Statistical Analysis Plan: 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-314d-MR added-on to treprostinil, inhalation solution (Tyvaso®) in subjects with pulmonary arterial hypertension
Study Number:	BPS-314*d*-MR-PAH-302
Study Phase:	3
Product Name:	Esuberaprost (Beraprost Sodium 314*d* Modified Release)
Indication:	Treatment of Pulmonary Arterial Hypertension
IND Number:	111,729
Sponsor:	Lung Biotechnology 1040 Spring Street Silver Spring, MD 20910 United States
Author:	[redacted]
Final Date:	13 September 2018

SIGNATURE PAGE

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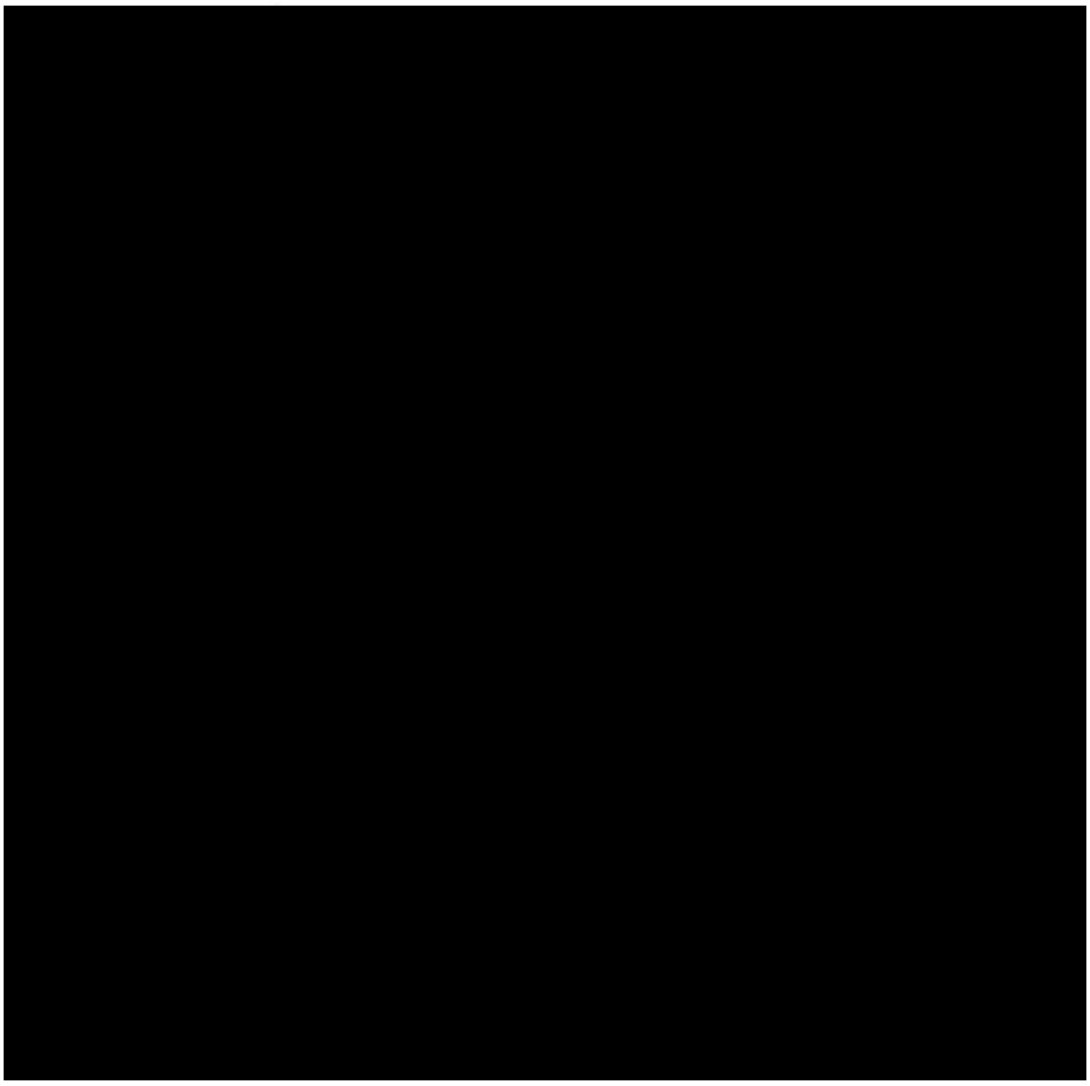
Final Date: 13 September 2018

Approved by the following:

Lung Biotechnology:



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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author(s)	Significant Changes from Previous Authorized Version
1.0	13 September 2018	[redacted]	Initial Version

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

6MWT	6-Minute Walk Test
AE	Adverse Event
BMI	Body Mass Index
BPS	Beraprost sodium
BPS-MR	Beraprost sodium-modified release
BPS-314d	Beraprost sodium 314d (esuberaprost)
BPS-314d-MR	Beraprost sodium 314d-modified release (esuberaprost tablet)
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
EoS	End-of-study
ERA	Endothelin receptor antagonist
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRT	Interactive Randomization Technology
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PDE-5	Phosphodiesterase Type 5
QID	Four times daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TFs	Tables and Figures
TtCF	Time to Clinical Failure
TtCW	Time to Clinical Worsening
UPI	Unique Patient Identification
US	United States
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the statistical methodology, as well as the rules and conventions, to be employed in the presentation and analyses of efficacy and safety data from Study BPS-314*d*-MR-PAH-302. The methods described herein conform to the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (1998) and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (1995).

The various sections of this document describe the planned tabulated summaries, graphics and and other figures (termed Tables and Figures [TFs]) to be presented in the clinical study report (CSR). A separate document will contain mock-ups of unique TFs.

All subjects in Israel who consent to participate in BPS-314*d*-MR-PAH-302 are required to co-consent to the companion study, BPS-314*d*-MR-PAH-302c, in order to receive inhaled treprostinil. Although inhaled treprostinil has been registered as a treatment for PAH in Israel, it was not commercially available at the time this study was implemented there. Therefore, Lung Biotechnology has implemented a companion study in order to provide initial and continued access of inhaled treprostinil to consenting subjects who are eligible to participate in the current study (BPS-314*d*-MR-PAH-302). Subjects in Israel are required to remain in the companion study in order to receive study drug under BPS-314*d*-MR-PAH-302; however, regardless of whether the subjects are randomized in BPS-314*d*-MR-PAH-302, those who meet eligibility criteria are permitted to continue in the companion study and receive inhaled treprostinil. The BPS-314*d*-MR-PAH-302 and BPS-314*d*-MR-PAH-302c studies are separate trials with distinct data collection goals. Data collection for the BPS-314*d*-MR-PAH-302c study is minimal, focusing only on exposure and overall safety for treprostinil, an approved product. Data gathered in the BPS-314*d*-MR-PAH-302 are comprehensive; they include the data gathered in the BPS-314*d*-MR-PAH-302c study for treprostinil exposure in subjects enrolled in both studies. Evaluation of the BPS-314*d*-MR-PAH-302c study data is unnecessary to the goals of this analysis plan, thus the companion study and any analyses of it are outside the scope of this SAP.

This SAP is based on study protocol, United States (US) Amendment 2 (dated 15 October 2014) and Israel Amendment 1 (dated 13 April 2015). It supersedes the statistical considerations identified in the study protocol. Any major deviations in this SAP from the statistical considerations of the protocol will be described and justified within the CSR. Lung Biotechnology (the sponsor) will follow this SAP in analyzing the study data. If during the course of the trial, the protocol or the set of Case Report Forms (CRFs) is modified in a way that affects the planned statistical analyses, a revised version of the SAP will be developed.

Only minor changes in the analyses shall be applied following the final version of the SAP. The CSR shall document minor changes.

Separate SAPs will be written to address the exploratory objectives of the hemodynamic, the plasma concentrations, and the exposure-response analysis for safety and efficacy endpoints.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the effect of esuberaprost (BPS-314d-MR) to placebo, each added to treprostinil, inhalation solution (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 pulmonary arterial hypertension (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 below 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 use the above criteria to provide an initial judgment of whether a suspected clinical worsening event has occurred. A blinded Event Adjudication Committee (EAC) will review all suspected clinical worsening events and make a final determination for each (see Appendix 1).

2.2 Secondary Objectives

The study protocol lists the following secondary objectives:

- To compare the effect of esuberaprost (BPS-314d-MR) and placebo each added to inhaled treprostinil 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 the 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 Functional Class where visits may be scheduled or unscheduled and
    - Lack of sustained improvement from the Baseline 6MWT (average at Baseline), defined by two consecutive visits of no sustained improvement from Baseline 6MWT (≤ 0 meters or too ill to walk, directly related to PAH); visits may be scheduled or unscheduled.
- To compare the effects of BPS-314d-MR to placebo on changes from baseline to each scheduled study visit, as applicable, for the following measures:
  - 6MWT
  - Borg Dyspnea Score
  - WHO Functional Class
  - N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels
- To evaluate the safety of BPS-314d-MR based on adverse events (AEs), clinical laboratory parameters, electrocardiogram (ECG) findings, physical examination, and vital signs.

The section for Efficacy and Safety Endpoints (Section 5) present explicitly-defined secondary endpoints (rather than general protocol-specified objectives).

2.3 Exploratory Objectives

The study has the following exploratory objectives:

- [redacted]

3 STUDY DESIGN

3.1 General Description

This Phase 3, multicenter, double-blind, randomized, placebo-controlled study is designed to assess the efficacy and safety of oral esuberaprost in subjects with PAH who are also treated with treprostinil, inhalation solution (Tyvaso). The study, which is initiated and sponsored by Lung Biotechnology PBC, formerly known as Lung LLC and Lung Biotechnology Inc. (sponsor), is being performed at study centers within the US and Israel.

The subject population includes males and females 18 to 80 years, inclusive, with a diagnosis of PAH that is either 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). For randomization, subjects must be WHO Functional Class III or IV and have declining or unsatisfactory clinical response to inhaled treprostinil therapy. The protocol defines unsatisfactory clinical response as having at least 90 days of uninterrupted inhaled treprostinil treatment, in which a stable dose of inhaled treprostinil has been received for at least 30 days prior to baseline/randomization, and still meeting the clinical criteria of a moderately-to severely-ill PAH patient, described in the protocol-defined inclusion/exclusion criteria. Subjects are permitted to receive other approved PAH therapies of an optimal, stable dose regimen for at least 30 days prior to the Baseline Visit and maintained throughout the study. Patients must sign informed consent prior to participation in any study procedure.

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 in order to ensure drug tolerability before being randomized. After having had 90 days of experience with inhaled treprostinil, a subject who continues to meet the eligibility criteria will be eligible to be randomized. Subjects who consent to the study and are currently taking inhaled treprostinil at the Screening Visit were randomized into the study after determination of eligibility criteria. Subjects are randomized to either esuberaprost or placebo through a centralized system, stratified by use of inhaled treprostinil (current user at the time of the Screening Visit: yes or no)). Following randomization, the subject, study site staff, the sponsor and the EAC all remain blinded to the treatment group assignment.

Baseline assessments are conducted over two consecutive days with Baseline 6MWT performed on each day; the mean value will establish the Baseline value. Subjects return to the study site at Weeks 4, 8, 12 (first Quarterly Visit), and for Quarterly Visits thereafter. During these study visits, subjects undergo all scheduled efficacy and safety assessments as defined by Appendix 1 of the study protocol. Between scheduled study visits, subjects will be contacted by phone to assess for possible clinical worsening events and to record any newly-occurring or changes to AEs or concomitant medications. Phone contact will 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 sponsor-approved sites in the US only. Subjects who volunteer to participate in the hemodynamic substudy will undergo a right heart catheterization 0 to 21 days prior to the Baseline Visit (prior to the first dose of IMP) and at the Month 6 Quarterly Visit (±7 days) at peak study drug blood levels (1 to 2 hours, ± 15 minutes, after administration of Investigational Medicinal Product [IMP; esuberaprost or placebo]).

An optional plasma concentration assessment will be offered to subjects at sponsor-approved sites. Subjects who participate will have blood drawn at the following time points: trough sample at the Week 4 Visit (15 minutes pre-dose, ± 5 minutes) and four blood samples during the Week 12 Visit (first Quarterly Visit) at 15 minutes prior to the second daily dose of study drug, and 15 minutes, 1 hour and 2.5 hours postdose; ± 5 minutes). If feasible, blood samples will be drawn for measurement of esuberaprost and treprostinil plasma concentrations following any serious adverse event (SAE).

Subjects will continue to participate in the study until the sponsor formally concludes the study when the prespecified number of Clinical Worsening Events has occurred (n=113). Initially, the investigator will judge whether a suspected clinical worsening event, the primary endpoint, has occurred; however, a blinded EAC, composed of medical experts in the PAH field and independent of the sponsor, reviews all suspected clinical worsening events and makes a final determination (refer to the study protocol). Following study conclusion, subjects will return to the study site for an End of Study (EOS) 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. A separate document will describe those analyses.

Subjects who withdraw consent for participation in the study or those whom the Investigator terminates prior to formal study conclusion will be weaned from IMP. They were asked to return to the study site for an EOS Visit to undergo all scheduled assessments.

3.2 Treatments

Eligible subjects are randomized to treatment with double-blind IMP.

All tablets of esuberaprost and matching placebo are to be taken four times daily (QID) without regard to meals. All subjects receiving other approved PAH therapies must be stabilized on an optimal dosing regimen for at least 30 days prior to the Baseline Visit and are required to maintain the same dose throughout the study.

Subjects randomized to esuberaprost are titrated to a target dose of 30 µg QID; 120 µg/day over a two-week period.

For the first two weeks after randomization, one tablet of IMP (esuberaprost or placebo) is administered QID. After two weeks on IMP, site personnel will contact the subject to monitor AEs and, as appropriate, instruct the subject to increase the IMP dose to two tablets QID. At the Week 4 Visit, subjects will receive IMP in bulk dosing cards, which will be the IMP packaging and configuration provided for the remainder of the study.

All doses of IMP are to be administered in conjunction with inhaled treprostinil. A subject who was unable to tolerate the targeted two tablets QID dosing regimen may continue in the study on one tablet QID dosing. At the Investigator's discretion, an observed rechallenge may be attempted using the target, two tablets QID dosing at either the Week 4 or Week 8 Visit.

The dosage for inhaled treprostinil, according to the package insert, is a maximum of 9 breaths per treatment session QID. The dosage of inhaled treprostinil is based on the subject's ≥90-day exposure where a stable dose is established for ≥30 days prior to the Baseline Visit. The number of breaths per treatment session should remain consistent throughout the subject's participation in the study.

3.2.1 Treatments Administered

3.2.1.1 Esuberaprost (Active IMP)

The active IMP in this study is esuberaprost (BPS-314*d*-MR), available as 15µg tablets for oral administration.

The target dose of esuberaprost is 30 µg QID (120 µg/day). Subjects are permitted to remain on study if the target dose is not tolerated; de-escalation back to the starting dose (15µg QID) should occur, followed by rechallenge to the target dose per the Investigator's discretion.

3.2.1.2 Placebo (Non-active IMP)

To preserve study blinding, the placebo tablets are identical in size, shape, color, and appearance to the esuberaprost tablets. The tablet packaging and configuration for placebo tablets are also identical to active tablets.

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 AEs and, as appropriate, instruct the subject to increase the study drug dose to two tablets QID.

3.2.2 Treatment Groups

Subjects who are taking a stable dose of inhaled treprostinil for the required duration and who met all other eligibility criteria are randomized 1:1 to esuberaprost or placebo as described in Section 3.2.4.

3.2.3 Patient Identification

Each screened subject receives a Unique Patient Identification (UPI) number (a unique 7-character alpha-numeric identifier) consisting of a 3-digit clinical site number and a 3-digit subject number, separated by a hyphen. The sponsor will assign site numbers to each clinical site. The subject number will be assigned by the Interactive Randomization Technology (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 is assigned the UPI of 301-001, the second, 301-002, etc.

The UPI remains the same throughout the study to identify uniquely the subject's 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. Subjects who discontinue from the trial will not be replaced.

3.2.4 Method of Assigning Subjects to Treatment Groups

All subjects are randomized using a centrally administered randomization scheme stratified by use of inhaled treprostinil (specifically, current use at the time of the Screening Visit: yes or no). Randomization is blocked but block sizes will not be disclosed to the investigators or sponsor to prevent inferences about possible treatment assignments for current or future subjects. An IRT system is utilized for the central randomization procedure. Once all entry criteria have been met at the Baseline Visit, the investigator or designee accesses the IRT (by phone or by web) to assign the subject a randomization number and the IMP corresponding to the assigned treatment group.

An independent biostatistician, designated by the sponsor, reviewed and approved the randomization scheme.

3.2.5 Blinding

During the entire study, treatment with inhaled treprostinil is open-label and therefore known to the Investigator and the subject.

Randomization to esuberaprost or placebo is double-blind. The investigator and study staff, the subjects, the monitors, the sponsor staff, the statisticians and programmers analyzing the data, and the EAC will remain blinded to treatment group allocation until the study database is locked. Esuberaprost and placebo are indistinguishable and are packaged in the same way to ensure study blinding.

Only if a subject's medical condition warrants, such as the occurrence of 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 medical emergencies, the sponsor medical monitor must grant prior approval to break the codes; however, the code may be broken on the investigator's request if 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.

4 SAMPLE SIZE AND STATISTICAL POWER

4.1 Design

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 (TtCW; Sections 2.1, and 5.1.1).

Only a few published articles discuss the observed rates of clinical worsening in patients treated with inhaled treprostinil. Benza et al (2011) reported that, in an open-label extension study of 206 PAH patients involved in an 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. They reported 12-, 24- and 36-month clinical worsening rates of 15%, 30%, and 50%, respectively.

Using the aforementioned published literature, the sponsor anticipates the one-year rate of clinical worsening will be approximately 15% for the population treated with inhaled treprostinil. As such, the sponsor considers the sample size necessary to show a clinically meaningful difference between the esuberaprost and the placebo groups treated with inhaled treprostinil to be prohibitively large. The sponsor intends to restrict recruitment to inhaled treprostinil subjects where an esuberaprost treatment effect will be more readily discerned. Following guidance from the Food and Drug Administration in 2012 (UCM332181) on clinical study enrichment strategies, the inclusion criteria of the current study (protocol, Section 5.2) specified that patients will be randomized into this study only if they are showing signs of deterioration after initial improvement on inhaled treprostinil treatment or have had a clinically suboptimal response to inhaled treprostinil treatment. The specific exclusion of subjects who are likely to be at a lower risk of clinical worsening will reduce the proportion of subjects available for recruitment; however, the targeted study population of those who have shown suboptimal response will be expected to have a higher event rate than would a broader population. Therefore, fewer subjects will be needed to test the hypothesized absolute effect size. Moreover, the target study population is one most likely to benefit from an additional therapy; without additional treatment, approximately 45% of these patients are expected to experience clinical worsening in a year.

Initial start-up activities and recruitment are restricted to ensure the safety of subjects. Therefore, the sample size calculations do not include the initial 6 months of the study to make certain the study has adequate power. The sample size calculations were based on the following assumptions:

- a one-year clinical worsening rate of:
  - 45% in the placebo group (inhaled treprostinil alone)
  - 25% in the esuberaprost group
- proportional hazards over time
- an accrual period of 1.5 years
- total follow-up time of 2.5 years (follow-up time for last subject randomized 1 year; total study duration 2.5 years)
- 0.01 two-sided significance level

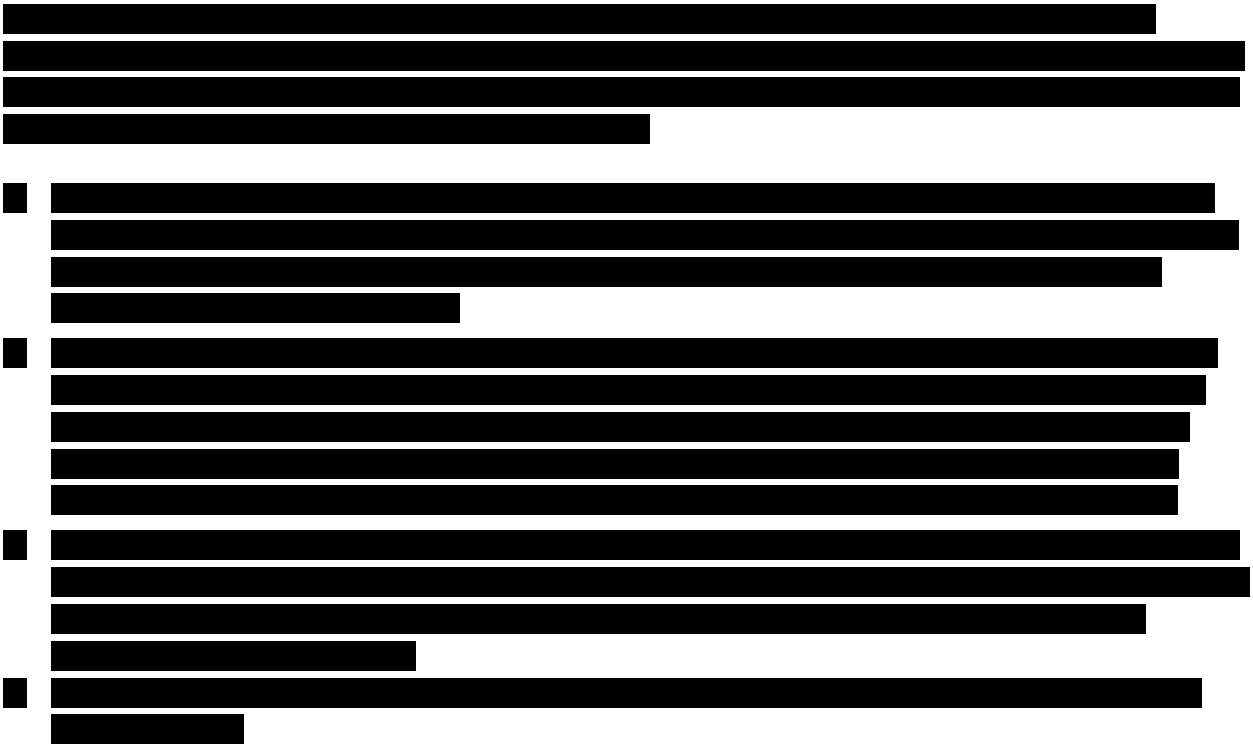
This study will randomize approximately 240 subjects (120 subjects per treatment group). Calculation of the sample size was based on the assumptions listed above. Under those assumptions, an exponential maximum likelihood test of equality of survival curves would require 113 events overall to detect a treatment difference at a power of 90% at a 0.01 two-sided significance level. Given the expected accrual period and follow-up time, an appropriate sample size is 240 subjects. There was no restriction or quota with respect to number of subjects by country.

Study sample size is based on a 0.01 two-sided significance level to provide sufficient power to observe 'substantial evidence' of effectiveness within a single clinical study. However, at the time of the analysis, the effect will be tests at a significance level of 0.05 (see Section 6.10). The power at a 0.05 two-sided significance level is 97%.

Sample size calculations were performed with nQuery Advisor 7.0 (2014) and PASS (Hintze, 2013) using sample size methods for the log-rank statistic based on Lakatos & Lan (1992).

4.2 Study Design Review

The sponsor has continuously monitored the overall (pooled) event and drop-out rates during the course of the study. Sample size may be increased during the study to maintain the planned target of 113 events. Only pooled blinded data will be used to increase sample size.



5 EFFICACY AND SAFETY ENDPOINTS

This section lists the study's efficacy and safety variables. Section 7 of the study protocol provides details regarding the description, timing, and collection of the variables. See the schedule of events in Appendix 1 of the study protocol.

5.1 Efficacy Endpoints

The efficacy analyses are defined in three stages for statistical inference. Stage 1 refers to the primary efficacy endpoint; Stage 2 to the key secondary endpoints; and Stage 3 to the other secondary endpoints. Section 6.10 addresses the planned formal testing to ensure control of type 1 error rate.

5.1.1 Primary Efficacy Endpoint (Stage 1)

The primary efficacy endpoint is the time to first occurrence of clinical worsening (see Section 2.1). The time is defined as follows:

> Time-to-clinical-worsening (TtCW, in days) = Date of first EAC-confirmed clinical worsening Date of randomization + 1.

In addition to the primary composite endpoint, individual components of TtCW (Section 2.1) will be presented and examined in an exploratory manner (see Section 6.12.7).

5.1.2 Key Secondary Endpoints (Stage 2)

The study has the following three key secondary efficacy endpoints:

1. TtCF as defined in Section 2.2.
   > Time-to-clinical-failure (TtCF, in days) = Date of first clinical failure composite endpoint Date of randomization + 1
2. Exercise capacity at Week 24 as measured by the change from baseline in distance walked on a 6MWT
3. PAH status at Week 24, as defined as the change from baseline in WHO Functional Class

5.1.3 Other Secondary Endpoints (Stage 3)

The study has the following other secondary outcomes:

- Outcomes at 24 weeks change from baseline in the following:
  - Borg Dyspnea Score
  - NT-pro-BNP levels
- Total mortality (censored at last contact if lost to follow-up or if vital status is missing at study termination)

5.1.4 Exploratory Endpoints

- [redacted]

[redacted]

5.2 Safety Variables

The following safety variables will be assessed:

- AEs
- Clinical laboratory parameters
- ECG findings
- Vital signs

5.3 Exploratory Endpoints

[redacted]

6 STATISTICAL METHODS

6.1 Datasets for Analyses

This study has the following three analysis populations:

- Randomized Population: All subjects randomized to the study. Tabulations for disposition of subjects will be generated from this population.
- Full Analysis Set (FAS) Population: All randomized subjects who received at least one dose of IMP (esuberaprost or placebo) in the study. Efficacy analyses will be conducted on this population. Subjects whose randomized treatment differs from the actual treatment received will be classified in their randomized treatment group.
- Safety Analysis Population: All randomized subjects who received at least one dose of IMP. Safety analyses will be conducted on this population. Subjects whose randomized treatment differs from the actual treatment received will be classified in the treatment group for actual treatment received. A subject who received some esuberaprost and some placebo will be assigned to the esuberaprost group.

A summary table presenting the number and percentages of subjects for each analysis populations will be presented by treatment group.

After the study database is locked and before treatment codes are unblinded, the sponsor will generate the list of subjects to be excluded from the FAS and Safety Analysis Populations.

The sponsor must approve this list before treatment is unblinded and thus before performing any analyses.

6.2 General Methodology

Treatment groups will be described as “Esuberaprost” and “Placebo” to correspond with esuberaprost with inhaled treprostinil and placebo with inhaled treprostinil, respectively.

Subjects who are not retained will not be replaced during the study; the data analysis will include the subjects who were not assessed in a manner described in the various sections that follow. Subjects completing the study will be defined as those on study, whether or not they have remained on IMP at time of the close of study or those subjects who have experienced a clinical worsening event during the study. Early terminations from the study or IMP for any other reason will be identified.

If an evaluation is repeated, such as to confirm an observed aberrant laboratory value, the analyses will use the later value. Evaluations from Unscheduled Visits are to be included with Scheduled Visits following these rules to the extent possible.

Continuous variables will be summarized with standard descriptive statistics such as mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum. For categorical data, descriptive analyses will be based on the number of subjects and related percentages.

Tabular presentations will display two columns of results, one for each treatment group, with the labels "Esuberaprost" and "Placebo". Throughout this analysis plan, the phrase "by treatment group" will refer to these two groups. If useful, some tables will include a third column representing the total population.

All tables will be presented in landscape format. For practical reasons, the point size may be reduced to (but not less than) 7 point for tables that contain too much information to fit into a single page. SAS version 9.3 or higher (2011) will be used. The sponsor's Biostatistics Department will analyze the efficacy and safety data.

Prior to unblinding, an addendum will be written that will describe the data conventions to be used to implement this SAP.

6.3 Definition of Analysis Time Points

6.3.1 Baseline

The protocol designates two days as 'baseline' for the protocol Baseline Visit: Day 1 (the day on which the subject is randomized) and Day 2 (the day the subject is first administered IMP). Analyses designated as a change from baseline will use the results of evaluations collected on the Day 1 Visit as the baseline, except for analyses of the 6MWT and Borg Dyspnea Score data, which will use the average of the Day 1 and Day 2 values. In the case of a single, missing Baseline Visit Day 1 or Day 2 value for 6MWT or Borg Dyspnea Score, the single value will be used as baseline.

For other variables, the baseline value will be defined as the value immediately prior to randomization. For some measures, the baseline will be as defined as the last evaluation closest to, but prior to, the first dose of IMP. If helpful for clarity, analyses will specify the time of baseline.

6.3.2 Change from Baseline

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

Change from baseline = Post baseline baseline

6.3.3 Study Day

Study day will be calculated relative to randomization (Baseline, Day 1). Specifically:

Study day pre-randomization = (Date of occurrence Date of randomization).
Study day on or post-randomization = (Date of occurrence Date of randomization) + 1.

6.3.4 Visit Windows

Evaluations will be counted as occurring at the Scheduled Visit designated by the protocol and as recorded on the eCRF irrespective of deviations from protocol-specified visit windows.

Unscheduled Visits will be mapped to Scheduled Visits for the purposes of analyses or summaries according to the following rules:

- Evaluations observed at Unscheduled Visits will be mapped to the Scheduled Visits if, and only if, the evaluations for that Scheduled Visit are missing and within a logical visit window. If more than one Unscheduled Visit is present, then the evaluation closest to the projected Scheduled Visit will be used.

The following rule will apply for mapping Unscheduled Visits to missing data for End of Study Visits:

- Evaluations observed at an Unscheduled Visit will be allotted to an End of Study Visit if, and only if, the End of Study Visit evaluations are missing and the Unscheduled Visit occurred on the same day as the End of Study Visit.

The following rule will apply for mapping End of Study Visits to Scheduled Visits:

- The End of Study Visit will be mapped to the next Scheduled Visit if the subject has completed the study, the End of Study Visit occurs within the window of the next planned Scheduled Visit, and the subject has not changed the dose of IMP. For example, this rule applies to the last site visit before a subject is transferred to an open label extension study while the subject is on IMP but not to subject who has weaned from study drug during early termination.

6.4 Data Handling

6.4.1 Stratification Variable

Subjects are randomized using a centrally administered randomization scheme stratified by use of inhaled treprostinil (current user at the time of the Screening Visit: yes or no) (Section 3.2.4). The clinical site enters the subject's inhaled treprostinil experience into the IRT system. If data entry errors occur and subjects are incorrectly stratified, no changes will be made to the assigned randomization, but subjects will be reclassified into the correct stratum for statistical analyses based on data from the concomitant medications CRF (100% source verified).

[redacted]

6.4.2 **Handling of Missing Data**

The sponsor acknowledges the implications of missing data on the integrity of study outcomes and, consistent with Fleming's recommendations (2011), implemented the following strategies to minimize the extent of missing data:

1. All subjects were allowed to continue in the study until the close of study, whether on IMP or not. Subjects were not to be summarily discontinued from the study, unless 1) the subject withdrew informed consent; 2) the subject met a primary endpoint and declined continuation in the study; or 3)) the subject continued to be non-adherent to study protocol after repeated attempts to correct (at least 6 months). However, the subject has the right to discontinue from the study at any time. All subjects who discontinue the study, unless they withdraw informed consent, will continue to be followed, to the extent possible, for vital status until the sponsor concludes the study.

2. Recent publications (Sitbon et al., 2015; Galiè et al., 2015) have shown that roughly 20% of subjects prematurely terminate from mortality and morbidity studies in PAH. The sponsor has throughout the study engaged with study investigators to encourage subjects' retention in the study, adherence with the protocol, and compliance with IMP.

3. While the study protocol is necessarily complex in order to obtain the scientific data to evaluate the safety and efficacy of the IMP, the sponsor designed the protocol in the manner that was not burdensome the subjects: 1) Much of the data collected for secondary endpoints is derived from assessments performed for 'standard of care' visits; 2) Study visits are minimal (quarterly) with permissive visit windows (± 10 days); 3) Use of optional substudies for exploratory endpoints; and 4) Sponsor-provided Tyvaso to all subjects in the study.

Methods for handling missing data will be described in the sections discussing each outcome.

No imputation is planned for missing safety or exploratory data.

6.5 Disposition of Subjects

The Randomized and FAS analysis populations will be used to describe subject disposition. The number and percentage of randomized subjects who completed and who discontinued (with reason for discontinuation) will be summarized by treatment group. In addition, a summary table will show subject status by clinical site.

A CONSORT diagram (Schulz et al 2010) will display the disposition by treatment group.

6.6 Protocol Deviations

Significant protocol deviations occurring during the study, major or minor, that could impact the completeness, accuracy, and/or reliability of the study data or that may affect a subject's rights, safety, or well-being will be determined by the sponsor (which will be completed prior to database lock) and will be presented for all subjects randomized.

6.7 Demographic and Other Baseline Characteristics

The following summaries will be based on the FAS population.

6.7.1 Demographic and Baseline Characteristics

Descriptive statistics will be presented overall and by treatment group for the following demographic data at randomization:

- age (in years);
- age (<65, ≥65 years);
- sex (males, females);
- race (white, black or African-American, Asian, other);
- ethnicity (Hispanic or Latino, non-Hispanic or Latino);
- weight (in kg);
- height (in m);
- BMI (in kg/m^2);
- smoking status (never, former, current smoked cigarettes/cigars); and
- country of clinical site (US, Israel).

6.7.2 PAH Disease Characteristics

Descriptive statistics presented overall and by treatment group for subjects' PAH history at randomization will include the following:

- PAH etiology [idiopathic or familial, associated with collagen vascular disease, associated with HIV infection, induced by anorexigens/toxins, associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥1 years)];

- background PAH therapy (Endothelin receptor antagonist [ERA], Phosphodiesterase Type 5 Inhibitor [PDE-5 inhibitor], inhaled treprostinil [experienced or naïve], and riociguat);
- background inhaled treprostinil (experienced or naïve)
- age of PAH diagnosis (date of diagnosis minus date of birth, in years);
- years of PAH (date of Screening Visit minus date of diagnosis);
- 6MWT and Borg Dyspnea Score at Screening;
- baseline average 6MWT;
- baseline average Borg Dyspnea Score; and
- baseline WHO Functional Class.

6.7.3 **Medical History**

Medical conditions and surgical history identified prior to randomization will be summarized overall and by treatment group. The number and percentage of subjects with any occurrence will be summarized by System Organ Class (SOC; alphabetically) and by preferred term in decreasing order of incidence.

For subjects experiencing the same medical condition multiple times, the summaries will count the condition only once for the corresponding preferred term. Similarly, the summaries will count a subject with multiple medical conditions within the same SOC only once for that SOC. SOCs will be tabulated alphabetically; within each SOC, preferred terms will be presented in decreasing order of incidence.

Medical conditions are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (the database will document the version current at time of data lock).

6.7.4 **Medications**

All medications will be coded using the WHO-Drug Global Dictionary (the database will document the version current at time of data lock).

Medications will be summarized overall and by treatment in two separate analyses, one for prior and one for concomitant medications. The number and percentage of subjects with any medication will be summarized by decreasing order of incidence. The number and percentage of subjects who have taken a medication within a primary drug category will be summarized by treatment group under that drug category by the most specific level available.

For these summaries, a subject taking the same medication multiple times will only be counted once for the corresponding most specific level available. Similarly, a subject who took multiple medications within the same drug category will be counted only once for that drug category. Prior medications will be presented in alphabetical order of drug category; within each drug category, drug most specific level available will be presented in decreasing order of incidence.

6.7.4.1 Prior Medications

Any medication or therapy reported before the first dose of IMP will be considered a prior medication.

6.7.4.2 Concomitant Medications

Any medication or therapy initiated after the first dose of IMP during the study will be considered a concomitant medication.

In addition, summary tabulations may be prepared to illustrate the extent and use of: 1) P-glycoprotein and BCRP inhibitors taken with IMP; 2) Concomitant meds that may be of interest from potential drug-drug interactions with IMP; and 3) Concomitant medications that are commonly co-administered for the treatment of PAH.

6.8 Treatment Compliance

Study drug accountability was to be performed on an ongoing basis by the study staff and checked by the monitor during site visits and at the completion of the study. Subjects were asked to return all unused study drug as well as the empty packages at each visit. The study coordinator or designee will document the unused study drug and verify that the quantity is consistent with the intended dosing schedule. 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. Treatment compliance will be presented by two analyses: by analysis of IMP pill count data and IMP dosing as reported during the study.

6.8.1 **Analysis of Pill Count Data**

Coupled with the typical issues of lost and irretrievable IMP tablets, the protocol allowed that a subject could dose adjust during the study, a dose interruption could occur if medically warranted, and subjects were asked to remain on study (on or off IMP) pending adjudication of the primary clinical worsening event, pill count data will not provide an absolutely accurate compliance measurement. The following will be calculated:

- the number of tablets dispensed during the study (Baseline Visit through End of Study Visit)
- the number of tablets returned during the study
- the number of used tablets (calculated as tablets dispensed minus tablets returned)
- the duration of exposure (see Section 7.1)
- the number of expected pills taken at 15 µg and 30 µg QID
- percent of used tablets for number of expected pills for 15 µg and 30 µg QID overall and by 20% increments

Descriptive statistics will be presented by treatment group and subgroups, including, but not limited to, age, sex, racial, country, PAH etiology, background PAH therapy, background inhaled treprostinil, baseline WHO (see Sections 6.7.1 and 6.7.2).

6.8.2 IMP Dosing

Sites were not required to record each dose of IMP taken during the study but IMP dosing was to be reported on the eCRF for first and last IMP dose as well as any doses taken while on site, any missed doses and any dose modification. The subjects are to receive QID dosing of IMP with some titration (see protocol). Three different summaries of compliance to IMP will be reported:

Summary of Daily Dosing

The first summary will measure if any of the 4 doses to be taken on a given day is taken than the subject is compliant for that day. The following will be calculated:

- the number of minimally compliant days [≥1 of QID doses taken during the study (Baseline Visit through End of Study Visit)]
- the duration of exposure (see Section 7.1)
- percent of minimally compliant days (as divided by duration of exposure) overall and by 20% increments

Summary of QID Dosing

The second summary will measure if all of the 4 doses to be taken on a given day are taken than the subject is compliant for that day. The following will be calculated:

- the number of maximally compliant days [all of QID doses taken during the study (Baseline Visit through End of Study Visit)]
- the duration of exposure (see Section 7.1)
- percent of maximally compliant days (as divided by duration of exposure) overall and by 20% increments

Summaries of IMP and Inhaled Treprostinil Dosing

The plan for administration of drug in this study was predicated on the hypothesis that dual dosing, hitting the receptors in two different ways at the same time, is beneficial. To measure the extent to which the dosing of IMP and inhaled treprostinil was performed nearly simultaneously, the two treatment groups will be compared with respect to the frequency of times dosing with IMP and inhaled treprostinil not separated by more than (a) 5 minutes and (b) 10 minutes.

Descriptive statistics will be presented by treatment group and subgroups, including, but not limited to, age, sex, racial, country, PAH etiology, background PAH therapy, background inhaled treprostinil, baseline WHO (see Sections 6.7.1 and 6.7.2). Other analyses may be performed as suggested by the data. Analogous summaries will be presented for use of inhaled treprostinil.

6.9 Analysis of Efficacy

All statistical analyses of efficacy will include the stratification variable, baseline inhaled treprostinil use, as a covariate. The sections that describe the analysis of the other secondary outcomes list other planned covariates.

Because the number of subjects in each investigational site is expected to be small, site will not be used as a covariate in the analyses. Moreover, no pooling algorithm will be used.

6.10 Hypothesis Testing

A three-stage process of hypothesis testing will be employed to control for the multiplicity of secondary endpoints.

6.10.1 Stage 1: Testing for Primary Endpoint

If, at a two-sided alpha level of 0.05, the comparison of esuberaprost to placebo on the primary endpoint, TtCW,

- is significant, then hypothesis testing will continue to Stage 2.
- is *not* significant, then formal hypothesis testing will stop.

6.10.2 Stage 2: Testing the Key Secondary Endpoints

Stage 2 hypothesis testing will employ the Simes' procedure for control of multiplicity (Simes, 1986). Testing in this stage will be at a two-sided Type I error rate of 0.05 for the three secondary endpoints:

- The comparison of esuberaprost to placebo on baseline-adjusted change from baseline 6MWT at Week 24
- The comparison of esuberaprost to placebo on TtCF
- The comparison of esuberaprost to placebo on worsening from baseline in WHO Functional Class at Week 24

Hypothesis testing will continue to Stage 3 only if at least one of the comparisons of esuberaprost to placebo on these endpoints is significant by the Simes' procedure. The Simes' procedure's critical value from the final significant test in Stage 2 will be carried forward and used for the critical value in Stage 3.

6.10.3 Stage 3: Testing for Other Secondary Endpoints

Stage 3 hypothesis testing will employ simple hierarchical testing on the pre-specified endpoints listed in Section 5.1.3. Testing in this stage will be performed at the final Simes' procedure's critical value carried forward from Stage 2.

If any comparison of esuberaprost to placebo is not significant at the critical value carried forward from Stage 2, then formal testing will stop.

As described in Section 5.1.3, endpoints in Stage 3 will be reviewed at the time of the Blinded Data Review (see Section 6.11) and the order of testing will be determined on the basis of clinical importance and likely statistical power. The order will be designed to protect Type I error rate.

Statistical analyses for exploratory endpoints not otherwise predefined for hypothesis testing will be presented as point estimates with associated 95% CIs.

6.12 Primary Efficacy Analysis

As described in Section 2.1, the primary efficacy outcome is the TtCW, measured in days, where clinical worsening is defined as the first occurrence of any of the following:

- Death (all causes)
- Hospitalization due to worsening PAH
- Initiation of a parenteral (infusion or sub-cutaneous) prostacyclin directly related to worsening PAH
- Disease progression

- Unsatisfactory long-term clinical response

As described above, a blinded Event Adjudication Committee (EAC) will review all suspected clinical worsening events and make a final determination for each (see Appendix 1). The EAC Charter, Version [redacted], specifies evidence to be provided to the EAC along with the general rules and criteria for EAC confirmation of a primary endpoint of clinical worsening. Because the EAC Charter cannot address every possible scenario, the EAC Charter shall be viewed as a framework under which the EAC will operate. Each case will be determined on the basis of a consensus of the EAC, the members of whom are independent experts in PAH. Please see Appendix 2 for general rules and criteria excerpted from the EAC Charter.

Subjects were not required to discontinue from the study after meeting a primary endpoint; thus, more than one clinical worsening event may be reported for the same subject. This section defines the calculation of time to each component of the primary outcome. The protocol specifies that investigators follow each subject for 30 days after the subject discontinues from the study to assess the occurrence of SAEs and for 90 days after the subject stops study medication for vital status. Further, the investigators are instructed to provide all clinical worsening events that occur after the primary clinical worsening event, as well as the vital status of all subjects at the time the sponsor terminates the study.

6.12.1 Death (All Cause)

Deaths that occur at any time from randomization to 90 days after the subject's last study visit is counted as a death for the primary efficacy analysis. All those still alive 90 days after their last visit are censored for death at the 90 day time even if it is known that they died after the 90 day window.

6.12.2 Hospitalization due to worsening PAH

Any hospitalization due to worsening PAH that occurs from randomization to the 30 days following subject's last study visit is counted as an event for the primary outcome. The date of the event is the actual date of hospitalization. All those without a reported hospitalization during the 30 days following their last visit are censored for hospitalization at the 30 day time even if it is known that they were hospitalized after the 30 day window.

6.12.3 Initiation of a Parenteral (infusion or sub-cutaneous) Prostacyclin

Any initiation of a parenteral prostacyclin, directly related to worsening PAH (transient use [≤ 7 days] for non-PAH related illness allowable, that occurs from randomization to the 30 days following subject's last study visit is counted as an event for the primary outcome. The date of the event is the actual date of transition to parenteral prostacyclin. All those without a reported parenteral prostacyclin during the 30 days following their last visit are censored for parenteral prostacyclin at the 30 day time even if it is known that they received parenteral prostacyclin after the 30 day window.

6.12.4 **Disease Progression**

Disease progression is assessed at each study visit. In order to declare disease progression, a subject must meet the 6MWT decrement criterion and worsening of PAH symptoms. To satisfy the 6MWT criterion, subject must attend two study visits for 6MWT measurements: initial test and confirmatory test. Any disease progression that occurs from randomization to the subject's last study visit is counted as an event for the primary outcome. The date of the event is the actual date of disease progression as defined by the initial 6MWT test. All those without a reported disease progression up to their last visit are censored for disease progression at the last study visit even if it is known that disease progression occurred after the last study visit.

6.12.5 **Unsatisfactory long-term clinical response**

Only subjects who have been on treatment for at least 24 weeks are eligible for meeting this definition. In order to declare unsatisfactory long-term clinical response, a subject must meet the 6MWT decrement criterion and show lack of sustained improvement in WHO functional class. Similar to disease progression, a subject must attend two study visits for 6MWT measurements: initial test and confirmatory test. Any unsatisfactory long-term clinical response that occurs from randomization to the subject's last study visit is counted as an event for the primary outcome. The date of the event is the actual date of unsatisfactory long-term clinical response (initial 6MWT test). All those without a reported unsatisfactory long-term clinical response up to their last visit are censored for unsatisfactory long-term clinical response at the last study visit.

6.12.6 **First Occurrence Derivation and Analysis**

Each subject will be assigned responses for each component of the primary efficacy endpoint. The response will be either the date the event occurred or the date of censoring. Then, the subject will receive one date as the outcome. For subjects who experience at least one of the component outcomes, the event date will be the earliest of the dates of the component outcomes. For those who do not experience any of the outcomes, the date of censoring will be the date of the last study visit.

Prior to unblinding, an addendum will describe in detail the methods to be used to account for missing data in the analysis of the primary outcome.

The TtCW (in days) will be analyzed using the SAS procedure LIFETEST to calculate the log-rank statistic and the associated p-value for testing whether the treatment groups differ. The program will be of the form:

```
proc lifetest data= set plots=survival;
    time TtCW * status(0);
    strata treprostinil_use /  group=treatment test=logrank;
    run;
```

The results of the statistical test for the primary study endpoint will be evaluated using a two-sided Type I error rate of 5%. A Cox Proportional Hazards Model (SAS PHREG) will be used to estimate the hazard ratio and its associated 95% confidence interval (CI). This model

will stratify by baseline treprostinil. Graphical displays and tabulations of TtCW will be presented by treatment group.

6.12.7 Supportive Analyses for Primary Analyses

Two distinct analyses will be performed for the components of the primary outcome.

1. "Contribution" outcome. A table will show the contribution of each component of the primary outcome.
2. "Incidence" outcome. Each component will be analyzed as a time-to-event variable.

These two analyses differ in that the analysis of the contribution shows only the first event in the primary outcome while the second considers the time to each component even if it is not the first event in the primary. For example, a subject who dies after experiencing disease progression would not show as a death in the analysis of the contribution of the component; however, the death of such a subject would be included in the second analysis.

Analysis of the "contribution" outcome will be descriptive. It will consist of a simple table showing the number of events of each type by treatment group contained in the primary outcome.

For the "incidence" outcomes, LIFETEST and PHREG will be used for each of the five individual components of the composite outcome. These analyses will use the component-specific dates of event or censoring. They will produce Kaplan-Meier curves, hazard ratios, 95% CIs, and other statistics as appropriate.

6.12.8 Sensitivity Analyses for the Primary Outcome

In addition to the primary and supportive analysis, two planned sensitivity analyses will be performed.

The first sensitivity analysis will mimic the methods Sitbon et al (2015) used in their primary analysis of selexipag in the GRIPHON study. As those authors say, "The primary analysis was an on-treatment analysis with follow-up data censored at the time selexipag or placebo was discontinued." The first sensitivity analysis will follow this method and censor subjects at the time they stopped study medication.

The second sensitivity analysis, which is really a set of analyses, will explore the impact of censoring and missing data. These analyses will use a tipping point approach, in which subjects will be censored at Day 1, Day 2, …, Day 90 after stopping study medication in order to explore the effect of various censoring rules on the inference from the study.

Because of the complexity of the primary and secondary outcomes, and the many possible ways that data might be censored or missing, the statistical team will examine the pattern of missing data and censoring for the pooled efficacy variables at the time of the Blind Data Review (see Section 6.11). At that point, armed with the knowledge of the patterns of divergence from full follow-up that actually occur in the trial, the sponsor may add additional sensitivity analyses, which will be described in an addendum to this SAP (completed prior to database lock).

6.13 Key Secondary Analyses

As described in Section, 5.1.2, the study has three key secondary outcomes. The following sections describe the plan for analyzing them.

6.13.1 Change from Baseline Six Minute Walk Test at Week 24

Descriptive statistics showing the raw values and changes from baseline for the 6MWT will be presented for each scheduled visit by treatment group.

A longitudinal model with change from baseline as the outcome variable, implemented through SAS PROC MIXED, will be used to analyze the data. The model will include all measurements of 6MWT. Baseline treprostinil use at time of randomization and baseline average 6MWT will be covariates. The model will include terms for the interaction between visit number and treatment. The contrast between treatment groups as Week 24 will be calculated from the model.

```
proc mixed data=(INPUT DATA SET) alpha=0.05;
    class subjid treatment treprostinil_use visitnum;
    model change_in_6MWT = baseline_6MWT treprositinal_use treatment visitnum
    visitnum*treatment /ddfm=kr;
    repeated visitnum / subject=subject type=UN r;
    lsmeans treatment*visitnum/diff om cl;
    run;
```

Note that visit numbers are used as categorical variables, not as continuous measures of time. Note also the use of *om* as an option in the *lsmeans* statement. This option allows the distribution of the categories, as observed in the data, to be used for the computation of the estimates.

Least square (LS) means for baseline-adjusted 6MWT for each treatment group, LS means of treatment group differences with their associated p-values and 95% CIs for both will be summarized and presented.

Multiple imputation, assuming that patients who stop study medication will adopt the experience in the placebo group, will be used to account for missing data. An addendum to this protocol, to be written before the data are unblinded, will present the SAS program to be used for the multiple imputation.

Sensitivity analyses will explore the extent to which multiple imputation of Week 24 data influences the interpretation of the outcome. One sensitivity analysis will assume that all subjects without Week 24 data would have continued on their assigned treatment through the end of the study; another sensitivity analysis will use the longitudinal model described above without any imputation for missing data. Other planned sensitivity analyses will be described in an addendum to this SAP, which will be completed after the Blind Data Review.

6.13.2 Time to Clinical Failure

As with TtCW, subjects who did not experience a clinical worsening and who did not receive at least 24 weeks of treatment will be censored at their last study visit.

The TtCF (in days) will be analyzed using the SAS procedure LIFETEST to calculate the log-rank statistic and p-value to compare treatment groups. The analysis statement will be of the form:

```
proc lifetest data= set plots=survival;
    time TtCF * status(0);
    strata treprostinil_use /  group=treatment test=logrank;
    run;
```

A Cox model, with baseline treprostinil use as a covariate, will be used to estimate the hazard ratio and its 95% CI.

Graphical displays, including Kaplan-Meier curves, and tabulations of TtCF and the individual components and the composite endpoint will be presented by treatment group.

Supportive and sensitivity analyses similar to those planned for TtCW will be conducted.

6.13.3 Worsening from Baseline of WHO Functional Class at Week 24

The WHO defines four functional classes for patients with PAH. In order to enter this trial, subjects had to be in Class III or IV. For the purpose of analysis of worsening WHO functional class, the WHO categorization will be augmented with a fifth class, death. At Week 24, each subject will be classified as improved, unchanged, or worsened from baseline. Those who die will be classified as worsened.

Multiple imputation will be used to impute those who are still alive but do not have a measurement of WHO Functional Class at Week 24. Predictor variables will be baseline and Week 12 WHO class, 6MWT, and Borg score. Imputation of missing data for subjects in either treatment group will be based on subjects in the placebo arm to minimize assumptions of missing at random for the treated group. One hundred datasets will be imputed and SAS PROC MIANALYZE will be used to compare the treatment groups will respect to the proportion of worsening from baseline in WHO Functional Class at Week 24 using Cochran-Mantel-Haenszel statistics stratified by baseline inhaled treprostinil use.

Summaries will include the rates by treatment, test statistic, p-value, and the odds ratio.

6.14 Other Secondary Analyses

The study has the following other secondary outcomes:

- Outcomes at 12 weeks change from baseline in the following:
  - 6MWT
  - WHO Functional Class

  - Borg Dyspnea Score
  - NT-pro-BNP levels
- Outcomes at 24 weeks change from baseline in the following:
  - Borg Dyspnea Score
  - NT-pro-BNP levels
- Total mortality (censored if lost to follow up)

6.14.1 Change from Baseline in 6MWT at Week 12

The model used to test the 6MWT at Week 24 (see Section 6.13.1) will be applied to Week 12; however, the contrast at Week 12 will be used instead of the contrast at Week 24.

6.14.2 Worsening from Baseline in WHO Functional Class at Week 12

The method described in Section 6.13.3 will be used to analyze the data at Week 12 substituting the phrase "Week 12" for "Week 24". For the multiple imputation, only baseline variables will be used.

6.14.3 Change in Borg Dyspnea Score at Weeks 12 and 24

The Borg Dyspnea Score is an 11 point scale measuring the degree of dyspnea from 0, or "nothing at all", to 10, or "panic level". Descriptive statistics of the raw and change from baseline values for Borg Dyspnea Score will be presented for each scheduled visit by treatment group. A score of 11 will be assigned to subjects who died. The Borg score will be treated as a continuous variable.

A longitudinal model will be used to describe the change from baseline in Borg score over time. Contrasts will be calculated at Weeks 12 and 24 to compare the treatment groups with respect to change. The outcome variable will be change from baseline. Independent variables will be treatment, inhaled treprostinil use baseline Borg, visit number, and the interaction of visit and treatment.

Multiple imputation, assuming that patients who stop study medication will adopt the experience in the placebo group, will be used to account for missing data. An addendum to this protocol, to be written before the data are unblinded, will present the SAS program to be used for the multiple imputation.

Sensitivity analyses will explore the extent to which multiple imputation of Week 24 data influences the interpretation of the outcome. One sensitivity analysis will assume that all subjects without Week 24 data would have continued on their assigned treatment through the end of the study; another sensitivity analysis use the longitudinal model described above without any imputation for missing data. Other planned sensitivity analyses will be described in an addendum to this SAP, which will be completed after the Blind Data Review.

6.14.4 **NT-pro-BNP at Weeks 12 and 24**

Descriptive statistics of the raw values and changes from baseline NT-pro-BNP will be presented for each scheduled visit by treatment group. Because the parameter is highly skew, the data will be log-transformed before analysis. A longitudinal model will be used to describe log NT-pro-BNP over time. The outcome variable will be the value at each time of measurement, not the change from baseline. Independent variables will be treatment, inhaled treprostinil use, baseline log NT-pro-BNP, visit number, and the interaction of visit and treatment. Contrasts will be calculated at Weeks 12 and 24 to compare the treatment groups with respect to level of the parameter.

These contrasts will be on the log scale. In order to provide summary statistics that are easily clinically interpretable, the estimates may be back transformed to the natural scale and the change from baseline may be calculated as the difference between the mean of the back-transformed estimates and the mean of the baseline value.

Multiple imputation, assuming that patients who stop study medication will adopt the experience in the placebo group, will be used to account for missing data. An addendum to this protocol, to be written before the data are unblinded, will present the SAS program to be used for the multiple imputation.

Sensitivity analyses will explore the extent to which multiple imputation of Week 24 data influences the interpretation of the outcome. One sensitivity analysis will assume that all subjects without Week 24 data would have continued on their assigned treatment through the end of the study; another sensitivity analysis use the longitudinal model described above without any imputation for missing data. Other planned sensitivity analyses will be described in an addendum to this SAP, which will be completed after the Blind Data Review.

6.14.5 **Total Mortality**

Vital status will be assessed for each randomized subject through the end of the study. All subjects who discontinue the study, either for premature termination or for meeting a primary endpoint of clinical worsening, will continue to be followed, to the extent possible, for vital status until the sponsor concludes the study. Subjects who are lost to follow-up will be censored at the date known alive. The total mortality (all cause death) in the two treatment groups will be evaluated with a Cox regression analysis to provide an estimated hazard ratio and corresponding 95% CI.

Time-to-death analyses will use the following SAS code with different rules for the variable *status(0)*.

```
proc lifetest data= set plots=survival;
    time TtCW * status(0);
    strata treprostinil_use /  group=treatment test=logrank;
    run;
```

Deaths are categorized as Cardiovascular related, PAH related, and other. A table will show the proportion of deaths, by treatment arm, in each category. Sensitivity analyses for this table will be described in an addendum to this SAP, which will be completed after the Blind Data Review.

6.15 Subgroup Analysis

Primary and secondary efficacy analyses will be conducted on the overall subject population. Subgroup analyses will be performed to explore the efficacy of esuberaprost in different subject populations. The subgroups will include, but not be limited to:

- age (<65, ≥65 years);
- sex (males, females);
- race (white, non-white);
- ethnicity (Hispanic or Latino, non-Hispanic or Latino);
- PAH etiology [idiopathic or familial, associated with collagen vascular disease, associated with HIV infection, induced by anorexigens/toxins, associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥1 years)];
- background PAH therapy (ERA, PDE-5 inhibitor, and riociguat);
- background inhaled treprostinil (experienced or naïve);
- baseline WHO Functional Class;
- years of PAH;
- baseline average 6MWT;
- baseline average Borg Dyspnea Score; and
- country of clinical site (US, Israel).

Continuous covariates will be presented by quartiles. Results will be presented using point estimates and associated 95% CIs both in tables and forest plots. Because the study was not designed to have high power for small or even moderate sized subgroups, these analyses will be considered exploratory.

7 ANALYSIS OF SAFETY

The safety assessments will consist of extent of exposure, AEs including SAEs, laboratory evaluations, vital signs, and ECG findings.

All safety analyses will be based on the Safety Population. No formal inferential testing will be reported for routine safety analyses.

7.1 Extent of Exposure

Exposure to study drug will be calculated as the date of last dose of IMP minus the date of the first dose of IMP plus 1. If the date of last dose of study drug was missing or unknown and the

last drug record had no return date, no assumption will be made for exact exposure. These analyses will include:

- Duration of exposure (in months)
- Number exposed by time (weekly to 3 months, 3-6 months, 6-12 months, 12-24 months, 24-36 months, ≥36 months)
- Number exposed by dose (15 µg, 30 µg) by time (weekly to 3 months, 3-6 months, 6-12 months, 12-24 months, 24-36 months, ≥36 months)
- Maintenance dose during the study (dose subject maintained on IMP after titration period)

Exploratory analyses may be conducted to assess IMP exposure within subgroups (see Sections 6.7.1 and 6.7.2). If appropriate, graphs will display the use of IMP over time.

Similar presentations will be made for inhaled treprostinil use during the study.

7.2 Adverse Events

AEs are recorded throughout the study and at early termination. They are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (the database will document the version current at time of data lock).

7.2.1 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the IMP or any event already present that worsens in either intensity or frequency following exposure to the IMP.

Only TEAEs occurring after IMP exposure will be summarized. Any AE starting prior to the first dose of IMP (i.e., during the screening period) will be excluded from the summary analyses.

The following notes the planned presentations of TEAEs. Other presentations for TEAEs may be produced to support the sponsor's review and analyses of events of special interest.

7.2.2 Date of Onset of Adverse Event

The onset date of each AE will be assigned the date recorded on the eCRF.

If the day part of the onset date is missing, then the onset date will be imputed as having occurred on the first day of the given month and year; however, when the first dose of IMP was taken in the same given month and year, then the onset date will be imputed as the day of the first dose of IMP.

If the month and day of the onset date are missing, then the onset date will be imputed as having occurred on the first month and first day of the given year; however, when the first dose of IMP was taken in the same given year, then the onset month and day parts will be imputed as the month and day of the first dose of IMP.

In the unlikely event that the onset date is fully missing, then the onset date will be set to the date of first dose of IMP.

If the imputed date is later than the reported stop date, the imputed date will be set equal to the stop date. This conservative scheme ensures that an AE with partial or complete onset date will be treated as a TEAE.

7.2.3 Intensity Rating

The Investigator classifies AEs into one of the following intensity categories: 'Mild', 'Moderate', and 'Severe' (see study protocol).

7.2.4 Relationship to Study Drug

The Investigator classifies AEs into one of the following categories with respect to IMP causality: 'Certain', 'Probably related', 'Possibly related', 'Unlikely to be related', 'Unrelated 'or 'Unassessable/Unclassifiable' (see study protocol).

For analytic purposes, 'Certain', 'Probably related', and 'Possibly related' will be classified as "Related" AEs and 'Unlikely to be related', 'Unrelated' and 'Unassessable/Unclassifiable' as "Unrelated" AEs.

7.2.5 Relationship to Background Therapy

The Investigator classifies AEs into one of the following categories with respect to background PAH drug causality, including treprostinil inhaled: 'Certain', 'Probably related', 'Possibly related', 'Unlikely to be related', 'Unrelated 'or 'Unassessable/Unclassifiable' (see study protocol).

For analytic purposes, 'Certain', 'Probably related', and 'Possibly related' will be classified as "Related" AEs and 'Unlikely to be related', 'Unrelated' and 'Unassessable/Unclassifiable' as "Unrelated" AEs.

7.2.6 Action Taken with Study Drug

For each AE, the investigator classifies the action taken with the IMP under one of the following: 'IMP Dose Increased', 'IMP Dose Not Changed', 'IMP Dose Reduced', 'IMP Drug Temporarily Discontinued', 'IMP Withdrawn', 'Unknown', or 'Not applicable' (see study protocol).

7.2.7 Summary of Treatment-Emergent Adverse Events

A summary of all TEAEs will present numbers and percentages of the following by treatment group:

- Subjects with at least one TEAE
- Subjects with at least one IMP-related TEAE
- Subjects with at least one TEAE related to PAH background medication
- Subjects with at least one serious TEAE

- Subjects with a TEAE leading to permanent discontinuation of IMP

7.2.8 Subjects with a TEAE leading to dose modifications of IMP Summaries of Adverse Events

TEAEs will be separately summarized by treatment group for the following:

- Total number of TEAEs, total number subjects with at least one TEAE
- TEAEs by severity
- TEAEs by relationship to IMP
- TEAEs by relationship to PAH background medication
- TEAEs by action taken with IMP
- TEAEs leading to study withdrawal

TEAEs will be presented in alphabetical order of SOC and by decreasing order of incidence of the preferred terms.

For these summaries, a subject having the same TEAE multiple times will only be counted once for the corresponding preferred term. Similarly, a subject who experienced multiple TEAEs within the same SOC will be counted only once for that SOC.

A subject experiencing the same TEAE multiple times or at multiple severities will only be counted once under that preferred term at the worst severity rating. Similarly, a subject who experiences the same TEAE multiple times or at multiple severities across multiple preferred terms within the same SOC will only be counted once for the worst severity rating within the SOC.

A subject experiencing the same TEAE multiple times or at multiple relationships to IMP will only be counted once for the worst relationship to IMP within a preferred term. Similarly, a subject who experiences the same TEAE multiple times or at multiple relationships to IMP across multiple preferred terms within the same SOC will only be counted once for the worst relationship to IMP within the SOC. The same procedure will be used for relationship to PAH background medication.

A subject experiencing the same TEAE multiple times or at multiple actions taken to IMP will only be counted once for the worst action taken with IMP within a preferred term. Similarly, a subject who experiences the same TEAE multiple times or at multiple actions taken to IMP across multiple preferred terms within the same SOC will only be counted once for the worst action taken to IMP within the SOC.

7.2.9 Subgroup Analysis

TEAEs will be summarized similarly within subgroups: male, female, <65 years old, ≥ 65 years old, Caucasian, Non-Caucasian, and each PAH etiology. Other subgroups may be examined if suggested by the data.

7.2.10 Clinical Laboratory Evaluations

Laboratory tests for serum chemistry, hematology, coagulation, urinalysis, and pro-NT-BNP were performed by a certified central laboratory [redacted], and laboratory results were forwarded to the site. Electronic data were automatically uploaded weekly into the subject's eCRF as specified with the eCRF vendor and [redacted].

If a clinical site used a local laboratory instead of the central laboratory, the local laboratory will provide the values to the investigator and the sponsor. These data will be included into the database. Results will be transformed for consistency into the same units and normal ranges used by the study's central laboratory ([redacted]), applying the formula:

$$y = (x - Li)\frac{Uc - Lc}{Ui - Li} + Lc$$

where x = original value, Li and Ui = lower and upper limits of normal for individual laboratory, Lc and Uc = lower and upper limit for central laboratory

If the lower limit of the central laboratory is 0, values below the lower limit of normal for a laboratory value prior to transformation will be assigned the value 0. If there is no upper limit for a test, the following formula will be used:

$$y = (x - Li)\frac{Lc}{Li} + Lc$$

In cases of missing units for a test, missing limits of central laboratory or an alternative test is performed than specified in the study protocol (e.g., absolute value instead of percent for hematology), transformed values will be set to missing; however, the non-missing flags for clinically significant values, as defined by the investigator, will be retained with transformed values for summaries. Transformed results for clinical laboratory tests will be used for all summaries and presentations. Summaries and presentations will be made using standard units.

Descriptive statistics for each clinical laboratory parameters (hematology, serum chemistry and coagulation) will be presented by treatment group at baseline, each post-baseline assessment, and End of Study visits for raw data and change from baseline (see Section 6.3.2).

Post-baseline clinically significant values, as defined by the investigator, for hematology, serum chemistry, coagulation, and urinalysis parameters will be summarized as transition tables from baseline to each post-baseline assessment and End of Study visits.

Tables will contain the number and percentage of subjects by treatment group with post-baseline clinically significant categories (low, high, and normal for hematology, chemistry, and coagulation; abnormal and normal for urinalysis) compared to baseline category for each parameter.

7.2.11 Vital Signs

Descriptive statistics for vital signs (temperature, heart rate/pulse, systolic blood pressure, diastolic blood pressure, respiration rate, weight, height, BMI) will be presented by treatment group at baseline, at each post-baseline assessment, and End of Study visits for the raw data and change from baseline.

7.2.12 ECG Evaluations

Descriptive statistics for ECG findings (heart rate, PR interval, QRS interval, QT interval, QTc interval (original and standardized across reports), sinus rhythm (normal, abnormal), ECG results (normal, abnormal), abnormality reported) will be presented by treatment group, at baseline, at each post-baseline assessment, and End of Study visits for raw data and change from baseline (see Section 6.3.2). Whenever more than one ECG are read occurs on the same day, the data summaries will use the average of these readings.

In addition, a summary of subjects with treatment-emergent clinically significant values will be presented by treatment group. Presentation will be made in order of decreasing incidence by type of abnormality with the number and percentage of subjects who experienced the type of abnormality.

7.3 Physical Examinations

Any value the Investigator judges to be a clinically significant abnormal change after the subject's consent to the study was to be recorded as an AE.

7.4 Interim Analyses and Data Monitoring

No formal interim efficacy analyses were planned or conducted.

An independent external statistical group ([redacted] performed interim safety analyses. Only the Data Safety Monitoring Board reviewed these data in order to monitor the safety of the subjects in the study. Lung Biotechnology and all other employees of [redacted] remained blinded throughout the conduct of this study.

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Appendix 1 Adjudication Committee Case Report Form

Appendix 2 EAC Charter: Event Adjudication