NCT# : NCT03657095

Clinical Trial Protocol: BPS-314*d*-MR-PAH-303

Study Title:	An Open-label Extension of BPS-314*d*-MR-PAH-302 in Pulmonary Arterial Hypertension Patients.
Study Number:	BPS-314*d*-MR-PAH-303
Study Phase:	3
Product Name:	Esuberaprost Sodium Tablets
IND Number:	111,729
Indication:	Pulmonary Arterial Hypertension
Investigators:	Multicenter
Sponsor:	Lung Biotechnology
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	13 September 2017

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

LIST OF CONTACTS

Study Sponsor:	Lung Biotechnology 1040 Spring Street Silver Spring, Maryland 20910 United States Phone: 301-608-9292 Fax: 301-589-0855
Sponsor Contact: Medical Monitor:	[redacted]
Serious Adverse Event (SAE) Reporting:	[redacted]
Central Laboratory:	[redacted]

SYNOPSIS

Sponsor: Lung Biotechnology

Name of Finished Product: Esuberaprost Sodium Tablets (Beraprost Sodium 314*d* Modified Release [BPS-314*d*-MR])

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

Study Title: An Open-label Extension of BPS-314*d*-MR-PAH-302 in Pulmonary Arterial Hypertension Patients

Study Number: BPS-314*d*-MR-PAH-303

Study Phase: 3

Primary Objective:
The primary objective of this study is to assess the safety and tolerability of long-term treatment with esuberaprost in subjects with pulmonary arterial hypertension (PAH).

Secondary Objective:
The secondary objective of this study will be to assess the efficacy of long-term treatment of esuberaprost in subjects with PAH.

Study Design:
This is a multi-center, open-label study for eligible subjects who were actively participating in the BPS-314*d*-MR-PAH-302 study at the time the study was concluded. Subjects will sign an informed consent to continue treatment for PAH with esuberaprost in this open-label extension (OLE) study. At the Enrollment Visit for this study, subjects will begin a blinded transition from the BPS-314*d*-MR-PAH-302 study to the OLE study over a 4-week period. The first dose for all subjects in this OLE study will be 2 tablets. During this blinded transition period, those subjects on active study drug in the BPS-314*d*-MR-PAH-302 study will continue with blinded active study drug 4-times daily (QID); those subjects on placebo study drug will receive one active tablet and one placebo tablet QID (blinded) during the first 2 weeks and increase to 2 active tablets QID (blinded) thereafter. After the first dose, the investigator may adjust the dose as medically warranted. The maximum dose for this study is 30 µg QID with a minimum accepted dose as 15 µg QID. For the first 4 weeks, contact with the subject should occur weekly to ensure up-titration to the fixed dose is tolerated and assess adverse events (AEs).

Subjects will return to the clinic at Week 4 to be supplied open-label esuberaprost and complete protocol specified procedures. At the Week 4 Visit, subjects will be dosed with two 15 µg tablets (30 µg total) of esuberaprost, administered orally QID (provided the target dose is tolerated) or follow the Investigator's (or designee's) directions if adjustment is needed. Following the Week 4 Visit, each subject will return to the clinic at Months 3, 6, 9, and 12, and quarterly thereafter for assessment.

At the conclusion of the study or if a subject discontinues the study prematurely, subjects will return to the clinic for an End-of-Study (EOS) Visit. Subjects will be provided instructions about down titration off esuberaprost sodium tablets by the investigator.

Study Population:
This study will include eligible subjects who were actively participating in the BPS-314*d*-MR-PAH-302 study at the time the study was concluded and who have consented to continue treatment for PAH with esuberaprost.

Up to 273 subjects are eligible to enroll.

Test Product, Dose, and Mode of Administration:
Esuberaprost sodium tablets (BPS-314*d*-MR), 15 µg. Subjects will be dosed with two 15 µg (30 µg) tablets administered orally 4-times daily (QID).

Duration of Treatment:
This study is expected to continue until the first of any of the following are reached: the study drug is commercially available, the sponsor discontinues the study, or offers enrollment in another study.

Safety Assessments:
Safety will be assessed by AEs, physical examination, vital signs, clinical laboratory parameters and electrocardiogram (ECG) findings.

Efficacy Assessments:
Efficacy will be assessed by six-minute walk distance (6MWD), the Borg Dyspnea Score, World Health Organization (WHO) Functional Class (FC), and N-terminal pro-brain natriuretic peptide (NT-pro-BNP).

Other Assessments:
Quality of life will be assessed for all subjects at Enrollment and Month 6 using the patient reported outcome (PRO) instrument, emPHasis-10.

For those subjects in the United States (US) who choose to participate and provide a separate informed consent, blood samples will be collected at Enrollment and at Month 3 (at any point during the site visit) for future biomedical research (e.g., biomarker and genomic analyses).

Statistical Methods:
The primary safety endpoint of this study is the incidence and severity of AEs associated with long-term exposure to esuberaprost in eligible subjects.

Secondary endpoints include:
- Exercise capacity as measured by unencouraged 6MWD
- Borg Dyspnea Score
- WHO FC
- NT-pro-BNP

Pertinent data will be summarized in tables, and all data will be presented in by-subject listings. No inferential analyses will be performed.

Date of Original Approved Protocol: 13 September 2017

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LIST OF IN-TEXT TABLES

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
BPS	Beraprost Sodium
BPS-314*d*	Beraprost Sodium 314*d*
BPS-314*d*-MR	Beraprost Sodium 314*d*-Modified Release
BUN	Blood Urea Nitrogen
Ca	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
CO_2	Carbon Dioxide
CRF	Case Report Form
ECG	Electrocardiogram
EOS	End-of-study
ERA	Endothelin Receptor Antagonist
FC	Functional Class
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
Hct	Hematocrit
Hgb	Hemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Prostaglandin I2 receptor
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
IV	Intravenous
K	Potassium
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Na	Sodium
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
OLE	Open-label extension
PAH	Pulmonary Arterial Hypertension
PGI_2	Prostacyclin
PDE-5i	Phosphodiesterase Type 5 Inhibitor
PRO	Patient reported outcome
PT	Prothrombin Time
PTT	Activated partial thromboplastin time
PVR	Pulmonary Vascular Resistance
QID	Four-times daily
QTc	QT interval corrected for heart rate
RBC	Red Blood Cell (count)
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
UAE	Unexpected Adverse Event
US	United States
USP	United States Pharmacopeia
WBC	White Blood Cell (count)
WHO	World Health Organization

1 INTRODUCTION

Pulmonary arterial hypertension (PAH), defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance (PVR), is a severe hemodynamic abnormality common to a variety of diseases and syndromes. There are three major factors thought to contribute to the increased PVR seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis. Treatment of PAH includes three pharmacological classes (prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-type 5 inhibitors (PDE-5i), and four different routes of administration: oral, inhaled, subcutaneous (SC), and intravenous (IV) (Galie 2013).

Intravenous prostacyclin therapy prolongs survival in patients with PAH (Barst 1996), and it is considered by many clinicians as the "gold standard" of care. Parenteral prostacyclins are typically reserved until later in the course of disease, although risks and challenges associated with the IV route of administration have led to the emergence of other routes of administration, such as inhaled treprostinil solution (Tyvaso® US Package Insert), and an oral formulation of treprostinil diethanolamine (Orenitram® US Package Insert). Inhaled delivery of prostanoids permit selective vasodilatory effects to the lung vasculature while minimizing systemic side effects.

Beraprost sodium (BPS) is an orally bioavailable prostacyclin (PGI_2) analogue that is comprised of a mixture of 4 stereoisomers. Of these, the pharmacologically active single isomer esuberaprost, exerts its actions by specifically binding to PGI_2 receptors on smooth muscle, vascular endothelium, and platelets (Nishio 1997). This results in vasodilatation, inhibition of platelet aggregation, and antiproliferation (Kurumatani 2009; Melian and Goa 2002; Demolis 1993).

Esuberaprost is being evaluated for the treatment of PAH in Study BPS-314*d*-MR-PAH-302. The study was designed to leverage the complementary mechanistic and pharmacokinetic differences between locally-acting inhaled treprostinil and the systemic delivery of esuberaprost, creating an effect that more closely approximates parenteral therapy compared to using either therapy alone, and thus, achieves a more effective and longer-lasting therapeutic effect, delaying time to clinical worsening.

This open-label extension study (OLE) BPS-314*d*-MR-PAH-303 is designed to evaluate and characterize the safety profile of esuberaprost by studying the long-term exposure of PAH patients with this drug. In addition, this study will provide observational data on the efficacy of long-term treatment of esuberaprost in patients with PAH.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of long-term treatment with esuberaprost in patients with PAH.

2.2 Secondary Objective

The secondary objective of this study will be to assess the efficacy of long-term treatment of esuberaprost in patients with PAH.

2.3 Other Objectives

Other study objectives include:

- To assess quality of life in all subjects at Enrollment and Month 6 using the patient reported outcome (PRO) instrument, emPHasis-10.
- To collect and archive blood samples at Enrollment and Month 3 in an optional assessment for future biomedical research (US subjects only).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multi-center, open-label study for eligible subjects who were actively participating in the BPS-314*d*-MR-PAH-302 study at the time the study was concluded. Subjects will sign an informed consent to continue treatment for PAH with esuberaprost.

Subjects who provide informed consent for this OLE study on or prior to the End-of-Study (EOS) Visit for BPS-314*d*-MR-PAH-302 may participate in the study, provided all other eligibility criteria are met.

At the Enrollment Visit in this study, subjects will begin a blinded transition from the BPS-314*d*-MR-PAH-302 study to the OLE study over a 4-week period. The first dose for all subjects in this OLE study will be 2 tablets. During this blinded transition period, those subjects who are on active study drug in BPS-314*d*-MR-PAH-302 will continue with blinded active study drug 4-times daily (QID); those subjects on placebo in the BPS-314*d*-MR-PAH-302 study will receive one active tablet and one placebo tablet QID (blinded) during the first 2 weeks and increase to 2 active tablets QID (blinded) thereafter. After the first dose, the investigator may adjust the dose as medically warranted. The maximum dose for this study is 30 µg QID with a minimum accepted dose as 15 µg QID. For the first 4 weeks, contact with the subject should occur weekly to ensure up-titration to the fixed dose is tolerated and assess adverse events (AEs).

Subjects will return to the clinic at Week 4 to be supplied open-label esuberaprost and complete protocol specified procedures. At the Week 4 Visit, subjects will be dosed with two 15 µg

tablets (30 µg total) of esuberaprost, administered orally QID (provided the target dose is tolerated) or follow the Investigator's (or designee's) directions if adjustment is needed. Following the Week 4 Visit, each subject will return to the clinic at Months 3, 6, 9, and 12, and quarterly thereafter for assessment.

At the conclusion of the study (see Section 3.3), or if a subject discontinues the study prematurely, subjects will return to the clinic for an EOS Visit. Subjects will be provided instructions about down titration off esuberaprost sodium tablets by the investigator.

See Appendix 1 Schedule of Events Table for assessments to be performed at each study visit.

3.2 Rationale for Study Design and Control Group

This OLE study continues the evaluation of esuberaprost over a longer duration, as well as evaluates the initial administration of esuberaprost in those subjects who previously received placebo. This study will help to better characterize the safety profile of esuberaprost, as well as provide a better understanding of longer term efficacy.

3.3 Study Duration and Dates

This study is expected to continue until the first of any of the following are reached: the study drug is commercially available, the sponsor discontinues the study, or the sponsor offers enrollment in another study.

4 STUDY POPULATION SELECTION

4.1 Study Population

273 subjects at investigational sites in the United States (US) and Israel were enrolled in Study BPS-314*d*-MR-PAH-302. This open-label extension (OLE) study will be open to eligible subjects who are actively participating in the BPS-314*d*-MR-PAH-302 study at the time the study is concluded. Subjects who discontinued treatment/participation in BPS-314*d*-MR-PAH-302 study will not be eligible for this study.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Subject must have been actively participating in Study BPS-314*d*-MR-PAH-302 when the sponsor concluded that study.
2. In the Investigator's opinion, subject must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent form (ICF) and must sign the form prior to the initiation of any study procedures.
3. 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 results in a low failure rate, i.e., less

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 BPS-314*d*-MR-PAH-302 EOS Visit / BPS-314*d*-MR-PAH-303 Enrollment Visit.
4. Subject must be willing and able to comply with study requirements and restrictions.

4.3 Exclusion Criteria

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

1. Subject is pregnant or lactating.
2. Subject is scheduled to receive another investigational drug, device, or therapy during the course of the study.
3. Subject is taking or intends to take any prostacyclin / prostacyclin analog or IP receptor agonist (EXCEPT FOR treprostinil, inhaled [Tyvaso®]).
4. Subject has any other clinically significant illness or other reason 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.

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Study Drug

The study drug is esuberaprost sodium tablets, available as 15 µg tablets for oral QID administration. Esuberaprost sodium tablets contain 15 µg of the drug substance, esuberaprost sodium (BPS-314*d*).

Esuberaprost sodium active and matching placebo tablets will be mounted in child resistant Dose Pak® wallet cards. Following enrollment, each subject will receive a study drug "transition kit" containing 4-weekly wallet cards to cover the first 4 weeks of the study, which will be subject-specific. The site staff will instruct the subject on the proper method and sequence of taking the tablets. Starting at the Week 4 Visit, 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.

5.1.2 Placebo

To preserve study blinding for the first 4 weeks of this study, the placebo tablets are identical in size, shape, color, and appearance to the esuberaprost sodium tablets.

5.2 Treatments Administered

After informed consent has been provided and at the Enrollment Visit for the OLE study, subjects will remain on site and take their scheduled dose of OLE study drug. The subject should remain in the clinic for approximately 2-3 hours for observation by study personnel.

5.2.1 Selection and Timing of Dose for Each Patient

At the Enrollment Visit in this study, subjects will begin a blinded transition from the BPS-314*d*-MR-PAH-302 study to the OLE study over a 4-week period. The first dose for all subjects in this OLE study will be 2 tablets. During this blinded transition period, those subjects who are on active study drug in the BPS-314*d*-MR-PAH-302 study will continue with blinded active study drug QID; those subjects on placebo in BPS-314*d*-MR-PAH-302 will receive one active tablet and one placebo tablet QID (blinded) during the first 2 weeks and increase to 2 active tablets QID (blinded) thereafter. After the first dose, the investigator may adjust the dose as medically warranted. The maximum dose for this study is 30 µg QID with a minimum accepted dose as 15 µg QID.

At the Week 4 Visit, subjects will receive esuberaprost sodium tablets in bulk dosing cards, which will be the study drug packaging and configuration provided for the remainder of the study (see Section 5.9).

At the conclusion of the study (see Section 3.3), or if a subject discontinues the study prematurely, subjects will return to the clinic for an EOS Visit. If necessary, the subject should be weaned off study drug at a maximum decrement of 1 tablet QID and a minimum decrement of 1 tablet QID per week (scenarios provided in Table 1). However, the transition strategy off study drug is at the Investigator discretion as medically warranted.

Table 1. Down-Titration of Esuberaprost

Maximum Scenario		Minimum Scenario	
Day 1	2 tablets QID	Week 1	2 tablets QID
Day 2	1 tablet QID	Week 2	1 tablet QID
Day 3	No tablets	Week 3	No tablets

5.3 Method of Assigning Patients to Treatment Groups

There is only one treatment arm in this OLE study. All subjects will receive active esuberaprost sodium tablets.

5.4 Blinding

Treatment during the first 4 weeks of this study is double-blind. Although all subjects will receive active esuberaprost sodium tablets, placebo subjects from the BPS-314*d*-MR-PAH-302 study will be up-titrating (1 active esuberaprost sodium tablet for the first 2 weeks and 2 active esuberaprost sodium tablets for the next 2 weeks); whereas, subjects who were on active study drug during the BPS-314*d*-MR-PAH-302 study, will continue to receive 2 esuberaprost sodium tablets. After the initial 4 weeks of the OLE study, all subjects will be receiving 2 tablets esuberaprost QID, and administering esuberaprost at the maximum dose (30 µg QID), if tolerated.

The investigator and study staff, the subjects, the monitors, and the sponsor will remain blinded to the treatment group allocation from BPS-314*d*-MR-PAH-302 study and to study drug during

the first 4 weeks of the OLE study. Blinding is necessary to minimize the introduction of bias during the database lock of the BPS-314*d*-MR-PAH-302 study.

The study drug and its matching placebo are indistinguishable and will be packaged in the same way to ensure study blinding for the first 4 weeks of the study.

5.5 Unblinding Procedures

An unblinding procedure will only be applicable in the first 4 weeks of the study. An Interactive Randomization Technology (IRT) manual will be provided to the study personnel that outlines unblinding procedures. Unblinding of a subject's treatment assignment may be conducted by either the Investigator or the medical monitor using IRT via the web or phone. Only if a subject's medical condition warrants, such as a medical emergency for which treatment requires knowledge of what dose of esuberaprost was given, may the investigator break the blind to determine if the subject received 15 µg or 30 µg of esuberaprost per dose. 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 medical monitor and 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.

5.6 Concomitant Therapy

Subjects are encouraged to continue co-administration of treprostinil, inhaled.

Background PAH therapies may be adjusted as medically necessary, with the exception that no prohibited medications are added. Initiation, discontinuation, or dose changes of anticoagulants, diuretics and non-PAH medications are allowable.

5.6.1 Prohibited Medications

No other prostacyclin / prostacyclin derivative or IP receptor agonist, with the exception of inhaled treprostinil, should be administered for treatment of PAH during this study. Transient use [≤7 days] is allowable.

5.7 Restrictions

5.7.1 Prior Therapy

Subjects must meet inclusion and exclusion criteria outlined in Sections 4.2 and Section 4.3, respectively.

5.7.2 Fluid and Food Intake

In general, subjects should follow their normal diet and fluid intake through the course of the study and maintain a consistency regarding when meals and study drug are taken.

5.7.3 Patient Activity Restrictions

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

5.8 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 noncompliance may lead to termination of the subject from the study after consultation between the investigator and the sponsor.

5.9 Packaging and Labeling

The sponsor will supply study drug for the study. Esuberaprost sodium tablets (15 µg) and matching placebo will be mounted in identical child resistant Dose-Pak® wallet cards. At the Enrollment Visit, each subject in the study will be assigned via the IRT, a study drug "transition kit". The subject-specific "transition kit" will contain 4 weekly wallet cards, one for each of the first 4 weeks of the study. Each designated wallet card will provide the appropriate daily dosing for the Weeks 1 through 4; they will contain 8 tablets per day, 2 for each of the 4 doses to be taken each day). The "transition kit" will contain the appropriate blinded treatment of either 2 tablets of esuberaprost per dose or 1 tablet of placebo and 1 tablet of esuberaprost per dose (for the first 2 weeks for former placebo subjects).

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

Study drug will be labeled in accordance with all applicable local regulations 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.

5.10 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.

5.11 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.

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 kit 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, all used and unused study drug will either be returned to the sponsor (or designee) per the sponsor's (or designee's) written instructions, or be destroyed by the site and destruction information entered in the IRT system.

6 STUDY PROCEDURES

All relevant data captured at the BPS-314*d*-MR-PAH-302 EOS Visit will be entered in the Enrollment Visit CRFs, as required by this protocol.

6.1 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 IRB or IEC approved 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.

In the US only, for the optional collection of blood sample for future biomedical research (see Section 6.9.2), a separate ICF must be signed by the US subjects agreeing to participate. A subject's participation in the OLE study will in no way be affected if he/she declines consent for the optional future biomedical research.

In order to provide seamless continuation of esuberaprost sodium tablet treatment, subjects must provide informed consent for this OLE study on or prior to the EOS Visit for the BPS-314*d*-MR-PAH-302 study.

6.2 Medical History

Medical and surgical history that was collected from each subject during the randomized, controlled, BPS-314*d*-MR-PAH-302 study will be used for this study. No repeat entry of data already entered in BPS-314*d*-MR-PAH-302 database will be necessary.

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

6.3 Physical Examination

A physical examination will be conducted by a qualified study clinician as outlined in the Schedule of Events (Appendix 1). 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 first dose of study treatment as part of the OLE study should be recorded on the Adverse Event CRF as an AE.

6.4 Vital Signs

Vital signs will be measured at all scheduled study visits. Subject height will be recorded at the Enrollment Visit and weight will be recorded at each study visit. Systolic and diastolic blood

pressure, heart rate, and temperature will be measured after a seated rest per the site's standard procedures.

Any values judged by the investigator to be clinically significant abnormal changes after subject's first dose of study treatment as part of the OLE study should also be recorded on the Adverse Event CRF as an AE.

6.5 Electrocardiogram Assessment

Twelve-lead electrocardiograms (ECGs) will be recorded following rest per the site's standard procedure in the semi-recumbent position at each study visit.

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 the subject's first dose of study treatment as part of the OLE study should also be recorded on the Adverse Event CRF as an AE.

6.6 Clinical Laboratory Tests

6.6.1 Laboratory Parameters

Blood and urine specimens for the measurement and evaluation of serum chemistry, hematology, coagulation, urinalysis, and N-terminal pro-Brain Natriuretic Peptide (NT-pro-BNP) will be collected at each study visit.

Subjects will be in a seated or supine position during blood collection. Clinical laboratory parameters will include those presented in Table 2. Blood samples will be sent by the site to a certified central laboratory for analysis. Results will be forwarded to the sites and electronically transferred into the study database.

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 the subject's first dose of study treatment as part of the OLE study should also be recorded on the Adverse Event CRF as an AE.

Table 2. 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
- Urobilinogen
	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
	
	Coagulation:
	- Prothrombin time (PT)
	- Activated partial thromboplastin time (PTT)
	
	Pregnancy test:
	- Urine pregnancy test at Enrollment Visit
	- Serum pregnancy test at all post-Enrollment study visits

6.6.2 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 taken at the Enrollment Visit, and a serum test will be performed at all post-Enrollment study visits.

6.6.3 Sample Collection, Storage, and Shipping

Analysis of laboratory specimens listed in Table 2 will be performed by a certified central laboratory. 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.

6.7 Dispensing Study Drug

Study site personnel will dispense appropriate supplies of esuberaprost (and placebo during the transition period) to subjects at each study visit. Subjects will be instructed to return all esuberaprost, including empty or partially used packages, to the appropriate study personnel at post-Enrollment site visits.

Esuberaprost dosing during the study will be recorded in the appropriate CRF. Detailed study drug disposition records will be maintained as previously described (Section 5.10).

6.8 Efficacy Assessments

Efficacy will be assessed as a secondary objective by continuing to evaluate the efficacy parameters from the BPS-314*d*-MR-PAH-302 study. The 6-Minute Walk Distance (6MWD), the Borg Dyspnea Score, World Health Organization (WHO) Functional Class (FC), and NT-pro-BNP, will be assessed at each post-Enrollment study visit.

6.8.1 Six-Minute Walk Distance

The 6-minute walk test (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 each post-Enrollment study visit.

Appendix 2 presents the standardized procedures for administration of the 6MWT.

If a subject is assessed for the 6MWT while using oxygen therapy, the use of oxygen should be recorded on the CRF. Oxygen use for all future 6MWTs should be conducted in accordance with the Investigator's clinical judgement.

6.8.2 Borg Dyspnea Score

The modified 0-10 category-ratio Borg scale is one in 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. Subjects may choose the number or the verbal descriptor to reflect presumed ratio properties of sensation or symptom intensity. Appendix 3 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.

6.8.3 WHO Functional Class

At the Enrollment Visit the investigator will classify the subjects for PAH severity using the WHO FC. Assessment for WHO FC for PAH should be made at each post-Enrollment study visit. See Appendix 4 for categories.

6.9 Other Assessments

6.9.1 Quality of Life Assessment

Quality of life will be assessed for all subjects at Enrollment and Month 6 using the PRO instrument, emPHasis-10. Refer to Appendix 6 for details.

6.9.2 Future Biomedical Research

For those subjects in the US who choose to participate and provide a separate informed consent, blood samples will be collected at Enrollment (prior to initial esuberaprost dosing in the OLE study) and at Month 3 Visits for future biomedical research (e.g., biomarker and genomic analysis). Biomarker and genomic samples will be collected pre-dose at the Enrollment Visit and a follow-up biomarker sample at any point during the visit for Month 3. Details about sample handling will be provided in Study Procedures Manual.

6.10 Adverse Events Assessments

6.10.1 Performing Adverse Events Assessments

The clinical site personnel will monitor all AEs throughout the study, from the time of the subject's signed informed consent for this OLE study until the end of the subject's study participation. 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 site 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, including AEs that are on-going at the EOS Visit from the BPS-314*d*-MR-PAH-302 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 esuberaprost. 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 5) 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.

6.10.2 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. Adverse events 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 and the SAE Report Form completed and submitted accordingly.

6.10.3 Severity

For each reported AE the investigator is responsible for grading its severity (or intensity) according to the criteria outlined in Appendix 5 and recording these data in the subject's source documents and on the AE page of the CRF.

6.10.4 Relationship

For each AE reported, the investigator is responsible assessing the likelihood that an AE is causally related to esuberaprost according to the criteria outlined in Appendix 5. These data must be recorded in the subject's source documents and on the AE page of the CRF.

6.10.5 Expectedness

The known and expected AEs due to the use of esuberaprost are described in the current Investigators' Brochure.

6.10.6 Clinical Laboratory Adverse Events

The investigator is responsible for reviewing the results of all laboratory tests as they become available. Any values judged by the investigator to be clinically significant abnormal changes after subject's first dose of study treatment as part of the OLE study should also be recorded on the Adverse Event CRF as an AE. 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.

6.10.7 Serious Adverse Events

6.10.7.1 Definition

A 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.

6.10.7.2 Reporting Serious Adverse Events

All SAEs, as defined in Appendix 5 and regardless of expectedness or causality, must be reported via email or fax within 24 hours of the investigator's knowledge of an SAE occurrence:

Email: **drugsafety@unither.com** (primary)
Fax: **1-919-313-1297** (backup)

The investigator or sponsor (if appropriate) must also notify their IRB, 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.

6.10.8 Treatment-Emergent Adverse Events

Treatment-emergent AEs will be defined as events that are newly occurring or worsening following treatment with esuberaprost at the Enrollment Visit.

The most frequently reported treatment-emergent adverse events (TEAEs; ≥ 10%) for esuberaprost tablets are headache, nausea, dyspnea, dizziness, diarrhea, upper respiratory tract infection, cough, fatigue, sinusitis, flushing, worsening PAH, urinary tract infection, and vomiting.

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

6.11 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. See Section 5.6.1 for prohibited concomitant medications.

6.12 Removal of Patients from the Trial or Study Drug

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. If necessary, the subject should be weaned off study drug at a maximum decrement of 1 tablet QID and a minimum decrement of 1 tablet QID per week (scenarios provided in Table 1). The transition strategy off of study drug is at the investigator discretion as medically warranted. If discontinuation from study drug is within the first 4 weeks of the OLE study, the down-titration will occur in a blinded fashion. 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.

6.13 Appropriateness of Measurements

The primary objective is to assess the safety of long-term treatment with esuberaprost and better characterize its safety profile. Evaluation of AEs, clinical laboratory tests, vitals, ECGs, and physical examinations are standard assessments of PAH drug safety and tolerability for patients with this disease.

The secondary objective of this study will be to describe the long-term efficacy of esuberaprost. Efficacy endpoints of 6MWD, Borg Dyspnea Score, WHO FC, NT-pro-BNP level, are standard evaluations of PAH.

7 STUDY ACTIVITIES

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

7.1 Enrollment Visit (Day 1)

Subjects who provide informed consent for this OLE study on or prior to the EOS Visit for BPS-314*d*-MR-PAH-302 may participate in the study, provided all other eligibility criteria are met.

The following procedures will be completed for enrollment into this OLE Study:

- Verify that the subject meets all inclusion/exclusion criteria (See Section 4.2 and Section 4.3)
- Enter any ongoing AEs from the BPS-314*d*-MR-PAH-302 study
- Record concomitant medications
- Perform a urine pregnancy test for women of child-bearing potential
- Enroll subject in IRT to receive the study drug kit number for the 4-week, blinded transition period
- **OPTIONAL / US SUBJECTS ONLY:** For subjects who consent to provide samples for future biomedical research, collect blood sample(s) prior to initial esuberaprost dose in this study
- Quality of life assessment using emPHasis-10
- Dispense study drug "transition kits" for the first 4 weeks of the study
- Observe and record study drug administration. Subjects should remain in the clinic for a 2-3 hour observation period following dosing to assess for any AEs.
- Record first study drug administration
- 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

7.2 Phone Calls

Subject should be contacted weekly between the Enrollment Visit and Week 4. After 2 weeks on study drug, the subject should be contacted to assess drug tolerability and instructed to begin using the Week 3 and Week 4 wallet cards that will be provided at the Enrollment Visit.

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

- Record study drug administration for dose changes, as applicable
- Record AEs
- Record concomitant medications

7.3 Week 4 Visit

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

- Perform a physical examination
- Record vital signs after seated rest
- Record WHO FC
- Record a 12-Lead ECG following rest in a semi-recumbent position
- Conduct an unencouraged 6MWT
- 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 AEs
- Record concomitant medications
- Provide subject with a 2-month supply of esuberaprost. If applicable, provide additional instructions/remind subject on importance of taking esuberaprost and inhaled treprostinil together.
- Record study drug administration for 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

7.4 Quarterly Visits

Subjects will return to the study site at Months 3, 6, 9, and 12 and Quarterly thereafter (± 10 days) for the following procedures:

- Perform a physical examination
- Record vital signs after seated rest
- Record WHO FC
- Record a 12-Lead ECG following rest in a semi-recumbent position
- Conduct an unencouraged 6MWT
- Record Borg Dyspnea Score
- Obtain blood and urine samples for clinical laboratory parameters (serum chemistry, hematology, coagulation, urinalysis and NT-pro-BNP)
- **OPTIONAL / US SUBJECTS AT MONTH 3 ONLY:** For subjects who consent to provide samples for future biomedical research, collect blood sample(s) at 3 months in this study
- **MONTH 6 ONLY**: Quality of life assessment using emPHasis-10

- Obtain serum pregnancy test for women of childbearing potential
- Record AEs
- Record concomitant medications
- Provide subject with a 3-month supply of esuberaprost. If applicable, provide additional instructions/remind subject on importance of taking esuberaprost and inhaled treprostinil together.
- Record study drug accountability
- Record study drug administration for 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

7.5 End-of-Study or Early Termination Visit

At the conclusion of the study (see Section 3.3) or if a subject discontinues the study prematurely, subjects will return to the clinic an EOS Visit for the following procedures:

- Perform a physical examination
- Record vital signs after seated rest
- Record WHO FC
- Record a 12-Lead ECG following rest in a semi-recumbent position
- Conduct an unencouraged 6MWT
- 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 AEs
- Record concomitant medications
- Record study drug accountability
- Record study drug administration and/or dose changes, as applicable

7.6 Unscheduled Visit

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 vital signs after seated rest
- Record a 12-Lead ECG following rest in a semi-recumbent position.
- Record WHO FC

- Conduct an unencouraged 6MWT
- 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 AEs
- Record concomitant medications
- Supply of study drug as applicable
- Record study drug accountability
- Record study drug administration for 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

8 QUALITY CONTROL AND ASSURANCE

The sponsor is responsible for ensuring that the study 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.

9 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.

9.1 General Considerations

The data collected in this study is observational and will be presented in listings and tables. No inferential statistical analyses are planned. All statistical analyses will be performed by the Sponsor's biostatistics department personnel (or appropriate designees) using SAS®, Version 9.4 or higher or other validated software.

Concomitant medications will be coded using the WHO-drug dictionary and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Coding dictionary versions will be specified in the statistical analysis plan and/or the study database.

9.2 Determination of Sample Size

This is an open-label study for all subjects who completed the BPS-314*d*-MR-PAH-302 study and were eligible to continue in this study, therefore no sample size calculation was performed.

9.3 Analysis Populations

All patients who receive at least one dose of esuberaprost will be included in the analyses.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects.

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 categorical variables (e.g., race, gender), the counts and proportions of each value will be tabulated.

9.5 Primary Endpoint

The primary objective of this study is to assess the safety and tolerability of long-term treatment with esuberaprost in patients with PAH. Descriptive analysis for safety assessments, including AEs, vital signs, clinical laboratory parameters and ECG findings, will be presented.

9.6 Secondary Endpoint

The secondary objective of this study will be to assess the efficacy of long-term treatment of esuberaprost in patients with PAH. Descriptive analysis for efficacy assessments, including 6MWD, the Borg Dyspnea Score, WHO FC, and NT-pro-BNP, will be presented.

9.7 Other Assessments or Analyses

Other study endpoint include the change in the PRO instrument, emPHasis-10, from Enrollment to Month 6.

9.8 Interim Analysis

No interim analysis is planned. However, given the open-label nature of the study, the sponsor may tabulate study data and present or publish such data during the course of the study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 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.

10.2 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 IRB, 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 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.

10.3 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.

10.4 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 esuberaprost, 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 laboratory 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 esuberaprost.

There will be a separate informed consent form for the optional future biomedical research (see Section 6.9.2). A subject's participation in the OLE study will in no way be affected if he/she declines consent for the optional assessment.

10.5 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.

10.6 Study Monitoring

In accordance with US 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. 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.

10.7 Case Report Forms and Study Records

The study 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 appropriately trained site staff. Data recorded in the CRF should be consistent with source documents. All relevant data captured at the BPS-314*d*-MR-PAH-302 EOS Visit will be entered in the Enrollment Visit CRFs, as required by this protocol.

10.8 Protocol Deviations

A protocol deviation is defined as an unplanned excursion from the approved protocol where the investigator or site personnel did not conduct the study according to the study protocol, applicable laws or regulations.

All study deviations will be documented for the clinical site, along with corrective actions where required. Study deviations may be discovered through a variety of sources, such as during the CRF review, telephone conversations, and site monitoring. Study deviations should be reported to the applicable IRB in accordance with IRB policies and/or local laws. When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. The sponsor will review all deviations from the study protocol. Corrective action and preventative action will be performed after protocol deviations are discovered during monitoring visits.

Deviations will be reported to the sponsor or designee regardless of whether medically justifiable or taken to protect the subject in an emergency. Study deviations should be reported as soon as possible upon notification of the deviation. Examples of deviations from the study protocol may include:

- No informed consent prior to starting any study procedure.
- Incorrect version of consent provided to subject.
- Enrollment of subject prior to IRB/IEC approval.
- Enrollment of subject during an IRB/IEC approval lapse.
- Subject did not meet inclusion/exclusion criteria.
- Required testing and/or measurements not performed or performed outside the allotted window of time.
- Incorrect dose or incorrect drug administered.
- Source data permanently missing.
- Adverse event not reported by investigator in the required regulatory time frame.
- Unauthorized physician performed study procedures

10.9 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.

10.10 Data Generation and Analysis

All data are submitted into a quality assured database 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.

10.11 Retention of Data

In accordance with US federal and other national regulations, ICH, and GCP guidelines, the investigator must retain study records for at least 2 years, or as local regulations apply, 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.

10.12 Financial Disclosure

Per 21 CFR 54, all investigators are required to complete a Financial Disclosure form prior to site activation, attesting to the fact that they are unaware of any financial conflicts of interest, or disclosing potential conflicts, including payments, proprietary interests and/or equity interests. Completed forms will be maintained in the Trial Master File.

10.13 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.

11 REFERENCE LIST

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Orenitram® U.S. Package Insert. United Therapeutics Corporation, 2017; Research Triangle Park, N.C. https://www.orenitram.com/pdf/Orenitram_Full_Prescribing_Information.pdf

Tyvaso® U.S. Package Insert. United Therapeutics Corporation, 2016; Research Triangle Park, N.C. https://www.tyvaso.com/pdf/Tyvaso-PI.pdf

Appendix 1 Schedule of Events

STUDY PROCEDURES	Study Visit Week[a]					
	Enrollment[b] (Day 1)	**Phone calls**	**Week 4** (± 3 days)	**Quarterly Visits** (± 10 days)	**End of Study or Early Termination Visit[c]**	**Unscheduled Visit(s)[d]**
Clinic Site Visit	X		X	X	X	X
Phone Calls[e]		X				
Informed Consent	X					
I/E Criteria	X					
Physical Examination			X	X	X	X
Vital Signs			X	X	X	X
6-Minute Walk Test / Borg Dyspnea Scale[f]			X	X	X	X
WHO Functional Class			X	X	X	X
Laboratory Parameters			X	X	X	X
Pregnancy Test[g]	X		X	X	X	X
12-Lead ECG			X	X	X	X
Enrollment	X					
Study drug[h]	X	X	X	X	X	X
Drug Accountability			X	X	X	X
AE Assessment[i]	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X
Quality of life assessment	X			X[j]		
Sample collection for future research	X			X[k]		

[a] Study Visits will take place at Week 4 and quarterly thereafter (i.e., Months 3, 6, 9, and 12).

[b] All subjects who provide informed consent for the study and meet the eligibility criteria (Section 4.2) will be enrolled. Eligibility will be determined at the EOS Visit in the BPS-314*d*-MR-PAH-302 study and subjects will be enrolled in this OLE study on the same day. Data captured at the BPS-314*d*-MR-PAH-302 EOS Visit will be entered in the Enrollment Visit CRFs, as required by this protocol.

[c] 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 EOS Visit and the Study Termination CRF will be completed.

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

[e] Phone calls: Contact with the subject should occur weekly for the first 3 weeks to ensure up-titration to the fixed dose is tolerated and assess AEs.

[f] 6MWTs and Borg should be conducted each post-Enrollment Visit.

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

[h] The initial dose in this study will be administered after enrollment. All doses administered at the study site, all dose changes, and the final dose should be recorded in subject dose administration log.

[i] 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 and the SAE Report Form completed and submitted accordingly.

[j] Enrollment and Month 6 only. Patient-reported outcome of emPHasis-10 will be performed at any time during the visit.

[k] At Enrollment and Month 3 in the US only. For subjects who consent, samples for future biomedical research will be collected at Enrollment (prior to initial esuberaprost dose in this study) and at Month 3 (at any point during the visit).

Appendix 2 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, the use of oxygen should be recorded on the CRF. Oxygen use for all future 6MWTs should be conducted in accordance with the Investigator's clinical judgement.

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 3 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 4 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 5 Adverse Events

The investigator or designee will probe each subject for any adverse events that 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 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 clinically significant for that subject, this is considered an AE.

INTENSITY

Adverse events will be graded on a 3-point scale and reported as indicated on the CRFs. 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:

- NOT RELATED: The AE is not related if exposure to the investigational product has not occurred, OR the occurrence of the adverse event is not reasonably related in time, OR the AE is considered unlikely to be related to use of the investigational product.
- POSSIBLE: The AE is reasonably related in time to the administration of the investigational product AND the AE could be explained by causes other than exposure to the investigational product.
- PROBABLE: The AE has a plausible time relationship to the investigational product administration or use AND the investigational product is more likely than other causes to be responsible for the AE, OR is the most likely cause of the individual AE.

ACTION TAKEN

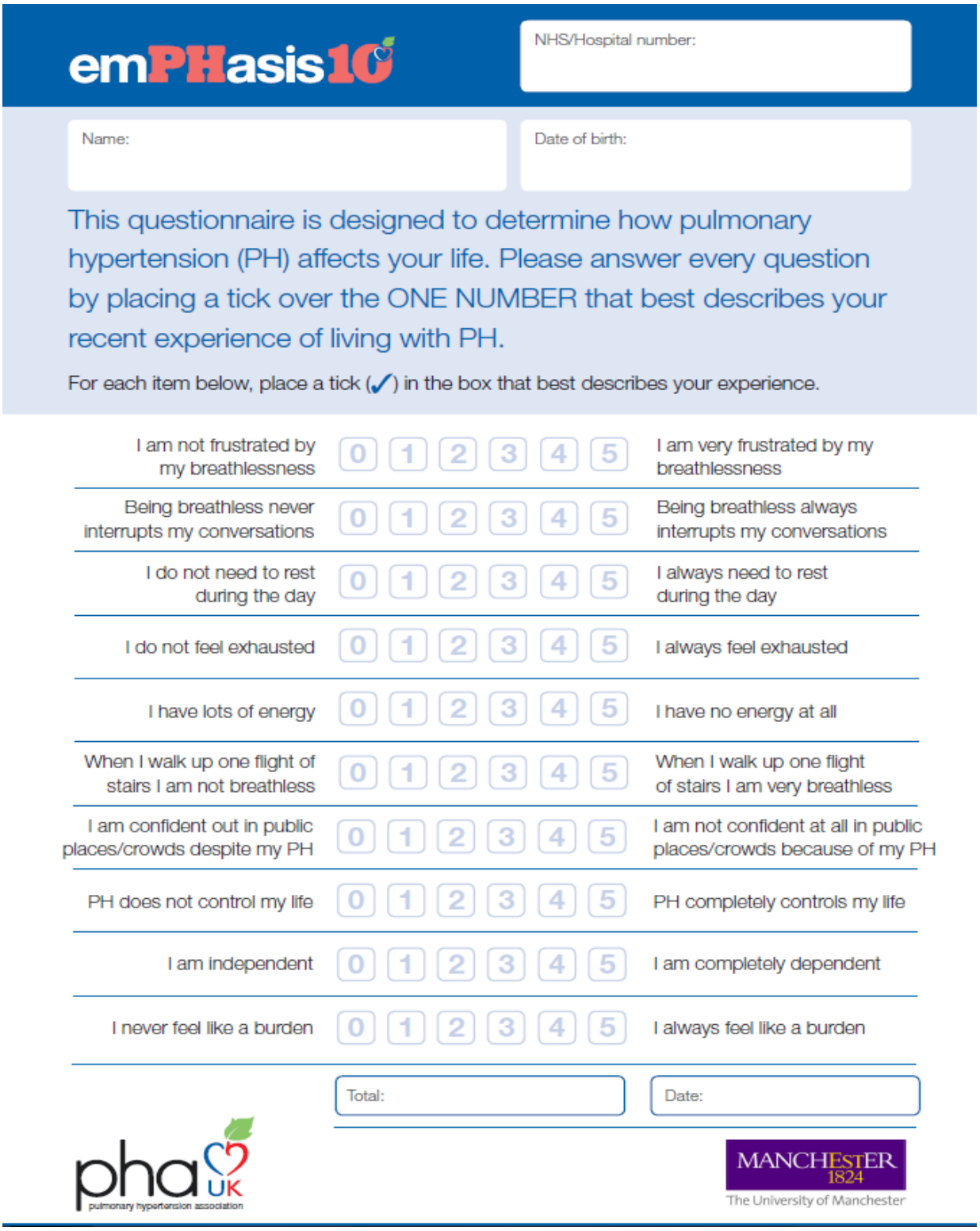
Action taken for an AE to treatment will be assessed as follows:

- 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: The subject was not on study drug at the start of the AE

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 sequelae, recovering/ resolving or unknown. If an AE is ongoing, the AE should be followed until resolution.

Appendix 6 Administration of the Quality of Life Assessment, Emphasis-10



emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK
pulmonary hypertension association

MANCHESTER 1824
The University of Manchester

Appendix 7 Sponsor Agreement

Study Title: An Open-label Extension of BPS-314*d*-MR-PAH-302 in Pulmonary Arterial Hypertension Patients

Study Number: BPS-314*d*-MR-PAH-303

Final Date: 13 September 2017

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 8 Investigator's Agreement

Study Title: An Open-label Extension of BPS-314*d*-MR-PAH-302 in Pulmonary Arterial Hypertension Patients

Study Number: BPS-314*d*-MR-PAH-303

Final Date: 13 September 2017

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.

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: _____