study drug will be labeled in accordance with all applicable U.S. federal to include at least the following information: the sponsor's name and address, protocol number, contents of the Dose-Pak® wallet cards, lot number, directions for use, storage conditions, and FDA caution statement. Each "starter kit" and bulk wallet card label will have a tear-off panel that will be placed into the subject's record.

6.10 Storage and Accountability

Study drug should be stored at approximately 25°C (77°F). Excursions between 15°C and 30°C (59-86 °F) that are experienced in pharmacies, hospitals, and warehouses are acceptable [USP Controlled Room Temperature, 2008]. Study drug should be protected from light and moisture and should not be frozen or exposed to heat. At the clinical site, study drug will be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the Investigators and their designees.

The Sponsor or designee is responsible for assuring that the quantity and quality of the study drug is adequate for the duration of the study.

Study drug should be used in accordance with the protocol, under the supervision of the Investigator or designee (e.g., the clinical site pharmacist or other personnel trained to store and dispense investigational drugs). The Investigator or designee must agree to supply study drug only to subjects enrolled in the study. Subjects must be given the study drug corresponding to their own randomization number.

The study coordinator, pharmacist or appropriate personnel at the investigational clinical site will deliver and retrieve study drug assigned to the subjects at each study visit. Subjects will be instructed to return all study drug, including all empty or partially used packages, to the appropriate study personnel on an ongoing basis.

6.11 Investigational Product Retention at Study Site

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received and comparing it with the accompanying packing list. The Investigator or designee will verify the accuracy of the information on the packing list, sign and date the acknowledgement of receipt, retain a copy in the study file, and acknowledge receipt of the shipment to the Sponsor via the IRT system.

In addition to study drug, study-specific Starter kits (devices and drug) will be dispensed by the study site. Re-supply of inhaled treprostinil will be managed through the specialty pharmacy through the duration of the study.

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records are to be maintained during the study and these records include:

- the amount of study drug received from the Sponsor,
- the study drug batch numbers,
- the amount dispensed to each subject,
- the dates of drug inventory movement,
- the initials of the person responsible for each drug inventory entry,
- the date and amount of unused drug returned from each subject,
- the amount of unused drug on site, available for future subject assignment

At each study visit, site personnel should assess drug dispensed, drug returned (including all empty or partially used wallets), and dosing information to confirm drug accountability and compliance. If any study drug was lost or damaged, its disposition should be documented in the subject's source documents as well as the in the IRT system. Accurate recording of study drug administration (including dispensing and dosing) will also be made in the appropriate section of the source documents and IRT system. Once a representative from the Sponsor has confirmed drug accountability for each subject, the Sponsor or its designee will instruct the Investigator on the return of all used and unused study drug.

7 STUDY PROCEDURES

7.1 Informed Consent

The Investigator and/or designee will explain study procedures to potential subjects prior to participation in this study. Those who agree to participate will sign and date the Institutional Review Board (IRB) approved Informed Consent Form (ICF) after reading the document and after the Investigator has answered any questions about the study. The Investigator and/or designee will also sign and date the ICF. Subjects will be given a copy of the ICF.

7.2 Medical History

Medical and surgical history will be collected from each subject during the Screening Visit and updated at the Baseline Visit, as applicable. The medical and surgical history will focus on relevant and significant past or present illnesses. The history will cover relevant areas such as head, eyes, ears, nose, and throat, cardiovascular; respiratory; abdomen; gastrointestinal/liver; kidney/urinary, genitalia/reproductive, musculoskeletal; endocrine, history of allergies or idiosyncratic responses to drugs, psychiatric, neurological; dermatologic, and extremities. This information will be used for assessing whether subject meets inclusion/exclusion criteria.

Current prescription and/or nonprescription medications will be assessed and entered in the concomitant medications CRF to enable tracking of any changes to prior medications which occur during the study. Nonprescription medications include vitamins and herbal preparations.

7.3 Physical Examination

A physical examination will be conducted by a qualified study clinician at Screening, Baseline, Study Visit Week 4, Week 8, Week 12 (first Quarterly Visit), at Quarterly Visits and at the End of Study Visit. Physical findings within the following categories will be assessed as relevant: mental status/mood; neurological; head, eyes, ears, nose, and throat; cardiovascular; respiratory; abdomen; gastrointestinal; musculoskeletal; hair and skin; and extremities. Any values judged by the Investigator to be clinically significant abnormal changes after subject's consent to the study should be recorded on the Adverse Event CRF as an AE.

7.4 Vital Signs

Vital signs will be measured at all scheduled study visits. Subject height will be recorded at Screening and weight will be recorded at each study visit. Systolic and diastolic blood pressure, heart rate, respiratory rate and temperature will be measured after at least 5 minutes of seated rest.

Any values judged by the Investigator to be clinically significant abnormal changes after subject's consent to the study should also be recorded on the Adverse Event CRF as an AE.

7.5 PAH History

Based on the subject's medical records, the PAH etiology and date of diagnosis will be entered into the CRF. Types of PAH allowed into the study are: idiopathic or familial, collagen vascular disease associated PAH, PAH associated with HIV infection, PAH induced by anorexigens/ toxins, or PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥1 years). This information will be used for assessing inclusion and exclusion criteria.

7.6 Pregnancy Test

A positive pregnancy test will exclude the subject from participation in the study. For females of childbearing potential, a urine pregnancy test will be performed at the Baseline Visit and a serum test at all other study visits.

7.7 ECG Assessment

Twelve-lead ECGs will be recorded following at least a 5-minute rest in the semi-recumbent position at the following visits: Screening, Baseline, Week 4, Week 8 (optional), Week 12, Quarterly and End of Study. At the Screening (as applicable) and Baseline Visits, ECGs should be measured within 1-2 hours, ± 15 minutes, after second or third dose of inhaled treprostinil. At all subsequent visits, e.g. Week 4 and beyond, ECGs should be measured within 1-2 hours, ± 15 minutes, after second or third dose of inhaled treprostinil and study drug combined.

Recordings will include lead II as a rhythm strip and contain at least 5 QRS complexes. ECG parameters collected include heart rate, as well as PR interval, QT interval, QTc interval, QRS duration, and any clinically significant abnormalities.

Any values judged by the Investigator to be clinically significant abnormal changes after subject's consent to the study should also be recorded on the Adverse Event CRF as an AE.

7.8 Clinical Laboratory Tests

7.8.1 Laboratory Parameters

Blood and urine specimens for the measurement and evaluation of serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP will be collected at Screening, Baseline, Week 4, Week 8, Week 12, at Quarterly Visits and at the End of Study Visit.

Subjects will be in a seated or supine position during blood collection. Clinical laboratory parameters will include those presented in Table 1. Results will be forwarded to the sites and electronically transferred into the study database. Eligibility for the study will be based upon laboratory parameters collected during the Screening phase of the study.

Any laboratory test result that the Investigator considers clinically significant may be repeated to rule out laboratory error. For tests where a persistent abnormality is considered to be drug related, repeat analyses will be performed until the cause is determined and either a return to normality occurs or the Investigator deems the abnormality to be of no clinical significance. Any values judged by the Investigator to be clinically significant abnormal changes after subject's consent to the study should also be recorded on the Adverse Event CRF as an AE.

Table 1 List of Laboratory Tests

Hematology:
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
  - Neutrophils (Total %)
  - Lymphocytes (Total %)
  - Monocytes (Total %)
  - Eosinophils (Total %)
  - Basophils (Total %)
 	
Urinalysis:
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
 	
Pregnancy test:
- Urine human chorionic gonadotropin (hCG) for females of childbearing potential – Baseline Visit only; Serum pregnancy test at all other scheduled visits
	Serum Chemistry:
	- Albumin (ALB)
	- Alkaline phosphatase (ALK-P)
	- Alanine aminotransferase (ALT; SGPT)
	- Aspartate aminotransferase (AST; SGOT)
	- Blood urea nitrogen (BUN)
	- Calcium (Ca)
	- Carbon dioxide (CO_2)
	- Chloride (Cl)
	- Creatinine
	- Gamma-glutamyl transferase (GGT)
	- Globulin
	- Glucose
	- Lactate dehydrogenase (LDH)
	- Phosphorus
	- Potassium (K)
	- Sodium (Na)
	- Total bilirubin
	- Direct bilirubin
	- Total protein
	- Uric acid
	- NT-Pro-BNP (not required to determine study eligibility)
	
	Coagulation:
	- Prothrombin time (PT)
	- Activated partial thromboplastin time (PTT)

7.8.2 Sample Collection, Storage, and Shipping

Analysis of laboratory specimens listed in Table 1 will be performed by a certified central laboratory. Results will be forwarded to the sites and electronically transferred into the study database. Detailed handling and shipping procedures will be provided in the laboratory manual to site personnel. All laboratory data results will be maintained as source documentation in the subject medical record.

7.9 Dispensing Study Drug and Tyvaso®

Study site personnel will dispense appropriate supplies of study drug to subjects at each study visit. Subjects will be instructed to return all study drug, including empty or partially used packages, to the appropriate study personnel on an ongoing basis.

For subjects who are currently taking inhaled treprostinil at the Screening Visit and who meet study eligibility criteria, Tyvaso starter kits will be provided by the clinical site during the Baseline Visit. For subjects who are not currently taking inhaled treprostinil at the Screening Visit and continue to remain study eligible, these subjects will be contacted by the specialty pharmacy to schedule device training, supply the Tyvaso® inhalation device and inhaled treprostinil and initiate of Tyvaso® treatment. The specialty pharmacy will maintain regular contact with the study subject until the subject achieves 90 days of experience on inhaled treprostinil. These subjects, when study eligibility criteria are met, will be randomized into the study. Re-supply of Tyvaso will be managed through a specialty pharmacy throughout the duration of the study.

Study drug dosing, including missed doses, during the study will be recorded in the appropriate CRF.

Detailed study drug disposition records will be maintained as previously described (Section 6.11).

7.10 Efficacy Assessments

7.10.1 Clinical Worsening

Clinical worsening will be assessed from randomization to the first of the following events:

To compare the effects of BPS-314*d*-MR to placebo in patients receiving inhaled treprostinil (Tyvaso®) on time-to-clinical-worsening (TtCW) defined as the time from randomization to the first of any of the following clinical worsening events:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure and requiring intensification of treatment; or
  - Lung or heart / lung transplantation; or
  - Atrial septostomy
- Initiation of a parenteral (infusion or sub-cutaneous) prostacyclin, directly related to worsening PAH (transient use [≤ 7 days] for non-PAH related illness allowable)
- Disease progression (all criteria required):
  - A decrease in six minute walk distance (6MWD) of at least 15% from Baseline (defined as the average of the two 6MWTs performed on sequential days of the Baseline Visit), or being too ill to walk as a consequence of PAH progression, confirmed by six-minute walk tests (6MWT) performed at 2 consecutive visits

  - Worsening of PAH symptoms, which must include either:
    - An increase in WHO Functional Class or
    - Worsening symptoms of right heart failure
- Unsatisfactory long-term clinical response (all criteria below required):
  - Receiving randomized treatment for at least 24 weeks
  - A decrease of at least 15% from Baseline (defined as the average of the two Baseline Visit 6MWTs) in 6MWD, or too ill to walk, directly related to PAH progression, at Week 24 and beyond; at 2 consecutive visits, and
  - Sustained WHO Functional Class III or IV symptoms for at least 24 weeks.

The Investigator will initially judge whether a suspected clinical worsening event has occurred based on the definition provided above. An EAC will be established by the Sponsor to review all suspected clinical worsening events and make a final determination. The Committee will be composed of medical experts in the PAH field, will be independent from the Sponsor, and will assess each event in a blinded fashion. Specific details regarding the Committee's membership, processes and procedures will be outlined in the EAC charter.

Subjects will continue their participation in the study until a clinical worsening event is confirmed by the EAC or the study is formally concluded by the Sponsor.

7.10.2 Clinical Failure

Clinical failure will be assessed from randomization to the first of the following events:

- Meets primary endpoint definition of clinical worsening, as confirmed by EAC, or
- Receives randomized treatment for at least 24 weeks and has:
  - Lack of sustained improvement from Baseline WHO Functional Class: defined by two consecutive visits of no sustained improvement from Baseline WHO FC, visits may be scheduled or unscheduled; and
  - Lack of sustained improvement from Baseline 6MWD (average at Baseline): defined by two consecutive visits of no sustained improvement from Baseline 6MWD (≤ 0 meters or too ill to walk, directly related to PAH), visits may be scheduled or unscheduled.

The Sponsor will derive the composite measures of clinical failure and TtCF from the data collected per the protocol. Unlike clinical worsening, neither a specific Investigator's assessment for clinical failure nor an EAC confirmation of suspected events will occur.

As above, subjects are expected to continue their participation in the study until a clinical worsening event is confirmed by the EAC or the study is formally concluded by the Sponsor.

7.10.3 Six Minute Walk Test

The 6MWT, which is designed to evaluate exercise capacity associated with carrying out activities of daily living, will be performed to evaluate potential treatment effects on exercise capacity at all scheduled study visits: Screening, Baseline (two 6MWTs, taken on consecutive days, before the start of study drug dosing), Weeks 4, 8, 12, Quarterly Visits and at the End of Study Visit. At the Screening Visit, the 6MWT should be measured within 1-2 hours, ± 15

minutes, after second or third dose of inhaled treprostinil or approximately 4-6 hours, ± 15 minutes, after waking if the subject has not begun inhaled treprostinil treatment yet. At both days of the Baseline Visit (Days 1 and 2), the 6MWT should be measured within 1 hour, ± 15 minutes, before the second or third dose of inhaled treprostinil. At all subsequent visits, e.g. Week 4 and beyond, the 6MWT should be measured within 1-2 hours, ± 15 minutes, after second or third dose of inhaled treprostinil and study drug combined. Appendix 3 presents the standardized procedures for administration of the 6MWT.

At any point in the trial, if a subject is assessed for the 6MWT while using oxygen therapy then all future 6MWTs should be conducted with the same oxygen flow.

7.10.4 Borg Dyspnea Score

The modified 0–10 category-ratio Borg scale consists of an 11-point scale with which the subjects rate the maximum level of dyspnea they experienced during the 6MWT. Scores range from 0 (for the best condition) and 10 (for the worst condition) with nonlinear spacing of verbal descriptors of severity corresponding to specific numbers. Subject may choose the number or the verbal descriptor to reflect presumed ratio properties of sensation or symptom intensity. Appendix 4 presents the standardized administration details for the Borg Dyspnea Score procedures the clinical site personnel should use. Each subject will provide a rating of dyspnea immediately following the 6MWT.

7.10.5 WHO Functional Class

At the Screening Visit the Investigator will classify the subjects for PAH severity using the World Health Organization (WHO) Functional Class. Assessment for WHO Functional Classification for PAH should be made at Screening, Baseline, Week 4, Week 8, Week 12 (first Quarterly Visit), at Quarterly Follow-up Visits and at the End of Study Visit. See Appendix 5 for categories.

7.10.6 NT-pro-BNP

Blood samples to be used for Plasma N-terminal pro-Brain Natriuretic Peptide (NT-pro-BNP; a biomarker of congestive heart failure) measurement will be collected at Screening, Baseline, Week 4, Week 8, Week 12 (first Quarterly Visit), at Quarterly Follow-up Visits, and at the End of Study Visit.

7.11 Other Assessments

7.11.1 Optional Plasma Concentration Assessment

An optional plasma concentration assessment will be offered at study sites that are capable of collecting, processing and storing samples, are approved by the Sponsor and agree to participate. Subjects electing to participate will have blood drawn at the following time points: A trough (15 minutes pre-dose, ± 5 minutes) blood sample at the Week 4 Visit, four blood samples (around the second daily dose of study drug) during Week 12 Visit at 15 minutes pre-dose, and 15 minutes, 1 hour and 2.5 hours post-dose (± 5 minutes), and, if feasible, for SAEs for measurement of BPS-314*d* and treprostinil plasma concentrations. Patients electing to participate

should be contacted one week (seven days) prior to the Week 4 and Week 12 Visits as a reminder to record their Tyvaso® and study drug dosing times during the week leading up to the study visit.

Blood sample collection kits and a laboratory operations manual will be provided to each site.

The blood samples will be handled and shipped according to the procedure outlined in Appendix 6. Given the implications for unblinding, the Sponsor will only receive plasma concentration results after the study has been officially completed and unblinded.

Unwillingness to volunteer for the optional plasma concentration assessment will not affect the subject's participation in the study.

7.11.2 Optional Hemodynamic Measurement Assessment

The objective of the optional hemodynamic assessment is to assess hemodynamic changes corresponding to treatment with BPS-314*d*. The optional hemodynamic assessment will be offered to all study subjects at study sites capable of conducting hemodynamic procedures and to those who are approved by the Sponsor and agree to participate. Subjects at the selected research centers will be offered the opportunity to volunteer in the assessment until the Sponsor closes enrollment. Hemodynamic measurements will be assessed by Right Heart Catheterization (RHC) as outlined in Appendix 8. For those subjects who consent to this assessment, the RHC procedure will be performed at the Baseline Visit (within 0-21 days prior to the scheduled Baseline Visit) and at the Month 6 Quarterly Visit (or within 7 days before or after). During the Baseline assessment the RHC should be performed prior to study drug dosing. At the Month 6 Quarterly Visit, the RHC should be performed at peak study drug blood levels (1-2 hours, ± 15 minutes, after the second or third dose of study drug administration).

Unwillingness to volunteer for the hemodynamic assessment will not affect the subject's or site's participation in the main study.

7.12 Adverse Events Assessments

7.12.1 Performing Adverse Events Assessments

The clinical site personnel will monitor all AEs throughout the study, from the time of the subject's Informed Consent signature until the end of the subject's study participation (see Appendix 1). At all study site visits and during phone calls to the subject by clinical site personnel, reports of AEs will be elicited by a verbal probe ("How are you feeling?"). Subjects will be encouraged to contact the clinic to report an AE at any time. Appropriate measures, including medical intervention and/or procedures, will be instituted if clinically indicated at the discretion of the Investigator.

All AEs occurring during the study must be documented in the subject's source documents and in the CRFs for AEs. For each AE, the Investigator will evaluate the intensity and seriousness, as well as the relationship to study drug and/or background therapies. Information relating to the AE, such as onset and cessation date and times, escalation, frequency, action taken, and outcome will also be documented (see Appendix 7) in the CRFs for AEs. Where possible, AEs should be

recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the CRFs for AEs, not the individual signs and symptoms.

7.12.2 Timing

Subjects with AEs that are ongoing at the subject's last study visit must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. AEs that are reported during the 7 days following the subject's last study visit will be recorded in the CRFs for AEs and followed until resolution or for up to the 30 days after the subject's last study visit, whichever comes first. All AEs that are ongoing after follow-up for 30 days will be recorded as ongoing in the CRF. The Investigator is expected to provide or arrange appropriate supportive care for any subject with ongoing AE(s).

Serious adverse events (SAEs) should be followed until they resolve or the event or their sequelae stabilize. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. Such supplementary assessments may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The CRFs for AEs should be updated with any new or additional information as appropriate.

If the subject reports or the Investigator learns of any new SAE that occurs up to 30 days after the subject's last study visit, the clinical site personnel will ensure that these data are recorded on the AE CRF.

For each reported AE the Investigator is responsible for grading its severity (or intensity) according to the criteria outlined in Appendix 7 and recording these data in the subject's source documents and on the CRF for AEs.

7.12.3 Severity

For each reported AE the Investigator is responsible for grading its severity (or intensity) according to the criteria outlined in Appendix 7 and recording these data in the subject's source documents and on the AE page of the CRF.

7.12.4 Relationship

For each AE reported, the Investigator is responsible assessing the likelihood that an AE is causally related to the study drug according to the criteria outlined in Appendix 7. These data must be recorded in the subject's source documents and on the AE page of the CRF.

7.12.5 Expectedness

The known and expected AEs due to the use of BPS-314*d*-MR are described in the current Clinical Investigators' Brochure.

7.12.6 Clinical Laboratory Adverse Events

The Investigator is responsible for reviewing the results of all laboratory tests as they become available. Abnormal laboratory values or test results should not generally be considered AEs, unless the Investigator deems the values or results a clinically significant abnormal change from baseline. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. Assessment of signs or symptoms or requirement for therapeutic intervention should be considered when determining clinical significance. Record clinically significant laboratory values on the CRFs for AEs using an appropriate diagnostic description.

7.12.7 Serious Adverse Events

7.12.7.1 Definition

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.12.7.2 Reporting Serious Adverse Events

All SAEs, as defined in Appendix 7 and regardless of expectedness or causality, must be reported to the pharmacovigilance monitor within 24 hours of the Investigator's knowledge of an SAE occurrence through submission of the SAE form in the CRFs. An updated SAE CRF should be submitted to the pharmacovigilance monitor upon receipt of the any new or revised information. The Investigator or Sponsor (if appropriate) must also notify their Institutional Review Board (IRB), Independent Ethics Committee (IEC) and/or other local equivalent body of the SAE, including any follow-up information. Copies of each report and documentation of IEC/IRB/local equivalent body notification and receipt will be kept in the Clinical Investigator's Study File.

7.12.8 Treatment-Emergent Adverse Events

Treatment-emergent AEs will be defined as events that are newly occurring or worsening from baseline following treatment with study drug.

BPS-314*d* is the active component of BPS-MR. The most frequently reported treatment emergent adverse reactions (≥ 10%) are headache, nausea, diarrhea, flushing, jaw pain, dizziness, pain in extremity, palpitations, pain, fatigue, vomiting, and hot flush.

The most common adverse reactions (≥ 10%) with Tyvaso are cough, headache, nausea, dizziness, flushing (blushing of the skin), throat irritation, pharyngolaryngeal (pharynx and the larynx) pain and diarrhea.

Prostacyclins, as a class, may increase the risk of bleeding and hypotension.

7.12.9 Overdose

Any clear or significant overdose, in the Investigator's judgment, that occurs during study participation must be reported to the pharmacovigilance monitor using an SAE form (see Section 7.12.7.2) within 24 hours of learning of its occurrence and must be followed to determine the outcome. In addition, the data must be entered on the CRFs for AEs and be fully retrievable by the Sponsor within 48 hours following the event. A subject who experiences an overdose may be withdrawn from the study at the discretion of the Investigator and the Medical Monitor.

7.12.10 Pregnancy

All subjects must be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant while participating in this study. Any pregnancy that occurs during study participation must be reported to the Medical Monitor using the Pregnancy Notification form within 24 hours of learning of its occurrence.

All pregnancies must be followed to determine outcome and must be reported to the pharmacovigilance monitor using the Pregnancy Reporting form within 24 hours of learning of the outcome. A subject who becomes pregnant will be discontinued from the study and the Investigator or designee should make all reasonable efforts to track the outcome of the pregnancy.

If a male subject's female partner becomes pregnant the Medical Monitor must be notified and all efforts should be made to track the outcome of the pregnancy with the same notification made to the Medical Monitor as defined above.

7.13 Concomitant Medication Assessments

Concomitant therapy includes any prescription and/or nonprescription medications taken in combination with study drug. All concomitant medications will be followed during the study and entered on the appropriate page of the CRF. Nonprescription medications include vitamins and herbal preparations.

7.14 Removal of Patients from the Trial or Study Drug

Subjects should be encouraged to complete the study, remain on study drug (even if only one tablet QID dosing is tolerated) until the conclusion of the study and to complete all required study assessments. However, a subject may voluntarily withdraw or be withdrawn from study at any time for reasons including, but not limited to the following:

- The subject wishes to withdraw from further participation;
- A serious or life-threatening adverse event occurs;
- The subject is noncompliant with the requirements of the protocol, or;
- The subject's behavior is likely to undermine the validity of his/her results.

If a subject is discontinued from the study, the Investigator must provide an explanation in the source documents and record the reason for termination in the appropriate CRF for that subject. The subject should be weaned from study drug prior to termination from the study. The Investigator should make every effort to perform all scheduled evaluations prior to withdrawal of study drug. A subject who discontinues because of an AE will be followed until the Investigator determines the AE has resolved, is no longer considered clinically significant, has been determined to be stable and unlikely to further evolve, or for 30 days, whichever comes first.

If a subject fails to return to the clinical site, the clinical site staff must document at least two phone calls were made to the subject, and a registered letter was sent to them requesting return of study drug and contacting study personnel before considering them lost to follow-up.

The study may be stopped at any time if continuation of the study represents a serious medical risk to the subjects. Such risk may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

When a subject withdraws from the study, the site should enter the reason for discontinuation into the subject’s source documents and in the subject’s CRF.

Vital status will be assessed for all randomized subjects at the formal conclusion of the study. For randomized subjects who terminate early, vital status will be assessed three months following discontinuation unless the formal conclusion of the study occurs within the three month time period. Study site personnel will record vital status information in source documents and record relevant information on appropriate CRFs.

7.15 Access to Open-Label Extension Study

Subjects who successfully complete this BPS-314*d*-MR-PAH-302 study as scheduled per protocol (i.e., treated until unblinding of the study) may be offered the opportunity to enroll in a long-term open-label extension study at the conclusion of the study.

Subjects who will not enroll in an open-label continuation protocol will be weaned off of study drug in a blinded manner. The maximum decrement should not exceed one tablet QID per day and the minimum decrement should be one tablet QID per week.

8 STUDY ACTIVITIES

Please refer to Appendix 1 for Study Time and Events table.

8.1 Screening Visit

A Screening Visit will occur from 3 days up to 120 days prior to the scheduled Baseline Visit. The following activities, after obtaining voluntary informed consent, will be performed at this visit:

- Evaluate Inclusion/Exclusion Criteria
- Record demographic information
- Record PAH history
- Record medical history
- Perform a physical examination
- Record WHO Functional Class
- Record vital signs after five minutes of seated rest
- Record a 12-Lead ECG following at least a 5-minute rest in a semi-recumbent position (if subject is on inhaled treprostinil, conduct ECG within 1-2 hours, ± 15 minutes, after the second or third dose of inhaled treprostinil)
- Conduct an unencouraged 6MWT (if subject is on inhaled treprostinil, between 1-2 hours, ± 15 minutes, after second or third dose of inhaled treprostinil or, if subject is Tyvaso naïve, approximately 4-6 hours, ± 15 minutes, after waking)
- Record Borg Dyspnea Score
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- Obtain serum pregnancy test for women of childbearing potential
- Record medications
- Record AEs

8.2 (2-Day) Baseline Visit Procedures

A 2-day Baseline Visit will be performed between 3-120 days after the Screening Visit. The Baseline Visit should occur when the subject achieves a minimum of 90 days of experience on inhaled treprostinil, with at least 30 of the 90 days at a stable dose.

Baseline Visit Day 1
Prior to randomization:

- Update medical history, as necessary
- Perform a physical examination
- Record WHO Functional Class
- Record vital signs after five minutes of seated rest

- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP); NT-pro-BNP not required to determine eligibility
- Obtain urine pregnancy test for women of childbearing potential
- Update prior and concomitant medications, as necessary
- Confirm Inclusion/Exclusion Criteria
- For optional RHC assessment: For subjects who consent to participate, RHC should be performed within 1-2 hours, ± 15 minutes, after the second or third dose of inhaled treprostinil. RHC may be performed within 0-21 days prior to the scheduled Baseline Visit.

Randomization and following:

- Randomize subject in IRT
- Conduct an unencouraged 6MWT within 1 hour, ± 15 minutes, before the second or third dose of inhaled treprostinil
- Record Borg Dyspnea Score
- Administer second dose of inhaled treprostinil
- Record a 12-lead ECG following at least a 5-minute rest in a semi-recumbent position between 1-2 hours, ± 15 minutes, after second or third dose of inhaled treprostinil
- Record concomitant medications
- Record AEs

Baseline Visit - Day 2

- Conduct an unencouraged 6MWT within 1 hour, ± 15 minutes, prior to second or third daily dose of inhaled treprostinil and study drug
- Record Borg Dyspnea Score
- Provide Tyvaso® starter kits, as appropriate for the subject, and document any training
- Provide study drug starter kit supply (Provide training/instructions for subject participation in the study: study drug (packaging, storage, accountability, etc.), daily QID dosing for study drug and inhaled treprostinil, etc.), regular telephone calls, date of next study visit and importance of attending all study visits, etc.
- Observe and record study drug and inhaled treprostinil co-administration. Subjects should remain in the clinic for a 2-3 hour observation period following dosing to assess for any AEs
- Record concomitant medications
- Record AEs
- For subjects electing to participate in the optional plasma concentration assessment, provide Week 4 and Week 12 (first Quarterly Visit) drug dosing record.

8.2.1 Study Drug Administration

Study drug administration will occur after all Baseline assessments, including the second 6MWT, and randomization are complete. Study drug will be dosed immediately before or after the subject administers dosing of inhaled treprostinil. Subjects should remain in the clinic for a 2-3 hour observation period following dosing to assess for any AEs. Following dosing the following procedures should occur:

- Record time and dose of study drug and inhaled treprostinil administration
- Provide training/instructions for subject participation in the study: study drug (packaging, storage, accountability, etc.), daily QID dosing for study drug and inhaled treprostinil, etc.), regular telephone calls, date of next study visit and importance of attending all study visits, etc.
- Subjects will be directed to call the clinical site coordinator or Investigator immediately if they experience a worsening of the disease-related symptoms or at any time to discuss study related issues

8.2.2 Phone Calls

Subject should be contacted weekly between the Baseline Visit through Week12 except for weeks with study visits, then monthly between Quarterly Visits through the end of study participation. After two weeks on study drug, the subject should be contacted to assess drug tolerability and instructed to increase the study drug dose by one tablet QID for a fixed dose of two tablets QID through the duration of the study. If a subject is unable to tolerate the two tablets QID dosing regimen, after appropriate assessment (e.g. OTC use to alleviate headache), and at the Investigator's discretion, the subject may continue in the study on one tablet QID dosing. An observed re-challenge may be attempted using the target, two tablets QID dosing, at either the Week 4 or Week 8 Visit.

During phone calls to the subject, the following information should be recorded:

- Record time and dose of study drug and inhaled treprostinil administration
- Assess and record AEs
- Record concomitant medications
- Assess clinical worsening

Subjects participating in the plasma concentration assessment should be contacted one week (seven days) prior to Week 4 and Week 12 (first Quarterly Visit) as a reminder to record their inhaled treprostinil and study drug dosing times during the week leading up to the visit.

8.3 Week 4 Procedures

Subjects will return to the study site at Week 4 (± 3 days) for the following procedures:

- Perform a physical examination
- Record WHO Functional Class

- Record a 12-Lead ECG following a 5-minute rest in a semi-recumbent position (conduct ECG within 1-2 hours, ± 15 minutes, following the second or third daily dose of study drug)
- Record vital signs after five minutes of seated rest
- Conduct an unencouraged 6MWT (1-2 hours, ± 15 minutes, after the second or third dose of inhaled treprostinil and study drug)
- Record Borg Dyspnea Score
- Assess clinical worsening
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- Obtain serum pregnancy test for women of childbearing potential
- OPTIONAL Plasma Concentration Assessment: Obtain two 10 mL trough (15 minutes pre-dose, ± 5 minutes) blood samples (Section 4.1.2). Subjects should be contacted one week (7 days) prior to the visit and reminded to record the timing of study drug and inhaled treprostinil dosing for the week leading up to the study visit.
- Record AEs
- Record concomitant medications
- Provide subject with a 1 month supply of study drug. Provide additional instructions/remind subject on importance of taking study drug and inhaled treprostinil together,
- Record study drug and inhaled treprostinil administration and/or dose changes, as applicable
- Record study drug accountability
- Remind subjects to call the clinical site coordinator or Investigator immediately if they experience a worsening of the disease-related symptoms or at any time to discuss study related issues

8.4 Week 8 Procedures

Subjects will return to the clinical site at Week 8 after randomization (± 4 days) for the following procedures:

- Perform a physical examination
- Record WHO Functional Class
- OPTIONAL assessment at Week 8: Record a 12-Lead ECG following a 5-minute rest in a semi-recumbent position (conduct ECG within 1-2 hours, ± 15 minutes, following the second or third daily dose of study drug and inhaled treprostinil)
- Record vital signs after five minutes of seated rest
- Conduct an unencouraged 6MWT (1-2 hours, ± 15 minutes, after second or third daily dose of study drug and inhaled treprostinil)
- Record Borg Dyspnea Score
- Assess clinical worsening
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)

- Obtain serum pregnancy test for women of childbearing potential
- Record AEs
- Record concomitant medications
- Provide subject with a 4 week supply of study drug. Provide additional instructions/remind subject on importance of taking study drug and inhaled treprostinil together, review study drug dosing, packaging, storage, etc.
- Record study drug and inhaled treprostinil administration and/or dose changes, as applicable
- Record study drug accountability
- Subjects to be reminded to call the clinical site coordinator or Investigator immediately if they experience a worsening of the disease-related symptoms or at any time to discuss study related issues

8.5 Week 12 (first Quarterly Visit) Procedures

Subjects will return to the study site for Week 12 (± 10 days) for the following procedures:

- Perform a physical examination
- Record WHO Functional Class
- Record a 12-Lead ECG following a 5-minute rest in a semi-recumbent position (conduct ECG within 1-2 hours, ± 15 minutes, following the second or third daily dose of study drug and inhaled treprostinil)
- Record vital signs after five minutes of seated rest
- Conduct an unencouraged 6MWT (1-2 hours, ± 15 minutes, after the second or third daily dose of study drug and inhaled treprostinil)
- Record Borg Dyspnea Score
- Assess clinical worsening
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- Obtain serum pregnancy test for women of childbearing potential
- Record AEs
- Record concomitant medications
- Provide subject with a 3 month supply of study drug. Remind subject of importance of taking study drug and inhaled treprostinil together, review study drug dosing, packaging, storage, etc.
- Record study drug accountability
- Record study drug and inhaled treprostinil administration and/or dose changes, as applicable
- Remind subjects to call the clinical site coordinator or Investigator immediately if they experience a worsening of the disease-related symptoms or at any time to discuss study related issues
- OPTIONAL Plasma Concentration Assessment: Obtain two 10 mL blood samples at the following four time points around the second daily dose of study drug: 15 minutes pre-dose,

and 15 minutes, 1 hour and 2.5 hours post-dose; ± 5 minutes) (Section 4.1.2). Subjects should be contacted one week (7 days) prior to the visit and reminded to record the timing of study drug and Tyvaso® dosing for the week leading up to the study visit.

8.6 Quarterly Visit Procedures

Subjects will return to the study site for Quarterly Visits (± 10 days) for the following procedures:

- Perform a physical examination
- Record WHO Functional Class
- Record a 12-Lead ECG following a 5-minute rest in a semi-recumbent position (conduct ECG within 1-2 hours, ± 15 minutes, following the second or third daily dose of study drug and inhaled treprostinil)
- Record vital signs after five minutes of seated rest
- Conduct an unencouraged 6MWT (1-2 hours, ± 15 minutes, after the second or third daily dose of study drug and inhaled treprostinil)
- Record Borg Dyspnea Score
- Assess clinical worsening
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- Obtain serum pregnancy test for women of childbearing potential
- Record AEs
- Record concomitant medications
- Provide subject with a 3 month supply of study drug. Remind subject of importance of taking study drug and inhaled treprostinil together, review study drug dosing, packaging, storage, etc.
- Record study drug accountability
- Record study drug and inhaled treprostinil administration and/or dose changes, as applicable
- Remind subjects to call the clinical site coordinator or Investigator immediately if they experience a worsening of the disease-related symptoms or at any time to discuss study related issues
- Optional RHC assessment: For subjects who consent to participate in the RHC assessment, perform RHC at the Month 6 Quarterly Visit (± 7 days), approximately 1-2 hours after dosing of study drug.

8.7 End of Study (or Early Termination) Procedures

All subjects should receive an End of Study Visit, if possible. Prior to this Visit, subjects will be contacted to determine whether they will enroll in the Open Label Extension Study. Subjects who elect to enroll in the extension study will be transitioned in a blinded fashion.

Subjects who do not elect to enroll in the open-label extension or who do not complete the current study will be weaned off of study drug at a maximum decrement of one tablet QID and a minimum decrement of one tablet QID per week. Following down-titration and discontinuation of study drug, the subject should return for an End of Study Visit for the following procedures:

- Perform a physical examination
- Record WHO Functional Class for PAH
- Record a 12-Lead ECG following a 5-minute rest in a semi-recumbent position (conduct ECG within 1-2 hours, ± 15 minutes, following the second or third daily dose of inhaled treprostinil, or, if enrolling in the open label extension study, conduct after second or third dose of inhaled treprostinil and study drug)
- Record vital signs after at least five minutes of seated rest
- Conduct an unencouraged 6MWT within1-2 hours, ± 15 minutes, after second or third daily dose of inhaled treprostinil, or, if enrolling in the open label extension study, conduct after second or third dose of inhaled treprostinil and study drug
- Record Borg Dyspnea Score
- Assess clinical worsening
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- Perform a serum pregnancy test for women of child-bearing potential
- Perform drug accountability (and collect remaining unused study drug and packaging for uses/partially used study drug)
- Record AEs
- Record concomitant medications
- Complete Study Termination CRF

8.8 Unscheduled Visit(s)

At the Investigator's discretion, subjects may visit the study site at any time. Unscheduled visits may involve, at the Investigator's discretion, the following procedures:

- Perform a physical examination
- Record WHO Functional Class
- Record a 12-Lead ECG following a 5-minute rest in a semi-recumbent position.
- Record vital signs after five minutes of seated rest
- Conduct an unencouraged 6MWT
- Record Borg Dyspnea Score
- Assess clinical worsening
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- Plasma concentration sample, if feasible, for drug related SAEs (obtain two 10 mL tubes)

- Obtain serum pregnancy test (for women of childbearing potential)
- Record AEs
- Record concomitant medications
- Supply of study drug as applicable. Remind subject of importance of taking study drug and inhaled treprostinil together, review study drug dosing, packaging, storage, etc.
- Record study drug accountability
- Record study drug and inhaled treprostinil administration and/or dose changes, as applicable
- Remind subjects to call the clinical site coordinator or Investigator immediately if they experience a worsening of the disease-related symptoms or at any time to discuss study related issues.

9 QUALITY CONTROL AND ASSURANCE

The Sponsor is responsible for ensuring that the trial is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. To this end, the clinical monitor will make periodic study site visits to assess compliance with the protocol, verify the data collected, and identify and resolve problems that may arise. The Investigator agrees to allow the monitor direct access to all relevant study documents and to allocate time to discuss findings and any relevant issues.

The Sponsor may conduct a quality assurance audit of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant study documents and to allocate time to discuss findings and any relevant issues. In addition, this study is subject to audit by the relevant Regulatory Authorities. If such a regulatory inspection occurs, the Investigator agrees to allow the inspector direct access to all relevant study documents.

10 PLANNED STATISTICAL METHODS

This section briefly describes the planned statistical analyses. A complete description of the methodology will be specified in a statistical analysis plan (SAP), which will be finalized prior to database lock. Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the statistical analysis plan and will not require a protocol amendment.

10.1 General Considerations

The primary efficacy endpoint is independently confirmed clinical worsening. The primary endpoint analysis will evaluate clinical worsening as the time from randomization to first clinical worsening event. The primary null hypothesis to be tested is that there are no differences in the hazard ratio for clinical worsening between BPS-314*d*-MR and placebo. The primary endpoint analysis will test the hypothesis of a reduction in clinical worsening with BPS-314*d*-MR, compared to placebo, as a time to event variable within a log-rank test. Randomized subjects for whom an independently confirmed clinical worsening event has not occurred during the study

will be censored. Sensitivity analyses to support the primary endpoint analysis will be conducted to examine outcomes under more restrictive criteria (e.g., loss to follow-up treated as an event).

Statistical analyses will be performed using two-sided tests. The strata will be included in all statistical analyses as a controlled variable. A 0.05 significance level will be used in all tests of treatment differences. In addition, for labeling purposes only, the experiment-wise Type I error will be controlled to a maximum of 5%. A gatekeeper strategy may be employed such that any secondary endpoints or subset analyses will be considered for statistical significance only if the primary endpoint is statistically significant. The type I family-wise error rate will be controlled at the 0.05 level of significance.

Data will be summarized by treatment group (and by visit when applicable). For parameters measured at baseline, the outcome variables of interest are the changes from baseline.

Summary statistics will include the mean, N, standard deviation, median, minimum, maximum, and the 25^{th} and 75^{th} percentile values for continuous variables, and frequencies and percentages for categorical variables.

The SAP will specify the details of the models to be used for the efficacy, safety and exploratory analyses. All statistical analyses will be performed by the Sponsor's biostatistics department personnel (or appropriate designees) using SAS®, Version 9.1 or higher or other validated software.

10.2 Determination of Sample Size

The primary efficacy endpoint is clinical worsening confirmed by an independent EAC. The primary efficacy endpoint analysis will evaluate clinical worsening as the time to first clinical worsening event.

A review of the literature show that few articles have been published which discuss the observed rates of clinical worsening with patients treated with inhaled treprostinil. Benza et al (2011) reported that, in an open-label extension study of 206 PAH patients involved in inhaled treprostinil registration trial, 12-, 18- and 24-month clinical worsening rates were 18%, 26% and 31%, respectively. Voswinckel et al (2009) investigated the long-term safety and efficacy of inhaled treprostinil in 24 PAH patients over approximately 3 years of follow-up in a small, open-label study. Reported were 12-, 24- and 36-month clinical worsening rates of 15%, 30% and 50%, respectively.

Based the aforementioned published literature, the anticipated one-year rate of clinical worsening is approximately 15% for the population treated with inhaled treprostinil. As such, the large sample size necessary to show a clinically meaningful difference between the BPS-314*d*-MR and the placebo groups treated with inhaled treprostinil would be prohibitive to the Sponsor to conduct this study. The Sponsor intends to restrict subject recruitment to inhaled treprostinil subjects where a BPS-314*d*-MR treatment effect will be more readily discerned. Following guidance from the FDA (2012) on clinical study enrichment strategies, the current study specifies in the inclusion criteria that the only patients who are showing signs of deterioration after initial improvement on inhaled treprostinil treatment or have had a clinically sub-optimal response to inhaled treprostinil treatment will be randomized into the trial. The specific exclusion of subjects

who are likely at a lower risk of clinical worsening will reduce the proportion of subjects available for recruitment but will expectedly increase the event rate among the complement sub-population targeted for recruitment and will allow fewer subjects needed to test the hypothesized absolute effect size. Thus, in restricting the population of this study to the sub-population most likely to benefit with an add-on therapy, it is expected that the observed one-year rate of clinical worsening will be approximately 45% for the subset of subjects targeted for this study.

Initial start-up activities and recruitment of subjects will be restricted to ensure subject safety. As such, the sample size determination calculations will not include the initial 6 months of the study to make certain of adequate powering for this study. The accrual period and follow-up period used will be 1.5 and 2.5 years, respectively. Thus, assuming a one-year rate of clinical worsening of 45% in the placebo (inhaled treprostinil alone) group, 25% in the BPS-314*d*-MR group (a 20% reduction from inhaled treprostinil therapy alone), proportional hazards over time, an accrual period of 1.5 years, a 0.01 two-sided significance level, and a total follow-up time of 2.5 years, an exponential maximum likelihood test of equality of survival curves would require 113 events and 116 subjects per treatment group to detect treatment difference at a power of 90% at a 0.01 two-sided significance level (or 97% power at a 0.05 two-sided significance level or approximately 90% power at a 0.05 two-sided significance level to detect a 13% reduction from an inhaled treprostinil rate as low as 30%). Therefore, this study will randomize approximately 240 subjects. Sample size calculations were performed using nQuery Advisor 7.0 using sample size methods for the log-rank statistic based on Lakatos & Lan (1992). Subjects who discontinue from the trial will not be replaced.

The Sponsor will continuously monitor the overall (pooled) event and drop-out rates during the course of the study. Sample size may be increased during the trial to maintain the planned power at between 80% and 90% and the intended trial duration. Only pooled blinded data will be used to increase sample size.

10.3 Analysis Populations

With the exception of the assessment of vital status until the formal close of the study, the statistical analyses or summaries for efficacy and safety parameters will include evaluations performed from randomization up to the date of the subject's last study visit or 30 days after the permanent discontinuation of study drug. Any additional evaluations will be included in the data listings only.

10.3.1 Intent to Treat Population

The intent to treat (ITT) population will contain all subjects randomized into the study. The analyses for the primary, secondary and exploratory efficacy endpoints will be made on the ITT population.

10.3.2 Per Protocol Population

The per protocol (PP) population will contain all subjects randomized into the study who are compliant with study drug until they either experience an EAC adjudicated event or the study is terminated. The specific definition of the PP population will be noted in the SAP. Analyses to

support the primary analysis of the primary, secondary and exploratory efficacy endpoints will be made on the PP population.

10.3.3 Safety Population

The safety population will contain any subject randomized into the study who receives any amount of study drug. Safety analyses or summaries will include all available data, as appropriate.

10.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for all randomized subjects. Baseline efficacy assessments will be included in these summaries for distance walked on a 6MWT, Borg Dyspnea Score, the WHO functional class and NT-pro-BNP levels. Additionally, non-randomized ("screening failures") may be summarized, as appropriate.

For continuous variables (e.g., age, weight), the number of non-missing and missing values and the median, mean, standard deviation, minimum, maximum, and appropriate percentiles will be displayed for each treatment group. For categorical variables (e.g., race, gender), the counts and proportions of each value will be tabulated.

10.5 Study Drug

The duration of exposure to study drug will be summarized for all randomized subjects. Compliance with the dosing regimen, based on supplied and returned tablet count information, will also be summarized.

10.6 Concomitant Therapy

Concomitant medications (medications present while on study drug) will be recorded throughout the study. These medications will be coded using the WHO drug dictionary. The number of randomized subjects using prior or concomitant medications will be categorized by the WHO drug category and preferred term, and presented for each treatment group. In any given category [e.g., drug category] a subject will be counted only once.

10.7 Study Disposition

Subject disposition will be tabulated for all randomized subjects.

10.8 Primary Efficacy Endpoint

The primary objective of the study is to compare the effects of BPS-314*d*-MR added to inhaled treprostinil to placebo on TtCW defined as the time from randomization to the first of any of the clinical worsening events as specified in Section 2.1. The occurrence of clinical worsening will be independently adjudicated by an EAC.

10.9 Secondary Efficacy Endpoints

Secondary efficacy endpoints will include and are defined as:

1. The composite endpoint of time-to-clinical-failure (TtCF), defined as the time from randomization to the first of any of the following events:
   - Meets primary endpoint definition of clinical worsening, as confirmed by EAC, or
   - Received randomized treatment for at least 24 weeks and has:
     - Lack of sustained improvement from Baseline WHO Functional Class: defined by two consecutive visits of no sustained improvement from Baseline WHO FC, visits may be scheduled or unscheduled; and
     - Lack of sustained improvement from Baseline 6MWD (average at Baseline): defined by two consecutive visits of no sustained improvement from Baseline 6MWD ($\leq$ 0 meters or too ill to walk, directly related to PAH), visits may be scheduled or unscheduled.
2. Exercise capacity at each study visit as measured by the change from baseline in distance walked on a 6MWT
3. Dyspnea associated with each 6MWT at each study visit, as defined as the change from baseline in the Borg Dyspnea Score
4. PAH functional class at each study visit as defined as the change from baseline in the WHO functional class
5. Congestive heart failure at each study visit, as defined as the change from baseline in NT-pro-BNP levels

The secondary objectives of the study are to compare the effects of BPS-314*d*-MR to placebo on all secondary endpoints. The Sponsor will derive the composite measures of clinical failure and TtCF from the data collected per the protocol. Unlike clinical worsening, neither a specific Investigator's assessment for clinical failure nor an EAC confirmation of suspected events will occur. The analysis strategy of TtCF will be similar to the analysis strategy used for TtCW. Continuous secondary efficacy variables, defined above as the change from baseline at each study visit, will be summarized and compared between treatment groups using the Wilcoxon rank-sum test, separately for each study visit. The SAP will specify the analysis strategy for all secondary efficacy endpoints.

Hypothesis testing of secondary efficacy endpoints may be conducted using a gatekeeper strategy such that any secondary endpoints will be considered for statistical significance only if the primary endpoint is statistically significant. Under closed testing procedures, the type I family-wise error rate will be controlled at the 0.05 level of significance. The SAP will detail the order of testing for secondary efficacy endpoints.

10.10 Exploratory Efficacy Endpoints

[redacted]

Sponsor until the data are formally locked and study is unblinded. The pharmacokinetic data may [redacted]

10.11 Safety Endpoints

10.11.1 Adverse Events

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent adverse events will be defined as those events, which are newly occurring or worsening from baseline. In all cases only treatment emergent adverse events will be summarized.

Treatment-emergent adverse events will be summarized by treatment group as the number and percentage of subjects having any treatment-emergent AE, having an AE in each body system, and having each individual AE. (*Note: In any given category [e.g., body system] a subject will only be counted once.*) Adverse events will further be categorized by severity, relationship to study drug, and action taken. Other information collected will be listed, as appropriate.

Any event starting more than 5 days after the final dose of study drug will be excluded from the above described tables and only listed, unless the event caused discontinuation from the study

10.11.2 Vital Signs

Vital sign data will be listed for each subject. Clinically significant values will be flagged. Data will be summarized by treatment group using mean change from baseline and proportions of subjects with clinically significant values.

10.11.3 Laboratory Data

Laboratory data will be listed for each subject. Laboratory data will be summarized for each treatment group by presenting the proportions of subjects with clinically significant abnormalities; shift tables, baseline to most extreme post-baseline value, using normal ranges; summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges), as appropriate.

10.11.4 Electrocardiogram

Results from the electrocardiogram (ECG) will be listed for each subject. These data will also be summarized for each treatment group by presenting subjects with newly occurring or worsening ECG abnormalities from baseline; shift tables, baseline to most extreme post-baseline value; summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges). Whenever multiple ECG readings are done on the same day, the average of these readings will be taken for the data summaries.

10.11.5 Physical Examination

Any clinically significant abnormality prior to randomization is to be recorded as medical history and tabulation of those events will occur within medical history summaries. Any clinically significant abnormal change from baseline post-randomization is to be recorded as an AE and tabulation of those events will occur within AE summaries.

10.12 Pooling of Clinical Sites

Study sizes within the clinical site are expected to be too small to allow stratification by clinical site in efficacy analyses. Any change to this approach will be specified in the SAP prior to database lock.

10.13 Interim Analysis

An interim efficacy analysis will be considered. The Sponsor will fully specify any interim efficacy analysis plan in the statistical analysis plan, including the personnel involved, the stopping rules, an alpha spending strategy, etc. if such an analysis is to be conducted. Interim safety analyses will be performed by an independent external statistician and reviewed only by an independent data safety monitoring committee. Lung Biotechnology Inc. will remain blinded throughout the conduct of this study.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

The term “Investigator” as used in this protocol and in the CRFs refers to the Principal Investigator at each study site, or another staff member listed as a Sub-Investigator on the study site Food and Drug Administration (FDA) Form 1572. The site Principal Investigator is ultimately responsible for the conduct of all aspects of the study at that site. The site Principal Investigator is also responsible for ensuring that all site staff working on the study are appropriately trained and supervised; staff training and delegation of responsibilities should be documented in the files.

Prior to shipment of study drug to the site, the Investigator must read, understand, and sign the Investigator Agreement in the protocol. The Investigator Agreement documents agreement to conduct the study according to the protocol, International Conference on Harmonization / Good

Clinical Practice (ICH/GCP), and Code of Federal Regulations (CFR). Additional requirements must be met by the Investigator and institution, as described below.

11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

Prior to study initiation at each site, the Investigator will obtain approvals for the study from their Institutional Review Board (IRB), Independent Ethic Committee (IEC), and/or other local equivalent body and provide the Sponsor with a copy of approval documentation. The relevant bodies must also review and approve the site's Informed Consent Form (ICF) and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to relevant bodies prior to the start of the study. If, during the study, it is necessary to amend either the protocol or the ICF, the Investigator is responsible for obtaining required approvals of these amended documents prior to implementation. Copies of the approval correspondence and approval letters must be sent to the Sponsor.

During the study, the Sponsor will compile an annual progress report for submission to their IRB, IEC and/or equivalent body as required. The Investigator will also provide a written summary of the study following study updates, completion or termination as appropriate.

11.3 Ethical Conduct of the Study

This study will be conducted according to ICH and GCP guidelines, and all applicable government regulations and Institutional research policies and procedures.

11.4 Patient Information and Consent

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The formal consent of a subject, using the IRB/IEC-approved consent form, must be obtained before any study procedure is undertaken. This ICF must be signed by the subject or legally acceptable surrogate, and the Investigator or designated research professional obtaining the consent.

The consent form and explanation will include; detailed information about BPS-314*d*-MR, the rationale for why it is being studied, frequency of dosing, and length of treatment, potential side effects and risks, safeguards and emergency procedures. Information will also be provided about the frequency and length of visits. The collection of all lab specimens will be described in detail. Subjects will be assured that their participation is voluntary and that withdrawal from the study would not jeopardize current or future treatment. All subjects will be informed of potential risks and benefits involved in the study, including side effects of BPS-314*d*-MR.

11.5 Patient Confidentiality

Every effort will be made to keep medical information confidential. The Sponsor, appropriate Regulatory Authorities, and the IRB/IEC governing this study may inspect the medical records

of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/IEC or appropriate regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects and any published study reports will not identify subjects.

11.6 Study Monitoring

In accordance with U.S. federal and other national regulations, ICH, and GCP guidelines, monitors for Sponsor or its designee will periodically contact the site and conduct on-site visits. The first monitoring visit will occur within the first few weeks after the first subject's Screening Visit. During these visits, the monitor will at a minimum: confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

11.7 Case Report Forms and Study Records

The study case report form (CRF) is the primary data collection instrument for the study. For this study, the CRF will be completed electronically. All data requested on the CRF must be recorded following the CRF completion guidelines to be provided to site personnel. Subject data will be entered in the CRF by appropriate site staff. Data recorded in the CRF should be consistent with source documents.

11.8 Oversight Committees

11.8.1 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB), independent of the Sponsor, will be established for the study. Operating under a formal charter, the DSMB will be comprised of three members: two physicians knowledgeable in the treatment of PAH and one statistician. Throughout the course of the study the DSMB will meet regularly to monitor the safety of the subjects in the study.

11.8.2 Endpoint Adjudication Committee

The study will have an Endpoint Adjudication Committee (EAC) composed of PAH physicians not otherwise involved in the conduct of the study. The EAC will operate under a formal charter. Throughout the course of the study the EAC will review clinical worsening events (the primary study endpoint). The EAC may meet with frequency based on the rate of enrollment and the rate of occurrence of clinical worsening events.

11.9 Access to Source Documentation

The Investigators agree to allow the monitors direct access to all relevant documents, including electronic records, and the Investigators will allocate their time and staff to discuss any findings or any relevant issues.

11.10 Data Generation and Analysis

All data are submitted into a quality assured database from the site and will be reviewed by the Sponsor. Data clarifications will be generated and the database will be edited as appropriate. The database will be final when all queries have been resolved and all data management quality assurance procedures are complete. A full audit trail of all entries and changes to CRFs will be maintained in the database structure.

11.11 Retention of Data

In accordance with U.S. federal and other national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must notify the Sponsor before any disposal or change in location of study records. The Investigator should ensure that the location considered for archiving study records is an appropriate facility for the secure storage of study documents and records.

11.12 Publication and Disclosure Policy

Manuscripts or abstracts for written or oral presentation by Investigators associated with this study must be submitted to the Sponsor at least 30 working days for approval before submission to any journal or meeting. Scientific comments by the Sponsor should be taken into consideration before submission. The Sponsor reserves the right to request revision of written or oral presentations or to deny such presentations if, in the opinion of the Sponsor, such activity would adversely affect the drug development program.

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Appendix 1 Schedule of Events

STUDY PROCEDURES	Study Visit Week									
	Screening[9]	**Baseline Day 1** (3-120 days)	**Baseline Day 2**	**Phone calls**	**Week 4** (± 3 days)	**Week 8** (± 4 days)	**Week 12 First Quarterly Visit** (± 10 days)	**Quarterly Visits** (± 10 days)	**End of Study or Early Termination Visit**[10]	**Unscheduled Visit(s)**[11]
Clinic Site Visit	X	X	X		X	X	X	X	X	X
Phone Calls[1]				X						
Informed Consent	X									
I/E Criteria[2]	X	X								
Demographics	X									
PAH History	X									
Medical History[3]	X	X								
Physical Examination	X	X			X	X	X	X	X	X
Vital Signs (height at Screening only)	X	X			X	X	X	X	X	X
Clinical Worsening Assessment				X	X	X	X	X	X	X
6-Minute Walk Test	X	X[4]	X[4]		X	X	X	X	X	X
Borg Dyspnea Scale	X	X	X		X	X	X	X	X	X
WHO Functional Class	X	X			X	X	X	X	X	X
Laboratory Parameters	X	X			X	X	X	X	X	X
OPTIONAL: Plasma Concentration[5]					X		X			X
OPTIONAL: RHC[6]		X						X		
Pregnancy Test[7]	X	X			X	X	X	X	X	X
12-Lead ECG	X	X			X	Optional X	X	X	X	X
Randomization		X								
Study drug & Tyvaso Administration instructions & record[8]	X Tyvaso only	X Tyvaso only	X	X	X	X	X	X		X
Drug Accountability					X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X	X	X	X

[1] Phone calls: Between the Baseline Visit and the Week 12 (first Quarterly Visit) subjects should be contacted weekly (except for weeks with study visits), then monthly between Quarterly Visits through the end of study participation.

[2] Inclusion/Exclusion criteria to be collected at the Screening Visit and updated at the Baseline Visit as needed (Sections 5.2 and 5.3).

[3] Medical history to include relevant and significant past or present illness or surgeries.

[4] 6MWTs at Baseline (Day 1 and Day 2) should be conducted post-randomization and prior to dosing study drug. 6MWTs at scheduled visits after Baseline should be performed between 1-2 hours, ± 15 minutes, after the second or third dose of inhaled treprostinil. During the run-in period, subjects should be guided through proper up-titration, monitored for appropriate dosing and offered additional training by phone or in-person as needed.

[5] Optional Plasma Concentration Assessment: For the Week 4 Visit collect two 10mL trough (15 minutes pre-dose, ± 5 minutes) samples; for Week 12 (first Quarterly Visit) collect two 10mL samples around the second daily dosing of study drug: 15 minutes pre-dose, and 15 minutes, 1 hour and 2.5 hours post-dose (± 5 minutes); subjects participating in the plasma concentration assessment should be contacted one week (7 days) prior to Week 4 and Week 12 (first Quarterly Visit) as a reminder to record their Tyvaso and study drug dosing times during the week leading up to the visit.

[6] Optional RHC assessment procedures may be conducted up to 21 days prior to the Baseline Visit and at the Month 6 Quarterly Visit (± 7 days). Baseline RHC should be performed prior to study drug dosing. The Month 6 RHC should be performed between 1-2 hours, ± 15 minutes, after the second or third dose of study drug and inhaled treprostinil.

[7] Pregnancy testing for females of childbearing potential. Urine test at Baseline Visit and serum test at all other clinic visits.

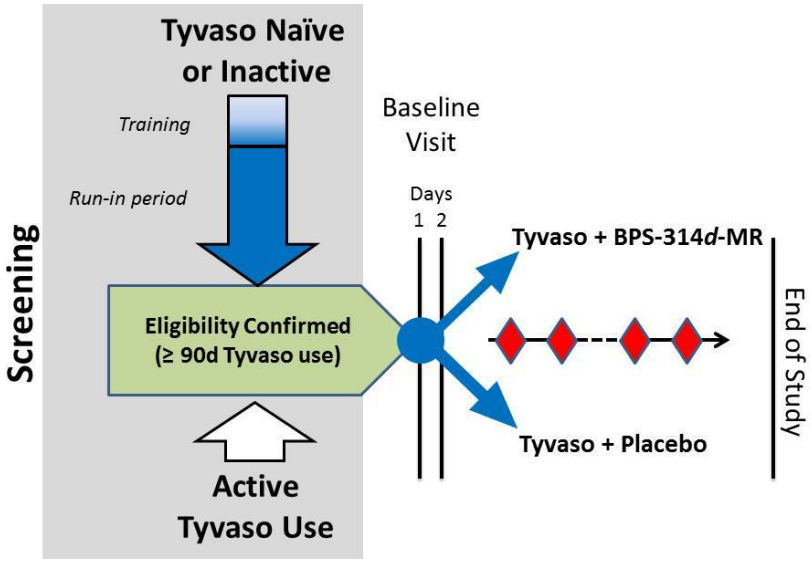
[8] All doses of study drug and inhaled treprostinil administered at the study site and all dose changes should be recorded in subject dose administration log.

[9] Subjects who consent to the study but are not currently taking inhaled treprostinil and who otherwise meet study eligibility criteria will enter a run-in period on inhaled treprostinil to achieve 90 days of experience, with 30 or more days at a stable dose, to ensure drug tolerability before being randomized. Subjects who consent to the study and are currently taking inhaled treprostinil at the Screening Visit should be randomized into the study as soon as eligibility criteria have been met. See Appendix 2.

[10] When the Sponsor concludes the study or the subject withdraws consent or is terminated from the study, the subject will be required, as applicable, to return to the study site for an End of Study Visit and the Study Termination CRF will be completed.

[11] An Unscheduled Visit may occur at any time and involve any of the procedures listed as deemed appropriate by the Investigator.

Appendix 2 Schematic of Study Entry Based on Tyvaso Use



Eligibility for the study is available to PAH patients regardless of their current Tyvaso use status.

1. *Tyvaso Naïve or Inactive* patients who meet candidacy criteria for the study protocol will be initiated on Tyvaso during the screening period, commencing with training and followed by a run-in period. Following completion of the 90 day run-in period, if eligibility is confirmed then patients will be randomized into the study.

2. Patients who are *Active Tyvaso Users* at the initiation of screening will continue with their current therapy. It is anticipated that patients will be promptly enrolled in the study as soon as eligibility is confirmed.

Following randomization, study subjects will receive Tyvaso and study drug for the duration of the study with clinical assessments (red diamonds) as identified in the study protocol.

Appendix 3 6-Minute Walk Test Procedures

General Procedures

The administration of the 6-Minute Walk Test and specifications of the testing area should be generally consistent with the American Thoracic Society (ATS, 2002) guidelines and the usual practice of the clinical site.

To the extent possible and to lessen the opportunity for bias, test administrators should not review the subject's prior 6MWT results before conducting the test. When the 6MWT is completed the test administrator *will not* tell the subject the distance walked. Results of the 6MWT should not be provided to the subject during the course of the study.

The area used for the 6MWT should be pre-measured at approximately 30 meters (100 feet) in length and approximately 2 to 3 meters (7 to 10 feet) in width. There should be no turns or significant curves to the 6-minute walk area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested but the clock will continue to run. At the end of 6 minutes, the tester will call "stop" while simultaneously stopping the watch and then measure the distance walked. At any point in the trial, if a subject is assessed for the 6MWT while using oxygen therapy then all future 6MWTs should be conducted in the same way with the same oxygen flow.

Instructions to the Subject

Subjects should be told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test will use the following exact dialogue with the subject:

"The purpose of this test is to find out how far you can walk in six minutes. You will start from this point and follow the hallway to the marker (e.g., chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the six minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"

"Please explain to me what you are going to do."

The person administering the test will then start the test by saying the following to the subject:

"Are you ready?"

"Start when I say "GO."

The person administering the test will tell the subject the time at 2 and 4 minutes by saying:

"You have completed 2 minutes."

And then by saying:

"You have completed 4 minutes."

No other instruction or encouragement will be given during the test. Eye contact with the subject should be avoided during the test.

Appendix 4 Borg Dyspnea Scale

Immediately following the 6MWT, the person administering the test will obtain a rating of dyspnea using the Borg Scale. The person will use the following dialogue:

"I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represent the greatest shortness of breath you have ever experienced in your life. If one of the numbers does not exactly represent how short of breath you are, then you can choose a fraction between. For example, if you had shortness of breath somewhere between 4 and 5, you could choose 4 ½."

Perceived Breathlessness (Borg Scale)

0 NOTHING AT ALL

0.5 VERY VERY SLIGHT (just noticeable)

1 VERY SLIGHT

2 SLIGHT

3 MODERATE

4 SOMEWHAT SEVERE

5 SEVERE

6

7 VERY SEVERE

8

9 VERY VERY SEVERE (almost maximum)

10 MAXIMUM

Appendix 5 WHO Functional Classification for PAH

Class I - Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II - Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III - Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV - Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increase by any physical activity.

Appendix 6 Plasma Concentration Samples: Handling and Shipping

BPS-314*d*-MR and Tyvaso® (Treprostinil, inhaled)

Blood Sample Collection and Processing

Detailed instructions for collection and processing will be specified in the Study Reference Manual. General instructions are as follows:

Sample Collection and Processing Instructions

For the Week 4 blood collection time point, collect 2 (two) 10mL blood samples at study drug trough(15 minutes pre-dose, ± 5 minutes) in a chilled, lavender-topped evacuated tube containing **K2EDTA** as an anticoagulant and immediately place the sample on ice.

For Week 12 (first Quarterly Visit), collect 2 (two) 10mL blood samples in chilled, lavender-topped evacuated tubes containing **K2EDTA** as an anticoagulant and immediately place the sample on ice. Samples should be collected around the second daily dosing of study drug: 15 minutes pre-dose, and 15 minutes, 1 hour and 2.5 hours post-dose.

The samples should be kept cold throughout all handling procedures. 1 (one) tube is collected for BPS-314*d*-MR analysis and another one for treprostinil analysis.

Within 15min after drawing the blood, centrifuge the sample at 4 °C for 15 minutes at 3000x g. There should be approximately 6mL of plasma per each full 10mL blood draw.

Pipette four (4) **EQUAL** aliquots of plasma into four (4) cryotubes of an appropriate size and labeled as A, B, C, D. Keep all cryotubes on ice until frozen. Once frozen place into freezer: either -20°C or -70°C. Samples A and B will be labeled as BPS samples. Samples C and D will be labeled as treprostinil samples.

Plasma Sample Shipment

Plasma samples from each cohort will be sent as two batches on separate days to Intertek Pharmaceutical Services. Samples A and C tubes will be packed in dry ice and shipped on a Monday; samples B and D tubes will be packed in dry ice and shipped on a Tuesday to Intertek for laboratory analysis. Shipping tubes should be individually packaged to prevent breaking and contamination of other samples. Plasma samples will be packed in Styrofoam boxes containing a generous supply of dry ice for 2-3 days in-transit.

All shipments must be accompanied by a packing list.

Prior to shipment of samples, the site will contact the sponsor-designated laboratory by fax or email. An advance electronic copy of the packing list will be provided to [redacted]

The shipping address and contact information for [redacted]

[redacted]

Appendix 7 Adverse Events

The Investigator or designee will probe each subject for any adverse events which may have occurred. When possible, always ask the same question when conducting the verbal probe in order to ensure uniformity between subjects. The subject should be asked:

"How have you been doing (feeling) since your last visit?"
"How are you doing (feeling) now?"

Based on the subject's response to these questions, the subject should be asked additional questions relevant to any specific complaint such as:

"Have you had this symptom in the past?"
"How severe is/was the symptom?"
"How often did the symptom occur?"
"How long did the symptom last?"
"Did you take any medication to treat the symptom?"
"Did you see a physician or go to the hospital because of this symptom?"

All adverse events should be fully documented on the CRFs.

DEFINITIONS

An **adverse event (AE)** is defined as any untoward medical experience/occurrence associated with the use of a drug in humans, whether or not it is considered drug related. An AE may include an intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance. AEs may also include worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures.

A **serious adverse event (SAE)** is an AE occurring that has results in any of the following outcomes:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred; it does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (i.e., substantial disruption of a person's ability to conduct normal life functions).
- Results in a congenital anomaly/birth defect in an offspring of a study subject
- Other medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, e.g., allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

An **unexpected adverse event (UAE)** is any AE not yet identified in nature, severity, or frequency in the current Clinical Investigators' Brochure or in the clinical safety updates.

Clinical Laboratory Changes: It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal laboratory test result, the Investigator needs to ascertain if this is a clinically significant change from baseline for that individual subject. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If a laboratory value is determined to be an abnormal change from baseline for that subject, this is considered an AE.

INTENSITY

AEs will be graded on a 3-point scale and reported as indicated on the Case Report Forms. The intensity of an AE is defined as follows:

- **Mild:** Discomfort noticed, but no disruption to daily activity
- **Moderate:** Discomfort sufficient to disrupt normal daily activity and/or requires symptomatic treatment
- **Severe:** Inability to work or perform normal daily activity and requires treatment

STUDY DRUG CAUSALITY

Relationship of an AE to treatment will be assessed as follows:

- **Certain:** The AE is **clearly** related to the investigational agent(s).
- **Probably Related:** The AE is likely related to the investigational agent(s).
- **Possibly Related:** The AE may be related to the investigational agent(s).
- **Unlikely to be Related:** The AE is doubtfully related to the investigational agent(s).
- **Unrelated:** The AE is **clearly** NOT related to the investigational agent(s).
- **Unassessable/unclassifiable:** The AE is cannot be judged because information is insufficient or contradictory.

BACKGROUND PAH DRUG CAUSALITY

Relationship of an AE to treatment will be assessed as follows:

- **Certain:** The AE is **clearly** related to the background PAH agent(s).
- **Probably Related:** The AE is likely related to the background PAH agent(s).
- **Possibly Related:** The AE may be related to the background PAH agent(s).
- **Unlikely to be Related:** The AE is doubtfully related to the background PAH agent(s).
- **Unrelated:** The AE is **clearly** NOT related to the background PAH agent(s).
- **Unassessable/unclassifiable:** The AE is cannot be judged because information is insufficient or contradictory.

ACTION TAKEN

Action taken for an AE to treatment will be assessed as follows:

- **Study drug dose withdrawn:** Study drug administration was stopped permanently as a result of the AE.
- **Study drug temporarily discontinued:** Study drug administration was temporarily discontinued as a result of the AE.
- **Study drug dose reduced:** Study drug administration was reduced as a result of the AE.
- **Study drug dose increased:** Study drug administration was increased as a result of the AE.
- **Study drug dose not changed:** There was no alteration in either the dose or regimen of the study drug.
- **Unknown:** Not known what occurred with study drug administration because information is insufficient or contradictory.
- **Not applicable:** Not applicable.

OUTCOME

The outcome of an AE should be recorded based on the status of the AE at study completion or premature discontinuation from the study. The AE outcome would be recorded as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequalae, recovering/resolving or unknown. If an AE is ongoing, the AE should be followed until resolution.

Appendix 8 Optional Hemodynamic Assessment

Hemodynamic measurements, such as mean pulmonary arterial pressure, cardiac index, and calculation of pulmonary vascular resistance, will be assessed by right heart cardiac catheterization as an optional sub- study for sites and subjects who agree. Measurements will include heart rate, pulmonary arterial pressure (systolic, diastolic and mean), systemic arterial pressure (systolic, diastolic and mean), right atrial pressure, pulmonary capillary wedge pressure, mixed venous oxygen saturation, systemic arterial oxygen saturation, cardiac output via the Fick or thermodilution methods.

Right heart catheterization should be performed under fluoroscopic guidance with a flow-directed catheter (Swan-Ganz). All procedures will be performed under local anesthesia with conscious sedation if clinically indicated. All hemodynamic determinations must be made after determining the zero reference level at the midaxillary line with the subject supine. To ensure reproducibility of this reference level for subsequent measurements and to avoid zero level drift, the transducer must be anchored at the midaxillary line, and before each measurement, this juxtaposition should be confirmed.

The subject may sit up prior to or after hemodynamic assessments, as permitted by the medical professional, but must be lying flat for at least 10 minutes prior to and during each hemodynamic assessment; hemodynamics must be stable during this time.

Hemodynamic values will be determined by serial measurements of hemodynamic parameters (specifically CO and PAPm) to demonstrate stability. Stable hemodynamics are defined by changes in CO and PAPm of less than or equal to 20% between two consecutive serial measurements. After hemodynamic stability is demonstrated, the hemodynamic and oxygen saturation variables from the last assessment used to demonstrate stability will be recorded in the CRF.

Systemic blood pressures may be obtained by cuff, and systemic arterial oxygen saturation may be obtained by pulse oximetry.

Appendix 9 Sponsor Guidance for Comorbid Conditions

The Sponsor recognizes that the pulmonary hypertension population is complex and diverse. In order to facilitate enrollment of appropriate subjects to this pivotal trial, Investigators are strongly encouraged to contact the medical director or study team when at least 2 of the following characteristics are present in a potential study subject:

- Age> 65
- Hypertension
- Diabetes mellitus
- Coronary artery disease, coronary revascularization, previous myocardial infarction or acute coronary syndrome
- Moderate or severe valvular heart disease
- Interstitial lung disease with FVC or TLC <70% predicted or HRCT showing moderate, diffuse interstitial disease
- Prior history of deep venous thrombosis or pulmonary embolus
- Chronic continuous oxygen use (>18 hrs./day)
- PCWP between 12-15mmHg or PVR < 4 woods units

NB: While most of these do not, by themselves, exclude the subject from enrollment, they may indicate a subject whose medical condition is atypical for PAH and further clarification is needed prior to a decision of enrollment is made.

Appendix 10 Sponsor Signatures

Study Title: A multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the efficacy and safety of oral BPS-314*d*-MR added-on to treprostinil, inhaled (Tyvaso®) in subjects with pulmonary arterial hypertension

Study Number: BPS-314*d*-MR-PAH-302

Original Protocol Date: 16 April 2013
Amendment 1: 17 December 2013
Amendment 2: 15 October 2014

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Appendix 11 Investigator's Signature

Study Title: A multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the efficacy and safety of oral BPS-314*d*-MR added-on to treprostinil, inhaled (Tyvaso®) in subjects with pulmonary arterial hypertension

Study Number: BPS-314*d*-MR-PAH-302

Original Protocol Date: 16 April 2013
Amendment 1: 17 December 2013
Amendment 2: 15 October 2014

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol

I agree to comply with the International Conference on Harmonization Guideline for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines set forth in 21 Code of Federal Regulations Parts 50, 54, 56 and 312 and any local regulations per country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without the prior written consent of Lung Biotechnology Inc.

I also have read the current Clinical Investigators' Brochure for BPS-314*d*-MR and acknowledge that review of the information contained in the Clinical Investigators' Brochure is a requirement for Investigators before using BPS-314*d*-MR in a clinical trial.

Signed: _____ **Date:** _____

Printed: _____