STATISTICAL ANALYSIS PLAN

Protocol Title:	EXPEDITE: A 16-Week, Multicenter, Open-label Study of Remodulin Induction Followed by Orenitram Optimization in Subjects with Pulmonary Arterial Hypertension
Protocol Number:	TDE-PH-402
Protocol Version/Date:	Original, 22 February 2018 Amendment 1, 09 April 2018 Amendment 2, 23 August 2018 Amendment 3, 24 June 2019
Investigational Product:	Remodulin Induction Followed by Orenitram Optimization
Sponsor:	UNITED THERAPEUTICS CORPORATION
SAP Version/Date:	2.0, 28 Apr 2022

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

Version	Version Date	Description
1.0	11 May 2020	Original signed version
2.0	28 APR 2022	SAP 2.0

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
CDISC	Clinical Data Interchange Standards Consortium
ECHO	Echocardiogram
CRF	Case report form
CSR	Clinical Study Report
FC	Functional Classification
ICF	Informed consent form
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal pro-brain natriuretic peptide
PAH	Pulmonary Arterial Hypertension
RHC	Right heart catheterization
RNA	Ribonucleic acid
RV	Right ventricular
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SDTM	Study Data Tabulation Model
SR	Sustained release
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TID	3 times daily
TSQM	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number TDE-PH-402. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the dose of Orenitram® (treprostinil) Extended Release Tablets achieved at 16 weeks after induction therapy with Remodulin® (treprostinil) Injection in Pulmonary Arterial Hypertension (PAH) patients.

2.1.2 Secondary Objective

The secondary objective of the study is to assess the effect of treatment with Orenitram (treprostinil) Extended Release tablets at 16 weeks after induction therapy with Remodulin (treprostinil) Injection on clinical response, safety, and tolerability.

2.1.3 Exploratory Objectives

Exploratory objectives of this study are evaluation of pharmacogenomics (genetic/ribonucleic acid [RNA] testing) and evaluation of biomarkers at Baseline, the Transition Visit, and Week 16.

2.2 Study Design

This is a 16-week, multicenter, open-label, uncontrolled study in subjects with PAH.

2.2.1 Overview

The study is a 16-week, open-label, multicenter, uncontrolled study in subjects with PAH.

The following study visits will occur during the 16-week study at the following time points:

- Screening
- Baseline
- Week 2 (Day 15 [±3 days]), Week 4 (Day 29 [±5 days]), Week 8 (Day 57 [±5 days]), Week 12 (Day 85 [±5 days]), and Week 16/Early Study Withdrawal (Day 113[±7 days])
- Transition Visit may occur at Weeks 2, 4, or 8 if the subject has achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. Transition may be reversed or stopped if necessary due to significant signs or symptoms of PAH or due to serious safety concerns.
- Post Transition Visit (7 to 14 days after the Transition Visit)

Table 1 Overall Schedule of Time and Events

Study Visit/Week	Screening[a]	Baseline[a,b]	Treatment Phase					
			Week 2[s]	Week 4[s,v]	Week 8[s]	Post Transition Visit[v]	Week 12	Week 16/ Early Study Withdrawal[c]
Day	-28 to -1	-14 to -1	15 (±3 days)	29 (±5 days)	57 (±5 days)	7 to 14 days after Transition Visit[v]	85 (±5 days)	113 (±7 days)
Informed consent	X							
Inclusion and exclusion criteria assessment	X	X						
Demographics	X							
PAH history[d]	X							
TSQM[e]		X	----------X[s]----------					X
emPHasis-10 questionnaire[e]		X	----------X[s]----------					X
PAH symptom score		X	----------X[s]----------					X
WHO FC	X	X	X	X	X	X	X	X
Swan-Ganz right heart catheterization[f]	X							
Medical history	X	X						
Prior PAH medications[g]	X	X						
Concomitant medications[g,h]	X	X	X	X	X	X	X	X
Physical examination[i]	X		----------X[s]----------					X
Vital signs[j]	X	X	X	X	X	X	X	X
CD4 count (for subjects with human immunodeficiency virus)	X							

Study Visit/Week	Screening[a]	Baseline[a,b]	Treatment Phase					
			Week 2[s]	Week 4[s,v]	Week 8[s]	Post Transition Visit[v]	Week 12	Week 16/ Early Study Withdrawal[c]
Day	-28 to -1	-14 to -1	15 (±3 days)	29 (±5 days)	57 (±5 days)	7 to 14 days after Transition Visit[v]	85 (±5 days)	113 (±7 days)
Clinical laboratory parameters (serum chemistry and hematology)	X	X	----------X[s]----------					X
Urine pregnancy test[k]	X	X	X[s]	X	X		X	X
Echocardiogram		X	----------X[s]----------					X
Serum NT-proBNP[l]	X	X	----------X[s]----------					X
Blood sample for pharmacogenomics (genetic/RNA)[m]		X						
Blood sample for biomarker evaluation (optional)[m]		X	----------X[s]----------					X
6MWT followed by heart-rate recovery (1 minute) and Borg dyspnea score[n]	X	X	X[o,p]	X[o,p]	X[o,p]	X[p]	X[p]	X[p]
Study drug dosing[q]		X[r,t]	X[r,t]	X[r,t]	X[r,t]	X[r,t]	X[r,t]	X[r,t]
Recording of adverse events	X	X	X	X	X	X	X	X
AE Bothersome Survey		X	----------X[s]----------					X
Periodic patient contact[u]		X	X	X	X	X	X	
Drug accountability[w]			X	X	X	X	X	X

6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test; ECHO, echocardiogram; eCRF, electronic case report form; FC, Functional Classification; IV, intravenous(ly); NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; RNA, ribonucleic acid; SC, subcutaneous(ly); TSQM, Treatment Satisfaction Questionnaire for Medication; WHO, World Health Organization

[a] Screening and Baseline assessments can be conducted up to 28 and 14 days prior to starting the Remodulin infusion, respectively. Screening must occur prior to Baseline assessments to confirm eligibility. Subjects with short-term musculoskeletal conditions (eg, sprained ankle) can be re-screened so that assessments aren't impacted by unusual or extenuating circumstances

[b] Following completion of Baseline assessments, subjects will be initiated on Remodulin at 2 ng/kg/min SC or IV in an inpatient or outpatient setting. IV Remodulin may be administered through an indwelling central venous catheter or a peripherally inserted catheter, as clinically indicated. For subjects receiving IV Remodulin through a central venous catheter, it is recommended that the central venous catheter be retained for at least 28 days after the transition from Remodulin.

[c] The assessments of Week 16/Early Study Withdrawal Visit can occur over 5 days so that assessments can take place on separate days if needed. All assessments should be conducted prior to withdrawing from the study, prior to discontinuation of Orenitram or Remodulin, and as close as possible to the last dose taken by the subject.

[d] The subject's PAH diagnosis date, past (noncurrent) PAH medications, PAH etiology, and WHO FC will be recorded.

[e] These patient-reported outcomes should be completed by subjects prior to other assessments and before imparting news regarding status of their disease. Subjects should be allowed to complete the questionnaires at their own pace, and with minimal help from others.

[f] Optional: RHC does not need to be conducted if the patient has an RHC within 180 days of Baseline with a cardiac index $\geq$2.0 L/min/m^2 with no changes in PAH medication regimen since the RHC. If an RHC is performed at Screening, values should be obtained for mean right atrial pressure (mRAP) and pulmonary vascular resistance (PVR) to calculate the Screening REVEAL 2.0 risk score.

[g] The subject's prior PAH medications and concomitant medications should be recorded on the eCRF.

[h] The Investigator will record the subject's concomitant medications and record whether the concomitant medication was used to treat an adverse event (including whether prostanoid adverse event or not). For this study, prostanoid adverse events include headache, diarrhea, flushing, nausea, jaw pain, extremity pain, and vomiting.

[i] A full physical examination is an evaluation of general appearance; mental examination; head, ear, eyes, nose, and throat examinations; and examination of dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurologic body systems.

[j] Vital signs include blood pressure, heart rate, respiration rate, height, and weight. Vital signs must be collected after 5 minutes of rest while seated. No other measurements or procedures should occur during the 5 minutes of rest. Vital signs will be collected prior to or at least 30 minutes after the 6MWT.

[k] Urine pregnancy tests will be conducted on all female subjects of childbearing potential. A negative urine pregnancy test is required of all female subjects of childbearing potential to be eligible for the study and remain enrolled as a subject.

[l] Blood samples for NT-proBNP must be drawn prior to conducting the 6MWT and will occur at the Screening Visit, Baseline Visit (prior to Remodulin initiation), the Transition Visit (prior to Orenitram initiation), and the Week 16/Early Study Withdrawal visit.

[m] Where local regulations allow, the subject's blood sample will be collected for pharmacogenomic (genetic/RNA) and biomarker analysis for those subjects who consent to the optional testing.

[n] The subject should rest (seated) for 10 minutes before each 6MWT. If the 6MWT is conducted using supplemental oxygen at Baseline, then all subsequent 6MWTs during the study should be conducted with supplemental oxygen. Similarly, if the Baseline assessment is conducted without supplemental oxygen, then subsequent assessments should also be conducted without oxygen. All efforts should be made to keep the supplemental oxygen flow rate consistent during the 6MWT. The supplemental oxygen flow rate must be recorded at every 6MWT, if applicable. The Borg dyspnea score and heart rate recovery (1 minute) should take place immediately following the 6MWT.

[o] At the Transition Visit, 6MWT should occur with the subject still on Remodulin therapy, before initiating the transition to Orenitram.

[p] When the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the subject's most recent dose.

[q] Study drug refers to both Remodulin and Orenitram.

[r] If the Investigator deems a subject unsuitable for transition to Orenitram due to significant signs and symptoms of PAH or any other serious safety concerns, the subject may remain on Remodulin for the duration of the study. The Investigator may reverse, or stop the transition to Orenitram due to concerns of subject safety.

[s] In addition to the scheduled assessments, additional testing will be performed at the Transition Visit as indicated. Subjects may transition at Weeks 2, 4, or 8 if they have achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. Transition may be reversed or stopped for subject safety.

[t] Subjects should be optimized on Remodulin therapy prior to transition to Orenitram; a dose should be achieved that improves the symptoms of PAH while minimizing excessive pharmacologic effects of Remodulin. Transition from Remodulin to Orenitram will occur over the course of 1 to 21 days.

[u] The study site will contact subjects daily during the first 2 weeks of the study, daily during the transition period (ie, while the subject is on both Remodulin and Orenitram), and twice weekly for the first 2 weeks after transitioning (ie, while the subject is on Orenitram and no longer on Remodulin). At all other time points during the study, subjects will be contacted once weekly.

[v] The Post Transition Visit occurs 7 to 14 days after transition from Remodulin to Orenitram is initiated. If the Transition Visit occurs at Week 2, the Week 4 visit can be substituted for the Post Transition Visit (ie, an extra visit is not necessary).

[w] Study site or pharmacy personnel should assess drug returned and dosing information to confirm drug accountability.

2.2.2 Randomization and Blinding

This study does not employ randomization. This is an open-label study.

2.2.3 Sample Size Determination

A sample size of approximately 35 evaluable subjects (i.e. completing the week 16 study visit without any major deviations which may interfere with study endpoints) was set for feasibility and to ensure a reasonable dataset to evaluate the Orenitram dose achieved, the clinical response to Orenitram after an induction period with Remodulin, and to assess the safety and tolerability of Orenitram after induction therapy with Remodulin. No formal sample size computation was performed with respect to the primary endpoint.

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary efficacy endpoint is the percentage of subjects achieving an Orenitram dose of 4 mg TID (or a total daily dose of 12 mg) or higher at Week 16 (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg).

The prescribed total daily dose will be used for the primary efficacy endpoint.

2.3.2 Secondary Endpoints

2.3.2.1 Safety Endpoints

Safety will be assessed using the Prostanoid Adverse Event (AE) scores captured by the AE Bothersome Survey at Baseline, the Transition Visit, and Week 16/Early Study Withdrawal.

The Investigator will administer the AE Bothersome Survey (provided in protocol Appendix E) at time points listed in Table *1* to collect information about prostanoid-related effects experienced by the subject, including headache, diarrhea, nausea, flushing, jaw pain, extremity pain and vomiting. For each prostanoid-related effect, whether the patient has experienced the effect, the degree of bothersome (from 1 - bothers me a lot to 4 - not at all bothersome), and days experiencing it (1 to 7) will be recorded.

Other safety assessments including the incidence of adverse events, clinical laboratory tests, vital signs, and physical examinations are described in Section 3.7.

2.3.2.2 Efficacy Endpoints

The secondary efficacy endpoints are to assess the effect of treatment with Orenitram after an induction period with Remodulin on the following parameters:

1. Change in 6-Minute Walk Distance (6MWD) from Baseline to the Transition Visit and Week 16
2. Change in Borg dyspnea score from Baseline to the Transition Visit and Week 16
3. Change in World Health Organization (WHO) Functional Classification (FC) from Baseline to the Transition Visit and Week 16
4. Change in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels from Baseline to the Transition Visit and Week 16

5. Change in Echocardiographic parameters from Baseline to the Transition Visit and Week 16

Echocardiogram (ECHO) examinations as assessed by central reader will be conducted at the time points listed in Table *1*. Several echocardiographic parameters will be collected, including: right atrial area (cm^2), tricuspid annular plane systolic excursion (mm), RV free wall strain (%), RV/left ventricular ratio at diastole, RV diastole (mm), LV diastole (mm), Eccentricity Index systole, Eccentricity Index diastole, RV Myocardial Performance Index; Pulmonary Artery Acceleration Time (msec) and presence of PV Notching (Non-evaluable, Present or Not Present); LVOT dimension (mm), LVOT vti (cm), ECHO Heartrate (bpm), cardiac output (Doppler method) (L/min) and presence of pericardial effusion (Present/ Not Present)

6. Change in PAH symptom score from Baseline to the Transition Visit and Week 16
7. The percentage of subjects that improve in each of the following 4 individual clinical parameters at Week 16 (6MWD, NT-proBNP, WHO FC, right atrial area) to a lower risk stratum, as defined by the 2015 European Society of Cardiology guidelines, compared to Baseline
8. The percentage of subjects that meet each of the following 4 individual clinical parameters at Week 16 in the low risk category, as defined by the 2015 European Society of Cardiology guidelines: 6MWD >440 meters, serum NT-proBNP <300 ng/L, WHO FC I or II, and right atrial area <18 cm^2
9. The percentage of subjects that either achieve an Orenitram dose of 4 mg TID (or a total daily dose of 12 mg) or higher at Week 16 (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg) or the percentage of subjects that achieve an Orenitram dose ≥2 mg TID and <4 mg TID (or a total daily dose ≥6 mg and <12 mg) at Week 16, with at least 2 of the following 3 clinical parameters at Week 16 calculated and summarized: 6MWD increase by ≥10% or ≥30 meters from Baseline, serum NT-proBNP reduction >30% from Baseline, or WHO FC I or II. This will performed using both prescribed total daily dose as well as actual dose taken.
10. The percentage of subjects that successfully transitioned to Orenitram at any dose and were successfully maintained on therapy at Week 16
11. Change in Subjects' Treatment Satisfaction Questionnaire for Medication (TSQM) responses and Health-related quality of life (emPHasis-10) questionnaires from Baseline to the Transition Visit and Week 16

The prescribed total daily dose will be used for secondary efficacy endpoints when applicable, unless otherwise stated.

TSQM

The questionnaire is provided in protocol Appendix G. The TSQM (version 1.4) comprises 14 items across four domains focusing on effectiveness (three items Q1-Q3), side effects (five items Q4-Q8), convenience (three items Q9-Q11), and global satisfaction (three items Q12-Q14) of the medication over the previous 2–3 weeks, or since the patient's last use. Except for item 4 (presence of side effects; yes or no), all items have five or seven responses, scored from one (least satisfied) to five or seven (most satisfied). Item scores are summed to give four

domain scores, which are in turn transformed to a scale of 0–100. Item 4 is not included for scoring. If an item score is missing and half of the items in the domain are complete, domain scores may be imputed from the person-specific mean score of completed items (i.e., the domain scores will be calculated as the total score of the completed items divided by the possible maximum total score of the completed items and times 100). For example, if a subject has Q1 = 5, Q2 = 2 and Q3 is missing, then domain score effectiveness = (5+2) / (7+7) * 100 = 50. The calculated domain scores will be listed.

emPHasis-10

The questionnaire is provided in protocol Appendix H. The emPHasis-10 comprises 10 items. Each item has a score scale of 0-5. The total score will be calculated as

Total score of answered questions X 10 / Number of answered questions.

The range of the total score is 0-50. If the number of answered questions is less than 7, the total score will be considered missing. The calculated total score will be listed.

Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be prespecified in this document but will be summarized at a later time by the study sponsorD.

REVEAL 2.0 risk score and French non-invasive risk score (Boucly 2017) will be summarized at Baseline, the Transition Visit, and Week 16. Change from Baseline to Transition, Baseline to Week 16, and Transition to Week 16 will also be summarized.

For subjects who consent to the optional pharmacogenomics (genetic/ribonucleic acid [RNA] testing) and biomarker testing, Baseline pharmacogenomics will be evaluated. Additionally, evaluation of biomarkers at Baseline, the Transition Visit, and Week 16, and change from Baseline to Transition, Baseline to Week 16, and Transition to Week 16 will be performed.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of Remodulin. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Nominal visits will be used for analysis. Number of weeks after transition visit will also be derived using the nominal visit.

3.1.3 Definition of Baseline and transition visit value

Baseline is defined as the last measurement prior to the initiation of Remodulin.

Transition visit value is defined as the last measurement prior to the first dose of Orenitram.

3.1.4 Definition of Treatment Phases

"Remodulin phase" is defined as the portion of the study when a patient is receiving Remodulin only.

"Transition phase" is defined as the portion of the study beginning at the Transition Visit when a patient is receiving both Remodulin and Orenitram. "Transition phase" ends at the last dose of Remodulin if the transition is "successful". "Transition phase" ends at the last dose of Orenitram if the transition is "unsuccessful" and reversed. "Transition phase" ends at the last dose of Orenitram and Remodulin if the transition is stopped.

"Orenitram phase" is defined as the portion of the study when a patient is receiving Orenitram only.

3.1.5 Summary Statistics

The efficacy and safety data in the study will be presented in summary tables and listings in the final clinical study report. Listings will be sorted by subject, visit, and time point assessment (if applicable). For summary tables, the data will be summarized by visits (including the Transition Visit) and time point assessment, if appropriate. For continuous variables in general, descriptive statistics will include the number of observations (non-missing values), mean, standard deviation (SD), median, inter-quartile range, minimum, and maximum. Change from Baseline will also be provided if applicable. For categorical variables, descriptive statistics will include the frequency and percentage in every category.

3.1.6 Hypothesis Testing

No formal statistical testing will be performed.

3.1.7 Multiple comparisons and multiplicity

No adjustments for multiplicity will be made in these analyses.

3.2 Analysis Populations

3.2.1 Safety Population

The Safety Population is defined as all subjects in the study who received study drug (Remodulin or Orenitram). All safety analyses will be performed on the Safety Population.

3.2.2 Per-protocol Population

The Per-protocol Population is defined as all subjects in the study who received study drug without any major deviations (which may interfere with efficacy evaluation).

3.2.3 Completer Population

The Completer Population is defined as all subjects in the study who complete the study without any major deviations (which may interfere with efficacy evaluation) and are receiving Orenitram at Week 16.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent), discontinued early during screening (screen failures), and enrolled will be summarized in total based on all screened subjects.

Counts and percentages of subjects who were enrolled, started Remodulin, began transition to Orenitram, completed transition to Orenitram, had to return to Remodulin, discontinued study drug prior to Week 16 visit assessments, and completed the study will be summarized based on all enrolled subjects. Reasons for early discontinuation from the study will also be summarized.

3.3.2 Protocol Deviations

The following listings and summary table will be provided for Safety Population:

1. Listing of Entry Criteria.
2. Listing of Entry Criteria Violations. The status of the entry criteria will be listed for all subjects. The listing will include the date of the initial screening assessment and a list of any specific entry criteria that were not met.
3. Summary of Entry Criteria Violations. If a sufficient number of violations occur, then the compliance to each criterion will be summarized.

Additional protocol deviations not captured in the CRF may be tabulated and listed based on criteria to be determined upon preparation of the final study report.

3.3.3 Analysis Populations

Counts and percentages of subjects in each of the 3 analysis populations (see section 3.2) will be summarized.

3.3.4 Demographic and Baseline Characteristics

The following demographic and Baseline characteristics will be summarized for each of the 3 analysis populations (see section 3.2):

- Sex
- Age
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Counts and percentages of subjects by PAH etiology will be provided. Days since initial PAH Diagnosis (as defined by RHC) will be summarized. Day of initial PAH Diagnosis will be imputed to the 15th if missing.

3.3.4.1 Hemodynamics

The following Right Heart Catheterization (RHC) parameters will be summarized for each of the 3 analysis populations:

- Mean pulmonary arterial pressure (mPAP) (mmHg)

- Pulmonary artery wedge pressure (PAWP) (mmHg)
- Left ventricular end diastolic pressure (LVEDP) (mmHg) (if available)
- Cardiac Index (L/min/m²)
- Heart Rate (beats/min)
- SAPs (mmHg)
- SAPd (mmHg)
- SAPm (mmHg)
- PAPs (mmHg)
- PAPd (mmHg)
- RAPm (mmHg)
- PVR (Wood Units)
- PCWPm (mmHg)
- SaO2 (%)
- SvO2 (%)
- CO Thermodilution (L/min)
- CO Fick (L/min)
- BSA (m²)

3.3.4.2 REVEAL 2.0 Risk Score

The following parameters, which are the components of the REVEAL 2.0 risk score, will be summarized for each of the 3 analysis populations at Baseline:

- WHO Group [APAH-CTD (+1), APAH-PoPH (+3), FPAH (+2), Other (+0), Not Available (+0)]
- Sex and Age [Male Age > 60 yrs (+2), No (+0)]
- eGFR (<60 mL/min/1.73m^2 or (if eGFR unavailable) renal inefficiency (+1), No (+0), Not available (+0)]
- NYHA/WHO Functional Class [I (-1), II (+0), III (+1), IV (+2)]
- Systolic blood pressure (SBP) [SBP < 110 mmHg (+1), ≥ 110 mmHg (+0)]
- Heart Rate (HR) [HR > 96 BPM (+1), ≤ 96 BPM (+0)]
- All-cause Hospitalizations within 6 months [Yes (+1) | No (+0)]
- 6-Minute Walk Test [< 165 m (+1), 165 m to 319 m (+0), 320 m to 439 m (-1), ≥ 440 m (-2)]
- NT-proBNP [NT-proBNP < 300 pg/mL (-2), NT-proBNP 300 to 1099 pg/mL (+0), NT-proBNP ≥ 1100 pg/mL (+2)]
- Echocardiogram [Mild, Moderate, or Severe Pericardial Effusion (+1), Trace or No Pericardial Effusion (+0), Not Available (+0)]
- Pulmonary Function Test [% predicted DLCO < 40% (+1), ≥ 40% (+0), Not Available (+0)]
- Right Heart Catheterization - mRAP [mRAP > 20 mmHg (+1) | ≤ 20 mmHg (+0) | Not Available (+0)]
- Right Heart Catheterization - PVR [PVR < 5 Wood units (-1) | ≥ 5 Wood units (+0) | Not Available (+0)]

REVEAL 2.0 risk score is also an exploratory efficacy endpoint and will be summarized at the Transition Visit and Week 16. Change from Baseline to Transition Visit, Baseline to Week 16, and Transition Visit to Week 16 will also be summarized.

3.3.5 *French Non-invasive Risk Score*

The French non-invasive method is performed according to the 2015 ESC/ERS pulmonary hypertension guidelines (Boucly 2017). This method evaluates the number of low-risk criteria using 3 modifiable clinical parameters, which are defined as the following:

1) WHO functional class I or II

2) 6-minute walk distance >440 meters

3) NT-proBNP <300 ng/L

The number of low-risk criteria is counted and thus, a patient can possess 0 to 3 low-risk criteria. The French non-invasive risk score is an exploratory efficacy endpoint and will be summarized for each of the 3 analysis populations at Baseline, the Transition Visit, and Week 16. Change from Baseline to Transition, Baseline to Week 16, and Transition to Week 16 will also be summarized.

3.3.6 *Concomitant Medications*

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version WHO-DDE B2, Mar 2017E. For summary purposes, medications will be considered as concomitant medications if they were taken at any time after the first dose of Remodulin (i.e. were ongoing or started after the first dose of Remodulin).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking concomitant medications by ATC class and preferred term will be summarized based on the Safety Population.

Counts and percentages of subjects' prior and current PAH background therapy (PDE5-I/sGC alone; ERA alone; PDE5-I/sGC+ERA; none) will be summarized by PAH medications separately based on the Safety Population.

3.3.7 *Study Drug Exposure*

A listing of Orenitram and Remodulin dose levels for each subject at each timepoint will be provided by visit.

A summary of Orenitram and Remodulin dose levels at each study visit will be provided for the Safety Population. Summary of dose levels at each study visit will also be provided for patients who transition at week 2, week 4, and week 8 separately. Change from baseline Remodulin dose levels will also be provided.

Days of exposure to study drug (Remodulin and Orenitram) will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be

summarized based on the Safety Population with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <4 weeks (<28 days)
- 4 -<8 weeks (28 - 55 days)
- 8 - <12 weeks (56 - 83 days)
- 12 - <16 weeks (84 – 111 days)
- ≥16 weeks (≥112 days).

Days of exposure to Remodulin and Days of exposure to Orenitram will also be summarized in the same way.

Number and percentage of subjects who initiated Remodulin in an inpatient vs. outpatient setting will be summarized.

Number and percentage of subjects who initiated Remodulin via IV or SC routes will be summarized

Number and percentage of subjects who switched between IV and SC routes for Remodulin will be summarized

For patients initiating Remodulin in the inpatient setting, the Remodulin dose at discharge will be summarized.

Number and percentage of subjects who initiated transition from Remodulin to Orenitram in an inpatient vs. outpatient setting will be summarized.

Summary statistics will be provided for:

- Time to Transition to Orenitram, calculated as date of first dose of Orenitram – date of first dose of Remodulin + 1
- Duration of inpatient stay (for applicable subjects) for Remodulin initiation
- Duration of transition (days receiving both Remodulin and Orenitram)
- Duration of inpatient stay (for applicable subjects) for transition to Orenitram
- Dose of Remodulin (ng/kg/min) at Transition Visit
- Prescribed total daily dose of Orenitram (mg) at the Post-Transition visit

All the above summaries will be based on the Safety Population.

3.4 Efficacy Assessment

Efficacy data will be summarized as specified in 3.4.1 and 3.4.2. The Week 16 visit and early study withdrawal will be reported separately in the efficacy tables.

The prescribed total daily dose will be used for the primary and secondary efficacy endpoints when applicable, unless otherwise specified.

3.4.1 Primary Efficacy Endpoint

The number and percentage of subjects achieving an Orenitram dose of 4 mg 3 times daily (TID) (or a total daily dose of 12 mg) or higher (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg) will be summarized for Week 16 for the Per-Protocol population. Subjects with missing data for prescribed total daily dose at Week 16 will be considered as not achieving the primary efficacy endpoint.

This will be repeated for the Completer Population.

3.4.1.1 Sensitivity analysis

To support the robustness and assess the sensitivity of the primary efficacy endpoint, the primary efficacy endpoint in 3.4.1 will be calculated using the actual dose taken for Orenitram dose (the sum of the morning, afternoon, and evening dose, where a missed dose is considered 0 mg). This analysis will be performed on both the Per-Protocol Population and the Completer Population.

3.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be summarized by visit, as applicable. The change from Baseline at each visit will be summarized for each parameter. For study visits occurring after the Transition Visit, the change from Transition Visit will also be summarized for each parameter in addition to the change from Baseline. The continuous secondary endpoints will also be summarized on Transition Visit and X Weeks Post Transition Visit in addition to the nominal visits. The value of interest listed in section 2.3.2.2 will be provided.

- 6-Minute Walk Distance (6MWD)
  - The subjects receiving oxygen during the time of the test will be listed
  - The subjects having unusual circumstances that adversely affected the walk will be listed
- Heart rate recovery after 6MWD
- Borg dyspnea score
  - The Borg dyspnea scores and their respective shifts from baseline and Transition Visit will be summarized for each assessment (i.e. number and percent of subjects who improved, worsened, or had no change)
- World Health Organization (WHO) Functional Classification (FC)
  - The functional class values and their respective shifts from baseline and Transition Visit will be summarized for each assessment (i.e. number and percent of subjects who improved, worsened, or had no change)
- N-terminal pro-brain natriuretic peptide (NT-proBNP)
  - The percent change from Baseline and Transition Visit will also be provided.
- Echocardiographic parameters
- PAH symptom score
  - Severity grade values (i.e., 0, 1, 2, or 3) for each symptom of PAH (fatigue, dyspnea, edema, dizziness, syncope, chest pain, and orthopnea) will be listed for all subjects. The severity grades and their shifts from baseline and Transition Visit will be summarized for each assessment.
- Subjects' TSQM responses and Health-related quality of life (emPHasis-10) questionnaires

- The number and percentage of subjects that successfully transitioned to Orenitram at any dose and were successfully maintained on therapy at Week 16
- The number and percentage of subjects that improve in each of the following 4 individual clinical parameters (6MWD, NT-proBNP, WHO FC, right atrial area) to a lower risk stratum, as defined by the 2015 European Society of Cardiology guidelines, compared to Baseline will be provided for the Transition Visit and Week 16.
- The number and percentage of subjects that meet each of the following 4 individual clinical parameters in the low risk category, as defined by the 2015 European Society of Cardiology guidelines: 6MWD >440 meters, serum NT-proBNP <300 ng/L, WHO FC I or II, and right atrial area <18 cm^2. This will be provided for the Transition Visit and Week 16.
- The number and percentage of subjects that either achieve an Orenitram dose of 4 mg TID (or a total daily dose of 12 mg) or higher (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg) or the percentage of subjects that achieve an Orenitram dose ≥2 mg TID and <4 mg TID (or a total daily dose ≥6 mg and <12 mg), with at least 2 of the following 3 clinical parameters: 6MWD increase by ≥10% or ≥30 meters from Baseline, serum NT-proBNP reduction >30% from Baseline, or WHO FC I or II. This will be provided for the Transition Visit and Week 16. This will be performed using both prescribed total daily dose as well as actual dose taken.

The continuous secondary endpoints may be analyzed using linear regression models with the endpoint [such as change in 6-Minute Walk Distance, change in log(NT-proBNP), and change in log(echocardiographic parameters) (performed by study sponsor at a later time) from Baseline to Transition Visit and Week 16] as the dependent variable and the baseline [or log(baseline)] value as a covariate. For endpoints modeled on the original scale, the predicted mean change from Baseline at the median baseline value will be provided, along with its associated standard error and 95% confidence interval. For endpoints modeled on the log scale, the predicted mean change from Baseline at the median log(baseline) value, with associated standard error and 95% confidence interval, will be back-transformed to the original scale and presented as the predicted geometric mean ratio to Baseline at the median baseline value. For each model fitted, the slope and its standard error and p-value will also be provided.

For patients in the Per-Protocol Population with a missing secondary efficacy endpoint at Week 16 for 6MWD, WHO FC, NT-proBNP or Echocardiographic parameters, the last observation carried forward (LOCF) method will be used, in addition to a separate complete case analysis. No imputation is needed for the Completer population.

The secondary efficacy endpoints will be summarized for the Per-Protocol Population, the Completer Population, and the subgroup of patients in the Completer Population who met the primary endpoint.

3.4.3 Exploratory Efficacy Endpoints

Baseline pharmacogenomics (genetic/ribonucleic acid [RNA] testing) will be evaluated. Evaluation of biomarkers at Baseline, the Transition Visit, and Week 16, and change from Baseline to Transition and Transition to Week 16 will be performed.

The exploratory efficacy endpoints will be prespecified in this document but performed at a later time by the study sponsor.

3.4.4 Subgroup Analysis

The primary efficacy endpoint may be summarized for the Per-Protocol and Completer Population within subgroups defined by age (Median value of IIT Population), gender, background PAH therapy at Baseline (1. none, 2. Endothelin Receptor Antagonist [ERA] alone, 3. Phosphodiesterase-5 [PDE-5] inhibitor/sGC stimulator alone, or 4. ERA + PDE-5 inhibitor/sGC stimulator), or baseline disease severity (as defined by 6MWD categories, WHO functional classification for PAH, REVEAL 2.0 risk score, time since PAH diagnosis).

3.5 Pharmacokinetic Assessment

No pharmacokinetic assessment is performed in this study.

3.6 Pharmacodynamic Assessment

No pharmacodynamic assessment is performed in this study.

3.7 Safety Assessment

Safety data will be summarized based on the Safety Population.

3.7.1 Adverse Events (AEs) and Prostanoid AEs

Adverse events will be captured from when the subject signs the informed consent form (ICF) until the subject completes the study or is withdrawn from the study. All AEs will be coded to system organ class and preferred term using MedDRA version v 21.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of Remodulin.

Adverse events related to study drug will be those with a causality of possibly or probably related.

The severity of a given AE is the maximum of all severities recorded during initial recording and all reassessments of the AE.

An overview of AEs will be provided including counts and percentages of subjects and event counts (an AE record regardless of reassessment, only contributes once into the event count) with the following:

- Any TEAEs (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study
- Any TEAEs leading to discontinuation of Remodulin
- Any TEAEs leading to discontinuation of Orenitram
- Any SAEs leading to death

Counts and percentages of subjects and event counts will also be presented by system organ class and preferred term for each of the categories in the overview, except SAEs, if there are at least 5 adverse events in the categories.

Figures for visualizing the number of days an AE falls into each AE severity category (Mild, Moderate, Severe) and changes in AE severity over time may be provided by sponsor.

For each of the "Prostanoid AEs" defined by section 3.3.1.9 of the protocol (headache, diarrhea, nausea, flushing, jaw pain, extremity pain, and vomiting):

- The counts and percentages of patients and event counts who report the Prostanoid AE will be summarized, as well as a breakdown of the maximum severity reported (e.g. mild, moderate, severe).
- This will be reported separately for each treatment phase.
- AEs that occur in more than one treatment phase (e.g. a 'severe' headache that began in the Remodulin phase that continued as a 'severe' or 'mild' to the Transition phase will be counted in both treatment phases, with corresponding severities based on the maximum severity in each phase) will be counted in each treatment phase.
- Changes in severity of Prostanoid AEs over the entire study period may be listed, summarized, and/or depicted graphically for each patient. This may be performed by the study sponsor.
- The number of days which the AE was reported and the corresponding severity may be summarized for each treatment phase (i.e. Remodulin phase, Transition phase, Orenitram phase). For these summaries, the AE Reassessment date will be used as the start and end dates for an AE which changes in severity, and the AE End Date will be the end date for the AE. This may be performed by the study sponsor.
    - Example:

    Headache occurring in Remodulin phase

    AE Start Date: 1/10/2022 severity: mild

    AE Reassessment Date 1: 1/22/2022 severity: moderate

    AE Reassessment Date 2: 2/01/2022 severity: moderate

    AE End Date: 2/05/2022

    Mild: 12 days (1/10/2022 to 1/22/2022)

    Moderate: 14 days (1/22/2022 to 2/5/2022)

    Severe: 0 days

A by subject listing will be provided for all of the AEs and listings will also be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.7.1.1 AE Bothersome Survey

Investigators will ask subjects about the prostanoid-related effects they experienced using the AE Bothersome Survey. For this study, adverse events of interest include headache, diarrhea, nausea, flushing, jaw pain, extremity pain, and vomiting. The survey is provided in protocol Appendix E. The number and percentage of subjects reporting each of the adverse events of

interest at Baseline, the Transition Visit, and Week 16/Early Study Withdrawal will be provided (Question 1).

For each symptom (headache, diarrhea, nausea, flushing, jaw pain, extremity pain, and vomiting), AE Bothersome Survey scores will be summarized at Baseline, the Transition Visit, and Week 16/Early Study Withdrawal for each question (Question 2, and Question 3). In addition, change from Baseline and change from Transition Visit will be provided. For each symptom, the following scoring system will be utilized and an overall Burden Score will be provided:

	1 day	2 days	3 days	4 days	5 days	6 days	7 days
Not at all	0	0	0	0	0	0	0
Bothers me a little	3	4	5	6	7	8	9
Bothers me some	5	6	7	8	9	10	11
Bothers me a lot	8	9	10	11	12	13	14

Points	Burden Score
0	Not at all burdensome
3 to 6	Mildly burdensome
7 to 9	Moderately burdensome
10 to 14	Very burdensome

3.7.2 Vital Signs and Clinical Laboratory Tests

Vital signs and clinical laboratory tests will not be listed or summarized.

4 ANALYSIS TIMING

4.1 Interim Analysis

An interim analysis will be performed when there are about 10 subjects that have conducted the Week 16/ Early Study Withdrawal Visit, to evaluate the safety of Orenitram after induction therapy with Remodulin. The safety profile will be used to check if it is consistent with the historical data on transitions gathered from previous studies.

The following summary tables and listings will be generated for the interim analysis based on the enrolled subjects who have conducted the Week 16/ Early Study Withdrawal Visit:

- Summary of disposition on enrolled subjects as described in section 3.3.1
- Summary of demographic and baseline characteristics will be provided as described in section 3.3.4
- Summary of REVEAL 2.0 risk score as described in section 3.3.5
- Summary of current PAH background medications as described in section 3.3.6
- Summary of study drug exposure (dosage and transition) will be provided as described in section 3.3.7
- The primary and key secondary endpoints (6MWD, Borg dyspnea score, WHO FC and NT-proBNP) will be summarized as described in section 3.4.1 and 3.4.2
- A listing of Remodulin and Orenitram dose levels for each subject at each timepoint will be provided by visit
- Overview summary of AEs as described in section 3.7.1

4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the pre-final analysis will be generated. Pre-final TFLs will be provided approximately 3 weeks after database lock.

4.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs will be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files will include: annotated case report forms (CRFs), reviewer's guide, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and Clinical Data Interchange Standards Consortium (CDISC) Define packages for both SDTM and ADaM data.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

An informal interim analysis is planned for publication purposes, targeting presentation at a PH conference occurring May 2020.

Sample size is updated to include approximately 35 evaluable subjects.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

REFERENCE

[1] Boucly, Athénaïs, et al. "Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension." European Respiratory Journal 50.2 (2017).