Document Type:	Statistical Analysis Plan	**Protocol / Study No.:**	TDE-PH-206
Final Date:	15 Aug 2017	**Total Number of Pages including Appendices:**	31
Classification:	Confidential		

Title:

A Multicenter, Open-Label, 24-Week, Uncontrolled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral Treprostinil Extended Release Tablets Following Transition from Remodulin or Inhaled Prostacyclin Therapy or as Add-on to Current PAH Therapy in De Novo Prostacyclin Pediatric Subjects Aged 7 to 17 Years with Pulmonary Arterial Hypertension

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
cMRI	Cardiac Magnetic Resonance Imaging
CPET	Cardiopulmonary Exercise Testing
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERA	Endothelin Receptor Antagonist
IQR	Interquartile Range
IV	Intravenous(ly)
LOCF	Last Observation Carried Forward
LV	Left Ventricular
LVEDP	Left Ventricular End-Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PDE5-I	Phosphodiesterase Type 5 Inhibitor
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetic(s)
PT	Preferred Term
QOL	Quality of Life
RV	Right Ventricular
RVEDV	Right Ventricular End-Diastolic Volume
RVEF	Right Ventricular Ejection Fraction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
sGC	Soluble Guanylate Cyclase
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event

Abbreviation	Definition
TID	Three Times Daily
UTC	United Therapeutics Corporation
VCO_2	Carbon Dioxide Output
VE	Minute Ventilation
VO_2	Oxygen Uptake
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1 PREFACE

This statistical analysis plan (SAP) provides further details of the planned analyses for the TDE-PH-206 study, as presented in the original protocol, dated 29 July 2014, and subsequent amendments. The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables, and figures which will be produced, are appropriate and complete to support valid conclusions regarding the study objectives and the completion of the clinical study report (CSR). Additional post-hoc or unplanned analyses, which are not defined in this SAP, may be performed to support the clinical development program. Such analyses will be documented in the CSR.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

2.1.1 Primary Objective

To assess the safety and tolerability of oral treprostinil extended release tablets in 3 cohorts of pediatric subjects with pulmonary arterial hypertension (PAH) aged 7 to 17 years:

- Cohort 1: Subjects transitioning from intravenous (IV) or subcutaneous (SC) Remodulin
- Cohort 2: Subjects transitioning from inhaled prostacyclin
- Cohort 3: As add-on to current PAH therapy in de novo prostacyclin subjects

2.1.2 Secondary Objective

1. To assess the effect of oral treprostinil on the following (assessed in all cohorts):
   - Cardiopulmonary exercise testing (CPET) with progressive cycle ergometry
   - Symptoms of PAH

- Panama and World Health Organization (WHO) Functional Classification
- 6-minute walk distance (6MWD) (with pulse oximetry and heart rate recovery monitoring)
- Borg dyspnea score
- Quality of life (QOL) assessed via the Pediatric Quality of Life Inventory (PedsQL) questionnaire
- Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Cardiac magnetic resonance imaging (cMRI)

2. To describe treprostinil pharmacokinetics (PK) in pediatric subjects with PAH aged 7 to 17 years.

3 STUDY DESIGN

This is a multicenter, open-label, safety and tolerability study of oral treprostinil administered 3 times daily (TID) (approximately every 8 hours with adjustments permitted based on the subject's lifestyle and schedule, but not sooner than every 6 hours) in pediatric PAH subjects 7 to 17 years of age (1) transitioning from continuous IV/SC Remodulin, (2) transitioning from inhaled prostacyclin, or (3) as add-on to current PAH therapies in de novo prostacyclin subjects. Eligible subjects will be assigned to a cohort based upon their PAH therapy at the time of enrollment.

Up to 7 study visits will occur during the 24-week study at the following time points: Screening, Baseline, Weeks 0 (Cohort 1 only; in-patient hospital stay Days 1 to 5), 3, 6, 12, and 24.

Cohort 1 Subjects

Following completion of Baseline assessments, including an 8-hour PK assessment while receiving IV/SC Remodulin within 7 days prior to the first dose of oral treprostinil, subjects in Cohort 1 will undergo an inpatient hospital stay lasting approximately 5 days to transition from IV/SC Remodulin to oral treprostinil. The target transition goal is 5 days and for the subject to be completely transitioned off IV/SC Remodulin prior to discharge from the hospital. Subjects will be discharged from the hospital after they have transitioned off IV/SC Remodulin, reached their target oral treprostinil dose, or as the Investigator deems appropriate. If necessary or if appropriate per Investigator discretion, subjects can prolong or complete the transition in an outpatient setting for a total transition time of up to 4 weeks.

The maximum time to titrate off IV/SC Remodulin is 4 weeks from the start of the transition; if the subject is not fully transitioned by Week 4, they will be removed from the study. If the subject is in the hospital during one of the scheduled study visits, the assessments for that visit will be conducted as scheduled during the defined visit window.

Cohort 2 and 3 Subjects

Following completion of Baseline assessments, the first dose of 0.125 mg oral treprostinil should be taken at the study site. Dosing of oral treprostinil will be initiated at 0.125 mg TID with food (approximately every 8 hours with adjustments permitted based on the subject's lifestyle and schedule, but not sooner than every 6 hours). Dose changes should be conducted under appropriate medical supervision in consultation with the study site.

Dose Optimization/Evaluation Phase for ALL Cohorts

Week 3, Week 6, and Week 12: Subjects will return to the clinic for the following assessments: vital signs, 6-minute walk test (6MWT)/Borg dyspnea score, Panama and WHO Functional Classification, symptoms of PAH, and safety assessments. At each visit, females of childbearing potential will undergo a urine pregnancy test. At Week 12, QOL (as measured by PedsQL questionnaire) and clinical laboratory assessments, including NT-proBNP testing, will occur.

Week 24 (or premature discontinuation): Subjects will return to the clinic for the following assessments: vital signs, physical examination, 6MWT/Borg dyspnea score, CPET, Panama and WHO Functional Classification, symptoms of PAH, QOL assessment, NT-proBNP, cMRI, clinical laboratory assessments, electrocardiogram (ECG), and safety assessments. Females of childbearing potential will undergo a urine pregnancy test. In addition, all subjects will undergo an 8-hour PK assessment.

4 RANDOMIZATION

No randomization will occur. All subjects will receive treatment with oral treprostinil. Subjects will be enrolled into a cohort based on their current PAH treatment regimen.

5 SEQUENCE OF PLANNED ANALYSES

A Data Safety Monitoring Board (DSMB) will meet after 5 subjects have enrolled in Cohort 1 and transitioned from IV/SC Remodulin to evaluate any safety concerns. The safety data will be prepared according to the separate DSMB analysis plan. The IV/SC Remodulin dose will be 25 to 75 ng/kg/min, inclusive, for the first 5 subjects enrolled in Cohort 1. Following the DSMB safety review, the dose range may be expanded to 25 to 125 ng/kg/min, inclusive, for the remaining subjects.

Additionally, if 2 or more of the first 5 subjects within any cohort meet the pre-specified stopping criteria, the DSMB will review the data prior to enrolling additional subjects into that cohort.

Analysis of PK samples may be performed, as warranted, to guide dosing.

Upon completion of all study subjects, after all outstanding queries are resolved and all data management quality assurance procedures are completed, the database will be locked. All data from the electronic case report form (eCRF), as well as data transmitted from external vendors for laboratory and PK presentation, will be included in the locked database. All final analyses will be performed on the final locked database.

6 SAMPLE SIZE CONSIDERATIONS

This study is intended to provide descriptive data only. A sample size of 40 subjects (25 transition [IV/SC Remodulin and inhaled prostacyclin] subjects and 15 de novo subjects) was selected for feasibility and to provide a reasonably large experience base with which to draw conclusions about the safety of the proposed protocol for (1) transition from moderate to high doses of IV/SC Remodulin to oral treprostinil, (2) transition from inhaled prostacyclin to oral treprostinil, and (3) initiation of oral treprostinil as add-on therapy in de novo prostacyclin subjects. No formal sample size computation was performed with respect to the primary objective of evaluating safety and tolerability, as only descriptive reporting of safety data is planned. The planned sample size of 10 to 15 subjects within a cohort is appropriate for further characterization of the safety, PK, and clinical benefit of oral treprostinil in this pediatric subject population with PAH.

7 ANALYSIS POPULATIONS

The Safety population will include all subjects who receive at least 1 dose of oral treprostinil.

The PK population will include all subjects who receive at least 1 dose of oral treprostinil and who provide adequate PK samples to estimate the treprostinil PK parameters. A subject's status in the PK population will be determined by the PK analysis and report writing vendor, [redacted], and provided to United Therapeutics Corporation (UTC) electronically.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All of the data included in the final locked database will be listed. In general, listings will be sorted by cohort, subject, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), and study day. For data collected on a fixed schedule, the assessment identifier will also be included on the listing.

In general, the data will be summarized by scheduled assessment (if applicable). For continuous variables, the summary statistics will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

Minimums and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal point. For discrete variables, summaries will include the frequency and percentage in each category. Percentages will be rounded to 1 decimal point. Whenever practical, categories of discrete variables will be ordered and labeled as they appear in the eCRF, and all categories represented on the eCRF will be included in summaries, even when they do not apply to any subjects in the study.

8.1 PREMATURE DISCONTINUATION AND MISSING DATA

Subjects may not complete the treatment period for a number of reasons, including but not limited to voluntary withdrawal, stopping criteria met, serious or life-threatening adverse event (AE), protocol deviation, behavior likely to undermine the validity of results, or pregnancy.

All available data from all safety subjects will be used as detailed in this SAP. Subjects will contribute the data available up to the point of study completion, or study discontinuation for any reason.

8.2 MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustment for multiple comparisons will be made in these analyses, as no formal hypotheses are being tested.

9 STUDY POPULATION

9.1 SUBJECT ACCOUNTABILITY

The listing of discontinued subjects will include all subjects who discontinued the study prematurely and will include cohort number, subject number, analysis population inclusion, date/time of last oral treprostinil dose, date subject discontinued from study, and reason for study discontinuation.

The listing of subject accountability will include all subjects who were screened for study participation. This listing will include cohort number, subject number, analysis population inclusion, informed consent date, enrollment status, reason for screen failure (if applicable), date subject completed or discontinued from study, completion status, reason for study discontinuation (if premature), whether subject was able to transition to oral treprostinil, and reason subject was unable to transition (is applicable). Any stopping criteria met will also be listed for each subject.

A listing of subjects excluded from the PK analysis will include cohort and subject number.

The number of subjects who were screened, failed screening (along with reasons for screen failure), enrolled in the study, included in the Safety population, included in the PK population, discontinued from study prematurely (along with reasons for premature discontinuation), and died during the study will be summarized by cohort and overall.

9.2 ELIGIBILITY CRITERIA

The eligibility criteria not met will be listed for all subjects, along with the date of the initial screening assessment. The listing will include all eligibility criteria not met by criterion

number, as noted in the protocol. If a subject meets all eligibility criteria, the listing will simply be blank for "Criteria not met." A footnote will be added to this listing referring the reviewer to the protocol for exact eligibility criteria language. Entry criteria not met will be summarized by cohort and overall, displaying the number of subjects with at least 1 violation, as well as the specific criterion violated.

9.3 PROTOCOL DEVIATIONS

Protocol deviations are collected via a Microsoft Excel spreadsheet outside of the eCRF. The Clinical Trial Lead will provide the final protocol deviation spreadsheet at the conclusion of the study, which will include the subject number, timing of the deviation (visit number), deviation category (i.e., efficacy, safety, PK, informed consent, visit window, etc.), deviation description, and the classification of the deviation (major/minor). A SAS dataset will be created from this spreadsheet and utilitized to create the listing of protocol deviations collected during the study for all subjects.

9.4 OTHER DESCRIPTIONS OF STUDY POPULATION

9.4.1 Demographics

All demographic data will be listed for the Safety population, including date of birth, age at diagnosis (years), age at enrollment (years), gender, ethnicity, and race. Age at diagnosis requires a calculation using the subject's date of birth and date of initial PAH diagnosis. Age at enrollment is calculated within the eCRF and will therefore be available in the raw datasets. Both ages will be rounded to 1 decimal place. Age at diagnosis, age at enrollment, gender, ethnicity, and race will be summarized by cohort for the Safety population. Age at diagnosis and age at enrollment will be summarized both descriptively and categorically using the age groups 7 to < 12 and 12 to ≤17 years.

9.4.2 PAH History

Pulmonary arterial hypertension history data will be listed, including date of initial PAH diagnosis, years since PAH diagnosis, and current PAH diagnosis. Current PAH diagnosis will be summarized by cohort.

9.4.3 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terms. These data and their coded values will be listed, including assessment date and all medical conditions collected. Subjects with no significant medical history will have "None reported" denoted on the listing. The number of subjects with at least 1 medical condition reported will be summarized by cohort, along with the medical conditions by the coded system organ class (SOC) and preferred term (PT). The listing and summary table will include a footnote denoting the MedDRA version used for coding.

9.4.4 Prior Therapy

Remodulin medication history data will be listed, including date Remodulin was first initiated, current Remodulin dose, Remodulin route, and date current Remodulin dose was initiated. Inhaled medication history data will be listed, including date Tyvaso first initiated, current number of breaths per session of Tyvaso, current number of sessions per day of Tyvaso, date current Tyvaso dose was initiated, date Ventavis first initiated, current dose of Ventavis per session, current number of sessions per day of Ventavis, and date current Ventavis dose was initiated. Background medication history data will be listed, including use of endothelin receptor antagonist (ERA) (yes/no), use of phosphodiesterase type 5 inhibitor (PDE5-I) (yes/no), use of soluble guanylate cyclase (sGC) stimulator (yes/no), and for each of the medication types, the generic name, date drug was first initiated, current total daily dose, and date current dose was initiated.

The summary of Remodulin medication history will include descriptive statistics on the current Remodulin dose and route for Cohort 1 only. The summary of inhaled medication history will include descriptive statistics of the current number of users, current number of breaths/current dose, and sessions per day for each medication (Tyvaso and Ventavis) by cohort. The summary of background medication history will include descriptive statistics of the current number of users, generic medication names, and current total daily dose for each medication type (ERA, PDE5-I, and sGC stimulator) by cohort.

9.4.5 Concomitant Medication

Concomitant medications data will be coded using the World Health Organization Drug Dictionary (WHODD). These data and their coded values will be listed, including medication name, start/end date (or ongoing), condition treated/indication, and AE, if applicable. The number of subjects reporting at least 1 concomitant medication will be summarized by cohort, along with the concomitant medications utilizing the name from the WHODD.

10 EFFICACY ANALYSES

All efficacy data will be listed for all enrolled subjects and summarized for all Safety population subjects.

10.1 TRANSITION TO ORAL TREPROSTINIL

The safety and tolerability of transitioning subjects from IV/SC Remodulin to oral treprostinil (Cohort 1) or from inhaled prostacyclin (Cohort 2) will be based on the percentage of subjects successfully transitioning to oral treprostinil. A successful transition is defined as a subject from Cohort 1 or 2 who is receiving oral treprostinil and no longer receiving IV/SC Remodulin or inhaled prostacyclin, respectively, at Week 4 and clinically maintained on oral treprostinil treatment through Week 24. A successful initiation of oral treprostinil (Cohort 3) will be defined as a subject who has been clinically maintained on oral treprostinil through Week 24. The number (percentage) of subjects who successfully transitioned to oral treprostinil, as well as those who did not successfully transition to oral treprostinil, will be summarized by cohort and overall. The reasons for unsuccessful transition will also be summarized for those subjects who did not successfully transition to oral treprostinil.

10.2 CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing will be completed at Baseline and Week 24 or premature termination. Exercise data will be sent to a central site and analyzed by a centralized specialist. Cardiopulmonary exercise testing entails measurements of oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE), and other variables.

The listing of CPET will include the scheduled visit; date/time of assessment; Remodulin, oral treprostinil, Tyvaso, and Ventavis dosing information prior to the CPET assessment, as

applicable; as well as baseline (pre-exercise) and exercise (post-exercise) peak VO_2, post-exercise peak watts and VE/VCO_2 slope, warm-up duration (minutes), exercise duration (minutes), and reason for test termination.

A summary of CPET will be produced for data collected before the exercise (labelled "baseline" on the CRF) and after the exercise (labelled "exercise" on the CRF), separately. The summary of CPET before exercise will include descriptive statistics for VO_2 at Baseline and Week 24 by cohort. The summary of CPET after exercise will include descriptive statistics at Baseline and Week 24 for warm-up duration (minutes), exercise duration (minutes), peak VO_2, VE/VCO_2 slope, and peak watts. Changes from Baseline to Week 24 in peak VO_2, VE/VCO_2 slope, and peak watts will also be descriptively summarized. These changes will be compared within cohorts using a paired t-test and p-values will be calculated for descriptive purposes; no formal hypothesis testing is planned. The number (percentage) of subjects reporting reasons for test termination will be summarized categorically (fatigue vs. other) by cohort.

The dosing information prior to testing (number [percentage] of subjects taking each medication type and last dose) will also be summarized by cohort using descriptive statistics.

10.3 SIX-MINUTE WALK TEST

The 6MWT is performed at Screening (optional), Baseline, Week 0 (Cohort 1 only), Week 3, Week 6, Week 12, and Week 24 or premature termination. At each of these visits, 6MWT recovery monitoring (heart rate and oxygen saturation measurements) will occur immediately prior to walk, immediately upon stopping the walk, 1 minute post walk, 2 minutes post walk, and 3 minutes post walk. The listing of 6MWT will include the assessment date/time; any Remodulin, oral treprostinil, Tyvaso, and Ventavis dosing information prior to the 6MWT assessment, as applicable; as well as whether subject attempted walk test (yes/no), reason not attempted (if applicable), total distance walked, Borg dyspnea score, oxygen receipt, and unusual circumstances. Recovery monitoring data (time point, heart rate, oxygen saturation, and total recovery time [minutes]) will be listed separately.

The summary of 6MWT will include the number (percentage) of subjects who received oxygen during the test and experienced any unusual circumstances during the test for each cohort.

The summary of 6MWD will include descriptive statistics for total distance walked by assessment visit and time point for each cohort. Changes from Baseline to each post-Baseline time point in total distance walked will also be summarized by cohort and compared within cohort using a Wilcoxon signed-rank test. P-values will be calculated for descriptive purposes; no formal hypothesis testing is planned.

As a sensitivity analysis, total walk distance data will be imputed using the LOCF method, regardless of the reason for early termination. The summary based on this imputation will follow the same layout as the no imputation analysis described above, while again using the Wilcoxon signed-rank test for descriptive purposes; no formal hypothesis testing is planned.

The summary of 6MWT recovery monitoring will include descriptive statistics for each cohort of heart rate (bpm) and oxygen saturation (%) at each of the 5 time points of assessment at each visit, as well as descriptive statistics of total recovery time (minutes).

10.4 BORG DYSPNEA SCORE

The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT. Scores range from 0 (for the best condition) to 10 (for the worst condition). The Borg dyspnea score is captured in tandem with the 6MWT at Screening (optional), Baseline, Week 0 (Cohort 1 only), Week 3, Week 6, Week 12, and Week 24 or premature termination, and will therefore be included in the 6MWT listing. The summary of Borg dyspnea score will present descriptive statistics of the Borg dyspnea score at each assessment time point by cohort. Change from Baseline will also be summarized by cohort.

10.5 PAH SYMPTOMS

PAH symptoms (fatigue, dyspnea, edema, dizziness, syncope, chest pain, and orthopnea) will be assessed at the Baseline visit prior to the initiation of oral treprostinil and at all subsequent visits, including each day during the Cohort 1 inpatient hospital stay. Scores range from 0 (no symptom experienced) to 3 (symptom severe or frequent). The scores for each symptom will

be listed for each cohort, subject, and time point in chronological order. The scores for each symptom will be categorically summarized separately by cohort at each visit assessment. Shifts from Baseline will also be summarized utilizing category shifts as well as descriptive statistics at each post-Baseline visit separately by cohort.

10.6 PANAMA FUNCTIONAL CLASS

The Panama Functional Class is collected at Screening, Baseline, Week 3, Week 6, Week 12, and Week 24 or premature termination. The listing will include the date of assessment and the functional class (I, II, IIIa, IIIb, and IV). The summary table will use descriptive statistics to present the number (percentage) of subjects within each functional class at each time point starting from Baseline. Shifts from Baseline will also be summarized utilizing the categories improved, no change, and deteriorated at each post-Baseline visit separately by cohort.

10.7 WHO FUNCTIONAL CLASS

The WHO Functional Class is collected at Screening, Baseline, Week 3, Week 6, Week 12, and Week 24 or premature termination. The listing will include the date of assessment and the functional class (I, II, III, and IV). The summary table will use descriptive statistics to present the number (percentage) of subjects within each functional class at each time point starting from Baseline and shifts from Baseline by cohort.

10.8 N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE

The NT-proBNP is collected at Baseline prior to starting oral treprostinil and repeated at Week 12 and Week 24 or premature termination. All results will be listed by cohort, subject, and assessment time point. The results will then be summarized using descriptive statistics at each time point and paired changes from Baseline by cohort.

10.9 PEDIATRIC QUALITY OF LIFE INVENTORY

Health-related QOL will be assessed via the 23-item child and parent PedsQL questionnaire at Baseline, Week 12, and Week 24 or premature termination. The listings of both child and parent inventories will include the date of assessment, which report was used (young child, child, or teen), and the answers to the physical, emotional, social, and school functioning scale questions.

The PedsQL questionnaire is converted to 6 scores for summarization and interpretation: 4 scale scores (1 each for Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning), a Psychosocial Health Summary Score, and a Total Scale Score. For ease of interpretability, items are reverse scored and linearly transformed to a 0 to 100 scale, so that higher scores indicate better quality of life. To reverse score, the 0 to 4 scale items are transformed to 0 to 100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

To create scale scores, the mean is computed as the sum of the items over the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score will not be computed. To create the Psychosocial Health Summary Score, the mean is computed as the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales combined. To create the Total Scale Score, the mean is computed as the sum of all the items over the number of items answered on all the scales.

The summaries of both child and parent inventories will present descriptive statistics for each of the 6 scores by cohort, as well as changes from Baseline to both post-Baseline visits.

10.10 CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging assessments were performed on all subjects aged 10 years and older at Baseline and Week 24 or premature termination. The following parameters were evaluated:

- Right ventricular (RV) mass index
- RV ejection fraction (RVEF)
- Left ventricular (LV) ejection fraction (LVEF)
- RV end-diastolic volume (RVEDV) index
- RV end-systolic volume (RVESV) index
- RV stroke volume index
- LV stroke volume index
- RV cardiac output indext

The cMRI measurements from images will be analyzed by a centralized specialist to control for bias and to reduce inter-reader variability. The results of these analyses will be transferred

to UTC for inclusion in the final study results. The listing of cMRI assessments will include the date/time of assessment as well as the parameters noted above for each visit assessment.

The summary of cMRI parameters will include descriptive statistics for each parameter at each visit as well as changes from Baseline by cohort. The following additional exploratory parameters, if collected, may also be included:

- Flow pattern through the main pulmonary artery by phase-sensitive gradient echo imaging
- Flow pattern through the right pulmonary artery by phase-sensitive gradient echo imaging
- Flow pattern through the ascending aorta by phase-sensitive gradient echo imaging
- RV:LV end-systolic diameter ratio
- Systolic septal flattening
- Right atrial size
- Presence of congenital heart disease
- Atrial or ventricular shunt

11 SAFETY ANALYSES

All safety summaries will be performed on the Safety population (see Section 7).

11.1 EXTENT OF EXPOSURE

Oral treprostinil dosing will be listed by cohort and subject. The listing will include the date/time of initial oral treprostinil dose, the initial dose (mg), and all subsequent dose changes with start date, morning dose, midday dose, and evening dose.

Remodulin dosing will be listed by subject for Cohort 1 subjects only. The listing will include the initial Remodulin dose (ng/kg/min) and all changes during the study, including the start date/time of the new dose as well as the new dose (ng/kg/min).

Tyvaso dosing will be listed by subject for Cohort 2 subjects only. The listing will include the number of initial Tyvaso breaths per session, the number of initial Tyvaso sessions per day, and all changes during the study; including the start date of new dose, number of breaths per session, and number of sessions per day.

Ventavis dosing will be listed by subject for Cohort 2 subjects only. The listing will include the initial Ventavis dose (X mcg with X mcg/mL), the number of initial Ventavis sessions per

day, and all changes during the study, including the start date of new dose, new dose, and number of sessions per day.

The oral treprostinil dosing and exposure summary will include descriptive statistics for initial oral treprostinil dose, oral treprostinil dose when Remodulin dose is 0.0, oral treprostinil dose at time of hospital discharge, oral treprostinil dose when subject is first off Tyvaso/Ventavis, and final oral treprostinil dose (mg) by cohort. Oral treprostinil dose will be calculated as the sum of the doses administered on a given day divided by the number of doses administered that day. The Remodulin dosing and exposure summary will include descriptive statistics for initial Remodulin dose (ng/kg/min). The Tyvaso dosing and exposure summary will include descriptive statistics for initial Tyvaso breaths per session and a categorical summary of number of initial Tyvaso sessions per day. The Ventavis dosing and exposure summary will include descriptive statistics for initial Ventavis dose per session and a categorical summary of number of initial Ventavis sessions per day.

Oral treprostinil doses will be plotted over time for each individual subject using a different plot for each cohort. The mean oral treprostinil doses will then be plotted over time on a single plot by cohort. Remodulin doses will be plotted over time for each individual subject (Cohort 1 only). Tyvaso doses will be plotted over time for each individual subject (Cohort 2 only).

11.2 BACKGROUND MEDICATION CHANGES

Endothelian receptor agonist, PDE5-I, and sGC stimulator dosing changes will be listed by cohort and subject. The listings will include if there were changes in the specific background medication (yes/no), the name of generic drug, the total daily dose, and the start date. The summary of background medication changes will include the number of subjects reporting any changes to each background medication type by cohort.

11.3 ADVERSE EVENTS

The AEs are collected from the time the informed consent form is signed until study termination. There are a number of AEs that are considered expected events given the underlying disease of study, PAH. These expected events attributable to PAH were not

recorded as an AE unless the event was serious or unusual with respect to intensity, frequency, or duration, or there was a reasonable possibility that it may have been caused by the study drug.

Adverse events will be coded using MedDRA PTs and SOC. All AEs reported in the eCRF will be listed, including non-treatment-emergent and treatment-emergent events. Non-treatment-emergent AEs are defined as those AEs starting prior to the date of first oral treprostinil dosing. Treatment-emergent adverse events (TEAEs) are defined as those AEs starting on or after the date of first oral treprostinil dosing. The listing will include cohort, subject number, verbatim term, PT, SOC, treatment-emergent status, start/stop date, seriousness, severity, frequency, relationship to oral treprostinil, action taken with oral treprostinil, relationship to background medication, action taken with background medication, and outcome.

The TEAEs will be summarized first in an overall summary, which includes the number of subjects with at least 1 TEAE, at least 1 oral treprostinil attributable TEAE, at least 1 serious TEAE, at least 1 TEAE leading to oral treprostinil discontinuation, at least one background therapy attributable TEAE, at least one TEAE leading to background therapy discontinuation, and any fatal TEAEs. The overall summaries will also include the number of events for each of these categories.

Non-treatment-emergent AEs will be summarized by cohort using PTs. The PTs will be sorted by decreasing overall frequency.

The TEAEs and serious TEAEs will be summarized by cohort using SOC/PT and PT, separately. The summaries will include the number and percentage of subjects reporting and the number of events reported for each SOC/PT and each PT, respectively, for each cohort, in order of decreasing overall frequency, both within SOC and PT.

The TEAEs will be summarized by severity within PT. The TEAEs and serious TEAEs considered attributable to oral treprostinil will be summarized by SOC/PT and PT, as

described above. The TEAEs leading to oral treprostinil discontinuation will be summarized by PT.

11.4 DEATHS

Information for all subjects who died within 30 days of the last dose of treatment, including the cohort, date of death, last oral treprostinil dose date, last oral treprostinil dose (mg), cause of death, PT, and relationship to oral treprostinil will be listed. The number and percentage of subjects who died will be summarized by cohort along with the causes of death reported.

11.5 DISEASE-RELATED EVENTS

Disease-related events that appeared or worsened (with clinical significance) during the study will be captured, including abdominal pain, anorexia, ascites, cool extremities, cor pulmonale, cough, cyanosis, hemoptysis, heart failure (or exacerbation of), hypoxia, loss of consciousness, nausea, pallor, palpitations/cardiac arrhythmia, paroxysmal nocturnal dyspnea, exacerbation of pulmonary hypertension, tachycardia, weight loss/gain, vasovagal reaction, and vomiting. The assessment of each of these disease-related events will be listed by cohort and subject. The number and percentage of subjects noting the onset or worsening of each of these events will be summarized by cohort.

11.6 VITAL SIGNS

Vitals signs (blood pressure [systolic and diastolic], heart rate, respiratory rate, and temperature [°C]) along with weight measurements will be captured during all study visits, including days of the inpatient hospital stay for Cohort 1. Height and body mass index were recorded at Screening only.

All vital sign assessments, including weight and height, will be listed by cohort, subject, and scheduled time point in chronological order using the units captured on the eCRF. Weight and height will be converted to a single unit for summarization; specifically, weight will be converted to kg and height will be converted to cm. The summary of vital signs will include descriptive statistics of the applicable parameters at each time point by cohort, including changes from Baseline.

11.7 CLINICAL LABORATORY EVALUATIONS

11.7.1 Hematology

Hematology laboratory evaluations were performed at Screening, Baseline, Week 12, and Week 24 or premature termination. Hematology data, including hemoglobin (g/L), hematocrit (fraction), red blood cell count (x 10^{12}/L), red blood cell morphology (as required), white blood cell count (x 10^{9}/L), and platelet count (absolute) (x 10^{9}/L) will be listed by cohort and time point, including collection date/time, reference range, and high/low flags.

The summary of hematology laboratory parameters will include descriptive statistics of all parameters at each time point (except Screening), including changes from Baseline by cohort. Additionally a shift table will be generated displaying the number (percent) of subjects with low, normal, and high values at baseline and each post-baseline visit.

Mean values of red blood cell count, hemoglobin, hematocrit, platelet count (absolute), and white blood cell count will be plotted across time starting at Baseline, using a different plotting symbol for each cohort. The time points plotted will be denoted as Baseline, Week 12, and Week 24. For plotting purposes, to prevent outlying values from skewing the majority of the data, the maximum y-axis value will follow the rule of 1.5 x IQR above the third quartile, calculated separately for each lab parameter. All values falling outside of the 1.5 x IQR limit will not be plotted. A footnote denoting this methodology will be added to each plot.

11.7.2 Clinical Chemistry

Clinical chemistry laboratory evaluations were performed at Screening, Baseline, Week 12, and Week 24 or premature termination. Clinical chemistry data, including sodium (mmol/L), potassium (mmol/L), bicarbonate (x 10^{9}/L), chloride (mmol/L), total bilirubin (umol/L), alkaline phosphatase (IU/L), alanine aminotransferase (ALT) (IU/L), aspartate aminotransferase (AST) (IU/L), blood urea nitrogen (BUN) (mmol/L), creatinine (umol/L), calcium (mmol/L), and albumin (g/L) will be listed by cohort and time point, including the collection date/time, reference range, and high/low flags.

The summary of clinical chemistry laboratory parameters will include descriptive statistics of all parameters at each time point (except Screening), including changes from Baseline by cohort. Additionally a shift table will be generated displaying the number (percent) of subjects with low, normal, and high values at baseline and each post-baseline visit.

Mean values of sodium, potassium, chloride, bicarbonate, calcium, albumin, total bilirubin, alkaline phosphatase, ALT, AST, BUN, and creatinine will be plotted across time starting at Baseline, using a different plotting symbol for each cohort. The time points plotted will be denoted as Baseline, Week 12, and Week 24. For plotting purposes, to prevent outlying values from skewing the majority of the data, the maximum y-axis value will follow the rule of 1.5 x IQR above the 3rd quartile, calculated separately for each lab parameter. All outlying values falling outside of the 1.5 x IQR limit will not be plotted. A footnote denoting this methodology will be added to each plot.

11.8 OTHER SAFETY MEASURES

11.8.1 Electrocardiogram

The ECG assessments will be completed at Baseline and Week 24 or premature termination. The ECG parameters collected will include heart rate, PR interval, QT interval, QRS duration, ECG results (normal/abnormal), and any abnormalities, including assessment of clinical significance and change from Baseline. The listing will include date/time of assessment as well as all parameters measured for each assessment time point by cohort and subject. All 12-lead ECG parameters will be summarized descriptively at each assessment time point by cohort.

12 PHARMACOKINETICS

Blood samples will be drawn from each subject at Baseline (Cohort 1 only) and Week 24 or premature termination to allow for the determination of the PK of oral treprostinil. At Baseline, 3 samples will be obtained for Cohort 1 subjects only at Time 0 (pre-dose) and at 4 and 8 hours after Time 0. At Week 24, all subjects will have 5 samples obtained at Time 0 (pre-dose) and at 2, 4, 6, and 8 hours after Time 0.

The listing of PK blood samples will include sample date/time, blood sample time point, whether sample was taken (yes/no), whether oral treprostinil was being taken (yes/no), date/time of previous day's oral treprostinil dose, previous day's oral treprostinil dose (mg), date/time of morning oral treprostinil dose, morning oral treprostinil dose (mg), time of midday oral treprostinil dose, midday oral treprostinil dose (mg), whether Remodulin was being taken (yes/no), date/time of last Remodulin dose change, last Remodulin dose (ng/kg/min), whether Tyvaso/Ventavis was being taken (yes/no), date/time of last Tyvaso/Ventavis dose, last number of Tyvaso breaths (per session), and last Ventavis dose (per session).

The PK bioanalytical work will be conducted by [redacted] will be conducting the PK analysis and writing the PK report. The PK report will be transferred to UTC for inclusion in the CSR.

13 APPENDICES

13.1 LIST OF TABLES

Table titles suggested here may be altered or edited as appropriate by the clinical data programmers while maintaining the original intent of the summary.

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14.1.1	Summary of Subject Accountability	_acct
14.1.2	Summary of Demographics	_demog
14.1.3	Summary of PAH History	_pahhx
14.1.4	Summary of Entry Criteria Not Met	_ic
14.1.5	Summary of Medical History	_mh
14.1.6	Summary of Remodulin Medication History	_remodhx
14.1.7	Summary of Inhaled Medication History	_inhalehx
14.1.8	Summary of Background Medication History	_backgr
14.1.9	Summary of Concomitant Medications	_cm
14.1.10	Summary of Oral Treprostinil Dosing and Exposure	_oral
14.1.11	Summary of Remodulin Dosing and Exposure	_remodulin
14.1.12	Summary of Tyvaso Dosing and Exposure	_tyvaso
14.1.13	Summary of Ventavis Dosing and Exposure	_ventavis
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14.2.1	Summary of Transition to Oral Treprostinil	_transition
14.2.2.1	Summary of Cardiopulmonary Exercise Testing Before Exercise	_cpet_before
14.2.2.2	Summary of Cardiopulmonary Exercise Testing After Exercise	_cpet_after
14.2.2.3	Summary of Dosing Prior to Cardiopulmonary Exercise Testing	_cpet_dose
14.2.3.1	Summary of 6-Minute Walk Test	_walk
14.2.3.2	Summary of 6-Minute Walk Distance During Week 0 for Cohort 1	_6mwd
14.2.3.3	Summary of 6-Minute Walk Distance	_6mwd
14.2.3.4	Summary of 6-Minute Walk Distance – LOCF Imputation	_6mwd_locf
14.2.3.5	Summary of 6-Minute Walk Test Recovery Monitoring During Week 0 for Cohort 1	_6mwt_recover
14.2.3.6	Summary of 6-Minute Walk Test Recovery Monitoring	_6mwt_recover
14.2.4.1	Summary of Borg Dyspnea Score During Week 0 for Cohort 1	_borg
14.2.4.2	Summary of Borg Dyspnea Score	_borg
14.2.5.1	Summary of Pulmonary Arterial Hypertension Symptoms During Week 0 for Cohort 1	_pahsymp
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Table Number	Table Title	Output Name
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14.2.9.1	Summary of Child Pediatric Quality of Life Inventory	_cpqol
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14.2.9.3	Summary of Cardiac Magnetic Resonance Imaging Parameters	_cmri
14.3.1.1	Overall Summary of Adverse Events	_ae
14.3.1.2	Summary of Non-Treatment-emergent Adverse Events by Preferred Term	_nonteae
14.3.1.3	Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term	_ae_soc
14.3.1.4	Summary of Treatment-emergent Adverse Events by Preferred Term	_ae_pt
14.3.1.5	Summary of Attributable Treatment-emergent Adverse Events by System Organ Class and Preferred Term	_relae_soc
14.3.1.6	Summary of Attributable Treatment-emergent Adverse Events by Preferred Term	_relae_pt
14.3.1.7	Summary of Treatment-emergent Adverse Events by Preferred Term and Severity	_ae_sev
14.3.1.8	Summary of Treatment-emergent Adverse Events Leading to Oral Treprostinil Discontinuation by Preferred Term	_ae_discon
14.3.1.9	Summary of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term	_sae_soc
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14.3.1.11	Summary of Serious Attributable Treatment-emergent Adverse Events by System Organ Class and Preferred Term	_relsae_soc
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14.3.1.13	Summary of Disease-related Events	_dre
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14.3.4.3.2	Summary of Hematology Shifts	_lbshft
14.3.4.4.1	Summary of Clinical Chemistry Laboratory Data	_lb
14.3.4.4.2	Summary of Clinical Chemistry Shifts	_lbshft
14.3.4.5	Summary of 12-Lead Electrocardiogram Parameters	_ecg

13.2 LIST OF LISTINGS

Listing titles suggested here may be altered or edited as appropriate by the clinical data programmers while maintaining the original intent of the listing.

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16.2.1.1	Listing of Discontinued Subjects	_disc
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16.2.2.1	Listing of Protocol Deviations	_deviate
16.2.2.2	Listing of Eligibility Criteria	_elig
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16.2.4.1	Listing of Demographics	_demog
16.2.4.2	Listing of PAH History	_pahhx
16.2.4.3	Listing of Medical History	_mh
16.2.4.4.1	Listing of Remodulin Medication History	_remodhx
16.2.4.4.2	Listing of Inhaled Medication History	_inhalehx
16.2.4.4.3	Listing of Background Medication History	_backgr
16.2.4.4.4	Listing of Background Medication Changes	_back_chg
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16.2.5.1.6	Listing of PDE-5 Inhibitor Dosing Changes	_pde
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16.2.6.5	Listing of Panama Functional Class	_pfc
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16.2.6.8.1	Listing of Child Pediatric Quality of Life Inventory	_cqol
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Appendix Number	Listing Title	Output Name
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16.2.8.3	Listing of Vital Signs	_vs
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13.3 LIST OF FIGURES

Figure titles suggested here may be altered or edited as appropriate by the clinical data programmers while maintaining the original intent of the figure.

Figure Number	Figure Title	Output Name
14.2.5.1	Plot of Oral Treprostinil Dosing Over Time for Cohort 1	_oral_c1
14.2.5.2	Plot of Oral Treprostinil Dosing Over Time for Cohort 2	_oral_c2
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14.2.5.4	Plot of Mean Oral Treprostinil Doses Over Time by Cohort	_oral_mean
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14.2.5.6	Plot of Tyvaso Dosing Over Time for Cohort 2	_tyv_c2
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