Statistical Analysis Plan

Protocol Title:	A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo Controlled, Multicenter Study of Rodatristat ethyl in Patients with Pulmonary Arterial Hypertension
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Sponsor:	Altavant Sciences GmbH Viaduktstrasse 8 CH-4051 Basel Switzerland US Agent: Enzyvant Therapeutics, Inc 2000 CentreGreen Way, Suite 350 Cary, North Carolina 27513 USA
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1. INTRODUCTION

This statistical analysis plan (SAP) document outlines the statistical methods to be implemented during the analysis and reporting of Study Protocol RVT-1201-2002, the double-blind phase, referred to as the Main Study. The purpose of this plan is to provide specific guidelines from which the analyses will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR). Analyses of the open-label extension (OLE) phase of the study will be described in a separate SAP and will be reported in a separate CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they are identified in Section 11. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Objectives and Endpoints

Table 1 describes the objectives and their corresponding endpoints. Note the endpoints are specified in order of the protocol specified *objectives*, and not the order of the *endpoints* specified in the protocol.

Table 1: Objectives and Corresponding Endpoints

Objectives	Endpoints/Criteria for Evaluation
Primary	
• To evaluate the effect of rodatristat ethyl on the percent change from baseline of pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) in patients with PAH	• Percent change from baseline to 24 weeks of PVR between an active arm and the placebo arm
Secondary	
To evaluate the effect of rodatristat ethyl from baseline to Week 24 on the following: o WHO FC o 6MWD o N-terminal pro-Brain Natriuretic (NT-proBNP)	To evaluate the effect of rodatristat ethyl from baseline to Week 24 on the following: o Change from baseline in WHO FC o Change from baseline in 6MWD o Change from baseline in NT-proBNP
Safety	
• To assess safety & tolerability of rodatristat ethyl in patients with PAH	• Change in safety parameters including AEs, vital signs, laboratory values, and electrocardiogram (ECG) assessments
Additional	
• Hemodynamics (cardiac index, mean pulmonary artery pressure [mPAP], mean right atrial pressure	• Change from baseline in cardiac index, mPAP, mRAP, SvO2 at rest and PAC

Objectives	Endpoints/Criteria for Evaluation
[mRAP], mixed venous oxygen saturation [SvO2], and pulmonary artery compliance [PAC]) • Time to Clinical Worsening (TTCW) defined as the first occurrence of a composite end point of: 1. Death from any cause, 2. Hospitalization for worsening PAH (any hospitalization for worsening PAH, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanoid therapy), 3. Disease progression defined as a decrease of more than 15% from baseline in the 6-minute walk distance (6MWD) combined with WHO FC III or IV symptoms at 2 consecutive visits separated by at least 14 days (adjudicated). • Death from any cause • Echocardiographic measures of right atrial size & RV function (tricuspid annular plane systolic excursion [TAPSE], tricuspid annular systolic velocity, and RV fractional area change) • Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire (PAH-SYMPACT) • Register to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 score	• TTCW • All-cause mortality • Change from baseline in right atrial size & RV function (TAPSE, tricuspid annular systolic velocity, & RV fractional area change) • Change from baseline in PAH-SYMPACT • Change from baseline in REVEAL Lite 2.0 Score
Exploratory	
• Time to Clinical Improvement (TTCI) • Actigraphy	• A > 10% increase in 6MWD or 30 meters AND an improvement to or maintenance of WHO FC II symptomatology, in the absence of a deterioration in clinical condition or death during the 24 weeks of the Main Study • Change from baseline in actual daily activity, (counts/minute) as determined by actigraphy: o Light to vigorous activity/day o Moderate to vigorous activity/day o Total movement/day o Best 6-minute walk effort
PK/PD (To be covered under a separate SAP)	
o To assess the PK of rodatristat ethyl and metabolites o To assess the effect of rodatristat ethyl on plasma and urinary 5-HIAA o To evaluate the effect of rodatristat ethyl on the plasma concentration of selexipag and ACT 33367	o Population PK parameters of rodatristat ethyl, active metabolite rodatristat ethyl, M15, and other metabolites o Change from baseline in 5-hydroxyindoleacetic acid (5-HIAA; plasma and spot urine concentration) o Plasma selexipag and ACT 333679 trough concentration at baseline and Week 4

2.2. Double-Blind Phase Study Design

This study will compare the efficacy, safety, and tolerability of 2 dosing regimens of rodatristat ethyl to placebo in subjects with PAH over a 24 week treatment period. Investigational product (IP) will be administered on the background of stable PAH therapy.

Approximately ninety (90) evaluable subjects will be enrolled. Subjects will be randomized 1:1:1 to placebo, 300 mg BID, or 600 mg BID of rodatristat ethyl.

Eligible subjects will be stratified based on the number of background PAH therapies they are receiving (1 vs 2 vs 3) and selexipag use (Yes/No). The number of subjects who are on a prostanoid infusion will be capped at 50% of the total enrolled. The number of subjects who are receiving selexipag will be capped at 20% of the total enrolled.

The study will consist of a Screening Period (up to 28 days in duration), a Baseline Period (Day 1), a 24-week Treatment Period (Main Study), and for subjects that early terminate or do not enroll an Open Label Extension (OLE), and a 4 week Follow Up Period (approximately 4 weeks after the last dose), for a total study duration of 32 weeks.

Subjects who complete the Main Study will have the option to enroll into an OLE and continue to receive rodatristat ethyl (those randomized to placebo will be re-randomized 1:1 to receive rodatristat ethyl 300 mg BID or 600 mg BID) for 6.5 years, until the Investigator or subject chooses to stop the IP, any stopping criteria in the Main Study are met, IP becomes commercially available, or the Sponsor stops the study for lack of efficacy or a safety signal (whichever preceding criteria comes first). In no case will a subject be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.

All participating subjects will be required to be on a stable background therapy for PAH with mono, dual or triple combination therapy (which may include currently approved prostanoid therapies) at the time of Screening. All subjects will maintain their standard of care (SOC) regimen at entry for the duration of the study. Refer to Section 6.6.2 for more details.

During the 24 week Treatment Period, in addition to the Day 1/Baseline Visit and a telemedicine or phone call at Week 2, subjects will return to the study center for safety, tolerability and efficacy-related assessments at Weeks 4, 8, 12, and 24, and a clinic or home visit at Week 18, as specified in the Schedule of Events Table, Section 1.3, as well as Follow-up at Week 28 (as applicable). Female subjects of childbearing potential will undergo pregnancy testing every 4 weeks and will be required to use 2 reliable methods of contraception to reduce the risk of pregnancy, at Screening, during the course of the study, and for at least 4 weeks following the last dose of rodatristat ethyl. Additional pregnancy testing in women whose menstruation is delayed or who have infrequent or irregular menstrual cycles should be completed as warranted.

2.2.1. Study Procedures

The overall schedule of activities for the Main Study is outlined in Section 1.3 of the study protocol. See study protocol for complete details.

2.2.2. Study Drug

Study drug is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study subject according to the study protocol. The IPs to be administered as part of this study are described in Table 2.

Table 2: Study Drug

Treatment Name	300 mg BID*	600 mg BID*	Placebo*
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	300 mg	300 mg	N/A
Dosage Level(s)	1 x 300 mg tablet + 1 x placebo tablet BID	2 x 300 mg tablets BID	2 x placebo tablets BID
Route of Administration	Oral	Oral	Oral
IP	Rodatristat ethyl	Rodatristat ethyl	Placebo
Packaging and Labeling	IP will be provided in bottles. Each bottle will be labeled as required per country requirement.		

*The components in rodatristat ethyl are provided in Section 3.2.2, Table 1 of the Investigator's Brochure. The active and placebo are formulated with the same excipients.
Abbreviations: BID = twice daily; IP = investigational product; N/A = not applicable

IP will be taken BID with food, approximately 12 hours apart.

Each subject will receive at least 4 bottles (1 kit) of IP at each clinic visit or by mail. There is enough IP in each kit for 4 weeks of dosing, including overage. The bottles of IP given at each clinic visit or by mail should be returned at the subsequent clinic visit for reconciliation and accountability.

The last dose of IP for the Main part of the study will be the last dose the night before the Week 24 visit (all Week 24 assessments will be collected post last dose).

2.2.3. Treatment Assignment, Blinding, and Randomization Methodology

This is a double blind study, with an open label extension (covered under a separate SAP). The Sponsor, Investigator, subject, and study site personnel will be blinded to all treatment group assignments. The Investigator will have the ability, in the IRT system, to unblind a subject, and the decision will reside solely with the Investigator. Prior to unblinding, if safety allows, the Investigator should contact the Medical Monitor to discuss the reasons for unblinding.

Eligible subjects will be stratified during the randomization process based on the number of background PAH therapies they are receiving (1, 2 or 3) and selexipag use. The number of subjects who are receiving a prostanoid infusion will be capped at 50% of the total number of subjects enrolled. The number of subjects who are receiving selexipag will be capped at 20% of the total number of subjects enrolled. Subjects will be randomized 1:1:1 to placebo, 300 mg BID, or 600 mg BID of rodatristat ethyl using an interactive randomization system.

At the time of Screening for entry into the OLE, all subjects will be re-randomized to receive either 300 mg BID or 600 mg BID rodatristat ethyl in an open-label fashion. Subjects will not know what they received in the Main Study until all subjects have completed the Main Study and the database is locked.

At the time of randomization, in the Main Study, subjects will be assigned a randomization number. Once this number has been assigned, it cannot be reused/reassigned.

Emergency unblinding procedures are outlined in section 6.4 of the study protocol and in the unblinding plan.

3. SAMPLE SIZE JUSTIFICATION

The sample size for this study was not based on a formal hypothesis testing. It is expected that 30 evaluable subjects per arm will provide sufficient data to assess safety and efficacy. Power calculations were conducted to examine the probability of detecting a difference among treatment groups for the percentage change of PVR from baseline.

A sample size of 90 subjects with 30 subjects to be randomized into 1 of the 3 treatment arms in a 1:1:1 randomization is planned. A sample size of 30 subjects per arm will provide at least 80% power at a significance level of 0.05 (2-sided hypothesis) to detect a treatment difference of 0.75 times of standard deviation (SD) in the percentage change from baseline of PVR from baseline between an active arm and the placebo arm. If the SD for PVR percent change is 24%, the study has 80% power to detect a difference of 18% between an active arm and the placebo arm.

4. GENERAL STATISTICAL METHODS

4.1. Reporting Conventions

Individual subject data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by subject. The primary data source will be used for all analyses. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All outputs will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonisation (ICH) E3 guideline, E3 Structure and Content of Clinical Study Reports, and formatted to the appropriate page size(s), font type, and font size according to Food and Drug Administration (FDA) guidance of Portable Document Format Specifications.

For categorical variables, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. If there are missing values, the number missing will be presented, but without a percentage. Percentages are rounded to 1 decimal place, unless otherwise specified.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to “Lost to Follow-up,” this reason will be included in the table with a count of 0. Percentages will be presented to 1 decimal place, with the exception of 0, which will be presented without percent, and 100, which will be presented without decimal places. Values less than 0.1% will be presented as “<0.1%.” Values less than 100% but greater than 99.9% will be presented as “>99.9%.”

For continuous variables, the number of subjects, mean, standard deviation (SD), median, 25th (Q1) and 75th (Q3) percentiles, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise specified will be as follows: mean, median, Q1, and Q3 to 1 more decimal place than the raw data, SD to 2 decimal places more than the raw data, and minimum and maximum to the same decimal places as the raw data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate.

Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified, in the table and listing shell. A full set of summary statistics will only be presented if 3 or more values are available. If there are less than 3 values, only the min, max, and N will be presented. The other summary statistics will be denoted as not calculated (NC).

For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX+1 (e.g., 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97).

All statistical tests comparing groups will be conducted at the 2-sided, 0.05 level of significance, unless otherwise specified. Summary statistics for each treatment group will be presented, as well as two-sided 95% CIs comparing groups will be provided.

4.2. Computing Environments

All descriptive statistical analyses will be performed using SAS software Version 9.3, unless otherwise noted.

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD), B3 Enhanced March 2021.

Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) SDTM Implementation Guide (IG) Version 3.3, ADaM Version 2.1, and CDISC ADaM IG Version 1.2 including most current occurrence and time to event IGs.

4.3. Partial Dates

Imputation of partial adverse event and concomitant medication dates are specified in Appendix 1, respectively.

All data recorded on the case report form will be included in data listings.

4.4. Data Conventions

The precision of original measurements will be maintained in summaries, when possible.

Quantitative safety laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purpose, the following will be imputed and stored within the analysis datasets:

- For values with <, the imputed value will be the numeric portion × 0.9.
- For values with >, the imputed value will be the numeric portion × 1.1.

Variables with a non-normal distribution that impacts the interpretation or validity of the planned analysis may have a data transformation applied (e.g., ln, $\log_{10}$).

4.5. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between one date (*date1*) and another later date (*date2*) will be calculated using the following formulas:

  duration in days = date2 – date1 + 1, where date1 ≥first administration date

  duration in days = date2 – date1, where date1 <first administration date

- Months – A duration expressed in months is calculated as the number of days divided by 30.4375
- Weeks – A duration expressed in months is calculated as the number of days divided by 7
- Years – A duration expressed in years between one date (*date1*) and another date (*date2*) is calculated using the following formulas:

  duration in years = (date2 – date1 + 1)/365.25, where date1 ≥first administration date

  duration in years = (date2 – date1)/365.25, where date1<first administration date

- Body Mass Index (BMI) – BMI is calculated using height (cm) and weight (kg) using the following formula:

  BMI (kg/m^2) = weight (kg) / ([height (cm)/100]^2)

- Change (CHG) – Change will be calculated as:

  Change = later value – earlier (i.e., baseline) value

- Percent change (PCHG) – Percent change will be calculated as:

  Percent change = ([Change] / earlier [i.e., baseline] value) × 100

4.6. Treatments

Table 3 presents how the dose groups will be presented on TFLs as treatment groups, including the order.

Table 3: Treatment Group Labels and Ordering

Treatment Group Label	Order on TFLs	
Placebo	1	
Rodatristat ethyl 300 mg BID	2	
Rodatristat ethyl 600 mg BID	3	
Total Rodatristat ethyl	4	

Treatment Group Label	Order on TFLs	
Overall (where specified)	5	For summaries where specified in Sections 6 and 8.2

Screen failures will be presented on by-subject listings where data is available.

4.7. Visits

4.7.1. Windows

Each visit will be denoted by its visit "Week". The first dose day is denoted as Day 1. In data listings, the relative study day of all dates from first dose will be presented.

Unless otherwise specified, scheduled assessments will be used for tabulated summaries. In the event of unscheduled visits, follow-up, or early treatment termination (ET) assessments, these will be reassigned to a scheduled visit for analysis purposes according to Table 4 (RHC), Table 5 (6MWT, WHO-FC, and NT-proBNP), Table 6 (Clinical Laboratory Evaluations, Vital Signs, ECGs), and Table 7 (Echocardiography and PAH-SYMPACT) for on treatment assessments. If multiple assessments occur within a single visit window, after reassignment of unscheduled visits and ET assessments, the assessment closest to the target day of the visit window will be used in the analysis. If there is a tie, the later assessment will be used in the analysis.

Table 4: Treatment Period Visit Windows: RHC

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section 4.7.2	
Week 24	169	2	197[c]

[a] Study day will be calculated from first dose of study drug.
[b] Baseline is defined in Section 4.7.2.
[c] Must be prior to first dose in the OLE.

Table 5: Treatment Period Visit Windows: 6MWT, WHO-FC, NT-proBNP

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section 4.7.2	
Week 4	29	2	42
Week 12	85	43	126
Week 24	169	127	182[c]

[a] Study day will be calculated from first dose of study drug.
[b] Baseline is defined in Section 4.7.2.
[c] Must be prior to first dose in the OLE.

Table 6: Treatment Period Visit Windows: Clinical Laboratory Evaluations, Vital Signs, and ECGs

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section 4.7.2	
Week 4	29	2	42
Week 8	57	43	71
Week 12	85	72	105
Week 18	127	106	147
Week 24	169	148	182[c]

[a] Study day will be calculated from first dose of study drug.
[b] Baseline is defined in Section 4.7.2.
[c] Must be prior to first dose in the OLE.

Table 7: Treatment Period Visit Windows: Echocardiography and PAH-SYMPACT

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section 4.7.2	
Week 12	85	2	126
Week 24	169	127	182[c]

[a] Study day will be calculated from first dose of study drug.
[b] Baseline is defined in Section 4.7.2.
[c] Must be prior to first dose in the OLE.

4.7.2. Definition of Baseline

The baseline value for 6MWD is the average of all walks prior to randomization.

Otherwise, for efficacy analyses the baseline value is defined as the last evaluation prior to randomization and for safety analyses, the baseline value is defined as the last evaluation prior to the first administration of study drug.

For ECG analyses, baseline is defined as the mean of triplicate assessments prior to the first administration of study drug. All available observations will be used in determining baseline, i.e. if there are less than 3 observations, the available observations will be used in determining the mean.

4.7.3. Definition of End of Treatment

The Main Study End of Treatment value will be defined as the Week 24 value, either scheduled or windowed per Table 6.

5. ANALYSIS POPULATIONS

Table 8 defines the analysis populations to be used.

Table 8: Analysis Sets

Analysis Sets	Description
Screened	All subjects who sign the informed consent form (ICF).
Safety	All subjects who receive any amount of study drug. Treatment assignment will be based on the treatment actually received.
Intent-to-Treat (ITT)	All subjects randomized into any one of treatment groups. Treatment assignment will be based on the randomized treatment.
Modified Intent-to-Treat (mITT)	All ITT population subjects with an evaluable baseline and at least 1 post baseline PVR assessment. Treatment assignment will be based on the randomized treatment.
Per Protocol (PP)	All mITT subjects who have completed treatment with ≥80% treatment compliance (actual, see definition in Section 8.1) without any major protocol deviations,. Treatment assignment will be based on the treatment actually received.
Treatment Completer	All mITT subjects who complete 24 weeks of treatment with no dose reductions or dose interruptions. Treatment assignment will be based on the randomized treatment. Sensitivity analyses may be conducted based on the treatment actually received. No missing data will be imputed for these analyses. Any substantial differences between conclusions based on the ITT, mITT and the completers' populations will be investigated.

6. STUDY POPULATION

6.1. Subject Disposition

Subject disposition will be summarized for the Screened population by treatment group, including Total Rodatristat ethyl and Overall. The summary will include:

- Number of subjects screened.
- Number of screen failures, i.e., screened but not randomized, with reasons for screen failure. The denominator for percentage of screen failures will be the number of subjects screened. The denominator for percentages for reasons for screen failures will be the number of screen failures.
- Number of subjects randomized (ITT population). The denominator for percentage of randomized subjects will be the number of subjects screened.

- Number randomized and not treated. The denominator for percentage of randomized and not treated subjects will be the number of subjects randomized.
- Number of subjects treated (Safety population). The denominator for percentage of treated subjects will be the number of subjects randomized.
- Number subjects in each analysis set. The denominator for percentage in each analysis set will be the number of randomized subjects (ITT population).
- Number who discontinued treatment early and reason(s) for discontinuation of treatment. The denominator for percentages will be the number of randomized subjects (ITT population).
- Number who discontinued from the main study prior to completing the study and reason(s) for discontinuation. The denominator for percentages will be the number of randomized subjects (ITT population).

The number and percentage of subjects randomized by geographical region and site will be presented by treatment group, including Total Rodatristat ethyl and Overall, for the ITT population.

A summary table will be produced of the randomization stratification factors and the combined stratum groups.

- Number of Background PAH therapies: 1, 2, or 3
- Selexipag Use: Yes, No
- Stratum Group 1: 1 Background PAH Therapy, Selexipag Use
- Stratum Group 2: 2 Background PAH Therapies, Selexipag Use
- Stratum Group 3: 3 Background PAH Therapies, Selexipag Use
- Stratum Group 4: 1 Background PAH Therapy, No Selexipag Use
- Stratum Group 5: 2 Background PAH Therapies, No Selexipag Use
- Stratum Group 6: 3 Background PAH Therapies, No Selexipag Use

If any randomization stratum has less than 5 subjects, the pooled stratum will be used as described in Table 9 below.

Table 9: Pooling of Randomization Strata

Stratum	Pooled Stratum
1 PAH Therapy excluding Selexipag	1 PAH Therapy
1 PAH Therapy including Selexipag	1 PAH Therapy
2 PAH Therapies excluding Selexipag	2 PAH Therapies
2 PAH Therapies including Selexipag	2 PAH Therapies
3 PAH Therapies excluding Selexipag	3 PAH Therapies

Stratum	Pooled Stratum
3 PAH Therapies including Selexipag	3 PAH Therapies

In addition, in case the site accidentally stratified a subject using the wrong stratification value, the derived stratification value reported in the eCRF data versus the one the site entered in the IRT during randomization process will be presented separately.

A by-subject data listing of study disposition information including the reasons for treatment and/or study termination will be presented for the Screened population. Also by-subject listings of informed consent and eligibility criteria details will be presented. A by-subject data listing including the reasons for exclusion from each analysis population will be presented.

6.2. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent including the subgroup of <65 years, ≥65 years
- Sex
- Race
- Ethnicity

Other baseline characteristics will include the following:

- Weight (kg)
- BMI (kg/m^2) including the following subgroup: <18 kg/m^2, 18 to <30 kg/m^2, ≥30 kg/m^2

PAH baseline characteristics will be summarized and listed separately and include the below parameters:

- Duration since PAH Diagnosis (years)
- PAH Classification (IPAH, HPAH, drug or toxin, PAH associated with connective tissue disease, PAH associated with congenital systemic pulmonary shunt, PAH associated with HIV)
- Number of PAH therapies
- WHO FC (I, II, III, IV)
- Baseline REVEAL Lite Score including the following subgroup: <6 vs ≥6
- Baseline 6MWD (meters)
- Baseline NT-proBNP (pg/mL)
- Baseline PVR (dynes/sec/cm^5)
- Baseline mPAP (mmHg), Baseline PCWP (mmHg), Baseline mRAP (mmHg), Baseline Cardiac Index (L/min/m^2), Cardiac Output (L/min), adjudicated values.

If date of PAH diagnosis is only partially known, i.e. the month or day is missing, it will be imputed as the closest to randomization date, where missing day is imputed as the last day of the month and missing day and month is imputed as December 31.

In addition, any subgroups specified in Section 7.1.7 for the above parameters will be included in summaries. Demographics and baseline characteristics will be summarized by treatment group, including Total Rodatristat ethyl and Overall, for the ITT, mITT, Safety, PP, and Treatment Completer populations. The mITT, Safety, PP, and Treatment Completer populations will only be presented if the analysis population differs from the ITT population by more than 10% total.

All demographic and baseline characteristics data will be presented in by-subject data listings using the ITT population.

No inferential statistical comparisons will be performed.

6.3. Protocol Deviations

Protocol deviations will be identified and documented in the clinical trial management system (CTMS) for inclusion in SDTM and ADaM. The protocol deviation data will be reviewed and assigned as important or non-important prior to database lock and unblinding.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

Important protocol deviations will be summarized by treatment group, including Total Rodatristat ethyl and Overall, for each deviation category using the ITT population.

All protocol deviations and separately only important protocol deviations will be presented in a by-subject data listing.

6.4. General Medical History

All medical history conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Medical history will be summarized by treatment group, including Total Rodatristat ethyl and Overall, by system organ class and preferred term, using the Safety population. Summaries will be ordered by descending order of the overall incidence of system organ class and preferred term within each system organ class.

General medical history data will be presented in by-subject data listings using the Safety population.

6.5. Non-Study Medications

6.5.1. PAH Medications

PAH medication currently being taken or taken within the past 3 months, as recorded on the PAH Medication eCRF, will be summarized with the number and percentage of subjects taking:

- Any Phosphodiesterase type-5 inhibitors (PDE-5i) and by type of PDE-5i (Sildenafil, Tadalafil, Vardenafil, or Other)

- Any Endothelin Receptor Antagonist (ERA) and by type of ERA (Ambrisentan, Bosentan, Macitentan, or Other)
- Any Soluble guanylate cyclase (sGC) and by type of sGC (Riociguat or Other)
- Any Prostacyclin and by type of Prostacyclin (Epoprostenol, Treprostinil, Iloprost, Selexipag, or Other)
- All possible combinations of the above

Concomitant PAH Medications, recorded on the Concomitant Medications eCRF, are defined as any medication coded to Anatomic Therapeutic Class (ATC) Level 4 ANTIHYPERTENSIVES FOR PULMONARY ARTERIAL HYPERTENSION or OTHER VASODILATORS USED IN CARDIAC DISEASES, or preferred names of EPOPROSTENOL or SELEXIPAG. Concomitant PAH Medications will be summarized and listed separately from other concomitant medications (see below, Section 6.5.2) by treatment group, including Total Rodatristat ethyl and Overall, for the Safety population.

6.5.2. Prior and Concomitant Medications

Prior medications are defined as medications that started before first study drug administration and either stopped before or continued after first study drug administration. Concomitant medications are defined as medications that are being taken while on study drug, within 28 days of last dose. Non-PAH concomitant medications are all other concomitant medications not included in the defined of PAH medications above (Section 6.5.1). Medications that are ongoing on the date of the first administration of study drug will be classified as both prior and concomitant. Any medication that cannot be confirmed as stopping before the start of study drug will be classified as both a prior and a concomitant medication. Imputation of partial dates is defined in Appendix 1.

Prior and non-PAH concomitant medications will be summarized separately and the number and percentage of subjects in each treatment group who took at least one prior (non-PAH concomitant) medication as well as the number and percentage of subjects who took each type of medication will be summarized by Anatomic Therapeutic Class (ATC) Level 2, ATC Level 4, and preferred name for the Safety Analysis Set. If a subject has more than one occurrence of the same preferred name, then the preferred name will be counted only once for that subject. Similarly, if a subject has more than one preferred name within ATC Level 4 or ATC Level 4 within ATC Level 2, then the subject will be counted only once in that ATC Level 4 or ATC Level 2.

7. EFFICACY ANALYSES

Primary analyses of efficacy endpoints will be performed using the ITT population. Additional analyses may be repeated using the mITT, PP, and Treatment Completer populations, if the populations differ by >5% of total subjects in the ITT population.

All efficacy endpoints, recorded and derived, will be presented in by-subject data listings.

For applicable efficacy analyses, if the assumptions of the planned parametric analyses are violated and inhibit the interpretation of the results, appropriate data transformations or non-parametric analyses will be performed to support the interpretation of the treatment effect.

7.1. Statistical/Analytical Issues

7.1.1. Adjustments for Covariates

For comparison of treatment groups with respect to change and percent change from baseline, analysis of covariance (ANCOVA) and restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) models will be used. The corresponding baseline value will be used as a covariate in the model.

7.1.2. Handling of Dropouts or Missing Data

The following methods will be implemented to address missing data for relevant primary, or secondary efficacy endpoints.

7.1.2.1. Missing at Random (MAR): Multiple Imputation

For the primary analysis of PVR, 6MWT, and NT-proBNP efficacy endpoints, subjects who miss an assessment for reasons other than death or other tolerability reasons, will be imputed using multiple imputation (MI) methodology based on the treatment group for time points at which no value is observed. An intercurrent event meeting will be held prior to database lock and unblinding with the medical monitor(s) and statistician(s) to review the missing efficacy assessments for each subject and determine if the missing data is MAR or missing not at random, (MNAR), i.e. informative missing.

MI will be performed under the assumption of MAR. Intermittent missing value(s) will also be replaced using MI. MI will impute 10 integer values using Markov Chain Monte Carlo (MCMC) methods assuming nonmontone missing, a seed of 100201, 500 burn-in iterations, 100 iterations between imputations, and a non-informative prior. The imputation models based on treatment group will include randomization stratification factors, baseline WHO FC, baseline 6MWD, and baseline value of the endpoint and all previous values of the endpoint at each time point. Other baseline characteristics that may be explored will be documented in the CSR. It is anticipated that the imputation model will converge but should it not do so terms will be removed from the model to achieve convergence. The effects of any such model adjustment will be investigated.

Change from baseline to each post-baseline visit will be calculated based on observed and imputed data. Results from the analysis of each of the 10 imputed datasets will be combined using PROC MIANALYZE (Rubin's imputation rules, Rubin 1987).

7.1.2.2. MNAR: Imputation for Deaths and Tolerability Reasons

For the primary analysis of PVR, 6MWT, and NT-proBNP efficacy endpoints, subjects who missed an assessment due to death, tolerability, or >10% change in parental prostainoid dose (including adding a new medication).will be imputed as the worst value in their planned treatment group at the specific visit.

7.1.2.3. Last Observation Carried Forward (LOCF)

For the WHO FC efficacy endpoint, if a subject is missing Week 24, their last observation will be carried forward to Week 24. If baseline is the last observation, it will be carried forward (BOCF).

7.1.2.4. Other Assessments of Missing Data

To assess the impact of missing data and robustness of the results, the following sensitivity analyses will be performed for the primary and secondary endpoints:

- Observed case analyses
- Treatment Completers population analyses

7.1.3. Planned Analyses

7.1.3.1. Interim Analyses and Data Monitoring

No formal interim analyses are planned for the study.

7.1.3.2. Data Monitoring

An external, multidisciplinary, Independent Data Monitoring Committee (IDMC) will review the progress of the study and perform interim reviews of unblinded safety and efficacy data at regular intervals and provide recommendations to the Sponsor whether the nature, frequency, and severity of AEs and AESIs associated with IP warrant the early termination of the study in the best interests of the subjects, whether the study should continue as planned, or whether the study should continue with modifications. The IDMC may also provide recommendations as needed regarding study design. While the IDMC will be asked to advise the Sponsor regarding future conduct of the study, including possible early study termination, the Sponsor retains final decision-making authority on all aspects of the study. Please see IDMC Charter for further details.

The Clinical Endpoint Adjudication Committee (CEAC) including three Pulmonary Arterial Hypertension (PAH) expert physicians will adjudicate the clinical worsening events (CWEs) per Clinical Endpoint Adjudication Charter.

The RHC data will be adjudicated by the blinded medical monitors per the RHC Adjudication Process Document.

7.1.3.3. Final Main Study Analysis

Any data values requiring investigation or correction will be identified while programming the datasets and Tables, Figures, and Listings (TFLs). The database will not be locked until the identified issues are resolved.

The final main study statistical analysis will be conducted when the last subject has completed the main study and will be based on the locked database.

7.1.3.4. OLE Analyses

The study includes an open label extension (OLE) phase. Details of OLE analyses will be described in a separate OLE SAP and reported in a separate CSR.

7.1.4. Multicenter Studies

The randomization is not stratified by site. Likewise, analyses of efficacy data will not be stratified by study site. The number and percentage of subjects randomized by geographical region and study site will be summarized by treatment group and for all subjects.

7.1.5. Use of an "Efficacy Subset" of Subjects

Not Applicable.

7.1.6. Multiple Comparisons/Multiplicity

In order to control the Type 1 error rate for the primary efficacy endpoint, the comparisons between each active arm and the placebo arm will be tested using the Hochberg approach, where the two p-values (600 mg vs placebo and 300 mg vs placebo) will be ordered largest to smallest as $p(1)>p(2)$.

1. If $p(1)<0.05$ then reject both null hypotheses.
2. If $p(1)>0.05$, but $p(2)<0.025$, then reject the null hypothesis associated with p(2).

7.1.7. Examination of Subgroups

Subgroups will be defined based on baseline values, unless otherwise specified, and only if there are a sufficient number of subjects in each category of the subgroup, defined as ≥5 subjects per treatment group. The primary and secondary efficacy endpoints will be presented based on observed data (no imputation) for the following subgroups:

- Age Group (<65 years vs ≥65 years)
- Sex (Male vs Female)
- Race (White vs All Other Races; Asian vs Non-Asian)
- Geographic Region (North America vs Europe vs Rest of World)
- Duration of Disease (≤5 years vs > 5 years)
- Baseline PVR (≤700 dyn/sec/cm^5 vs > 700 dyn/sec/cm^5)
- Baseline WHO FC (II vs III)
- Baseline 6MWD (<450 meters vs ≥450 meters)
- Baseline NT-proBNP (≤300 pg/mL vs > 300 pg/mL)
- Baseline REVEAL Lite Score: <6 vs ≥6
- Baseline use of Selexipag (Yes vs No)
- Baseline use of Parenteral Prostacyclin (Yes vs No)
- Baseline use of Endothelin Receptor Antagonist (ERA; Yes vs No)

- Number of Background PAH Therapies. (<3 vs ≥3)
- Type of PAH: Idiopathic, Heritable, Drug and Toxin induced, Associated with CTD, Associated with Other (Congenital Systemic Pulmonary Shunt or HIV)

Additional subgroup analyses and/or revision of above subgroup definition may be specified after database lock to accommodate available data as appropriate.

7.2. Primary Efficacy Analysis

The primary efficacy analysis will test the following hypothesis:

- H_0: The mean change from baseline in PVR at Week 24 is equal between placebo and rodatristat ethyl.
- H_1: The mean change from baseline in PVR at Week 24 is different between placebo and rodatristat ethyl.

In cases of missing data occurring at Week 24, missing data handling rules are specified in Section 7.1.2.

Percent change from baseline in PVR at Week 24 will be analyzed using an analysis of covariance (ANCOVA) model with terms of treatment, randomization strata and baseline PVR. Estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs will be presented by treatment group. In addition, the LS mean difference comparisons between each active dose and placebo, the StdErr of the difference, and 95% CI of the difference will be presented.

In order to control the Type 1 error rate, the comparisons between each active arm and the placebo arm will be tested using the Hochberg approach, where the two p-values (600 mg vs placebo and 300 mg vs placebo) will be ordered largest to smallest as $p(1)>p(2)$.

1. If $p(1)<0.05$ then reject both null hypotheses.
2. If $p(1)>0.05$, but $p(2)<0.025$, then reject the null hypothesis associated with p(2).

Assumptions for the ANCOVA will be checked, and if not satisfied, parametric analyses will be corroborated with appropriate nonparametric analyses, such as the Wilcoxon rank sum test stratified by randomization strata. The Hodges-Lehmann estimation of location shift and confidence interval will be produced. If the model residuals are not normally distributed, ANCOVA analysis based on ranked data will be performed.

7.2.1. Additional Analyses of the Primary Endpoint

The rodatristat ethyl treatment groups will also be pooled and compared to placebo.

In addition to the primary endpoint, PVR values, change from baseline, and percent change from baseline to all visits will be analyzed in the same manner described above.

Summaries will be provided for the subgroups as specified in Section 7.1.7 for the ITT Population. A forest plot of the LS differences and 95% CIs will be presented for Placebo versus Rodatristat ethyl 300 mg BID and Placebo versus Rodatristat ethyl 600 mg BID for the ITT and Treatment Completer populations.

7.3. Secondary Efficacy Analyses

7.3.1. Change from Baseline to Week 24 in WHO FC

The secondary efficacy analysis will test the following hypothesis:

- H_0: The distribution of change from baseline in WHO FC at Week 24 is equal between placebo and rodatristat ethyl.
- H_1: The distribution of change from baseline in WHO FC at Week 24 is different between placebo and rodatristat ethyl.

The analyses will compare placebo and rodatristat ethyl on the distribution of change from baseline in WHO FC at Week 24 using an ordinal logistic regression with treatment group and randomization strata as factors. The number and percentage of subjects in each category (-II, -I, no change, +I, +II) will be presented by treatment group.

7.3.1.1. Additional Analyses of WHO FC

The rodatristat ethyl treatment groups will also be pooled and compared to placebo.

The same analyses specified above for Week 24 will be performed at Week 4 and 12.

In addition, treatment groups will be compared on response based on the following distributions of subjects at each visit using a stratified Cochran-Mantel-Haenszel (CMH) test (stratified by the randomization stratification factors) and a Fisher's exact test:

- WHO FC I or II vs WHO FC III or IV
- Any improvement in WHO FC vs no improvement
- Any worsening in WHO FC vs no worsening

7.3.2. Change from Baseline to Week 24 in 6MWD

The secondary efficacy analysis will test the following hypotheses:

- H_0: The distribution of change from baseline at Week 24 in 6MWT distance (meters) is equal between placebo and rodatristat ethyl.
- H_1: The distribution of change from baseline at Week 24 in 6MWT distance (meters) is different between placebo and rodatristat ethyl.

The change from baseline at Week 24 in 6MWT distance (meters) will be analyzed using the aligned rank stratified Wilcoxon test [Hodges, J. L., Jr. and Lehmann, E. L. 1962] [Mehrotra, D. V., et al 2010] with the randomization stratification factors as strata. In this test, the endpoint values are first aligned across the randomization strata using the stratum-level Hodges-Lehmann location shift estimates, and the aligned values are then analyzed using a Wilcoxon rank sum test. The output from this analysis will be used to provide a 2-sided p-value and corresponding Hodges-Lehmann location-shift estimate of the overall treatment difference with 95% confidence interval (CI). SAS implementation code for the aligned rank stratified Wilcoxon test is below

```
PROC NPAR1WAY DATA=data WILCOXON ALIGN=STRATA(HL) HL
CORRECT=NO;
CLASS trtp;
VAR chg;
STRATA strata;
ODS OUTPUT HodgesLehmann=hlstats_a;
RUN;
```

7.3.2.1. Additional Analyses of 6MWD

The rodatristat ethyl treatment groups will also be pooled and compared to placebo.

Additional analyses of the percent change from baseline in 6MWD will be analyzed the same manner. Analyses will be repeated for the Treatment Completer population.

Summaries will be provided for the subgroups as specified in Section 7.1.7. A forest plot of the Hodges-Lehman estimate of the median treatment differences and 95% CIs will be presented for Placebo versus Rodatristat ethyl 300 mg BID and Placebo versus Rodatristat ethyl 600 mg BID for the ITT and Treatment Completer populations.

In addition to the secondary endpoint, 6MWT distance, change from baseline, and percent change from baseline to all visits will be analyzed in the same manner described above.

The 6MWT change from baseline will also be categorized as follows:

- ≥ 30-meter decline or ≥ 10% decline (Worsening)
- < 30-meter decline or < 10% decline to < 30-meter improvement or 10% improvement (No Change)
- ≥ 30-meter improvement or ≥ 10% improvement (Improvement).

The categorical change from baseline will be summarized by visit for each scheduled post-baseline visit. For each post-baseline visit ordinal logistic regression will be performed with 6MWT categorical change from baseline (Worsening, No Change, Improvement) as the dependent variable and factors for treatment group and randomization strata. Estimates of the proportional odds ratio comparing placebo and rodatristat ethyl and the 95% CI of the odds ratio will be presented. An odds ratio greater than 1 favors the rodatristat ethyl treatment group.

7.3.3. Change from Baseline to Week 24 in NT-proBNP

The secondary efficacy analysis will test the following hypotheses:

- H_0: The mean change from baseline at Week 24 in NT-proBNP is equal between placebo and rodatristat ethyl.
- H_1: The mean change from baseline at Week 24 in NT-proBNP is different between placebo and rodatristat ethyl.

Rodatristat ethyl and placebo will be compared on change from baseline using a REML based MMRM model including fixed effects for randomization strata, treatment group, categorical time point, and the treatment group × time point interaction, and with the baseline value included as a covariate. In cases of missing data occurring at Week 24, missing data handling rules are specified in Section 7.1.2.

The unstructured covariance model will be used. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR (1)], AR(1), heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. All visits will be included in the model, with the primary comparison at the Week 24 visit.

Estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs will be presented by treatment group. In addition, the LS mean difference comparisons between rodatristat ethyl and placebo, the StdErr of the difference, and 95% CI of the difference will be presented.

Descriptive statistics for NT-proBNP scores, change from baseline, and percent change from baseline will be presented by visit for each treatment group.

Assumptions for the REML based MMRM model will be checked, and if not satisfied, parametric analyses will be corroborated with appropriate nonparametric analyses, such as the Wilcoxon rank sum test stratified by randomization strata. The Hodges-Lehmann estimation of location shift and confidence interval will be produced. If the model residuals are not normally distributed, ANCOVA analysis based on ranked data will be performed.

7.3.3.1. Additional Analyses of NT-proBNP

The rodatristat ethyl treatment groups will also be pooled and compared to placebo.

In addition to the secondary endpoint, NT-proBNP, change from baseline, and percent change from baseline to all visits will be analyzed in the same manner described above.

Sensitivity analyses will be performed based on observed cases using the ITT population. Analyses will be repeated using the Treatment Completer population.

Summaries will be provided for the subgroups as specified in Section 7.1.7 for the ITT Population. A forest plot of the LS differences and 95% CIs will be presented for Placebo versus Rodatristat ethyl 300 mg BID and Placebo versus Rodatristat ethyl 600 mg BID for the ITT and Treatment Completer populations.

An additional sensitivity analysis will evaluate the rate of decrease (ie, slope) of NT-proBNP using a general linear mixed effects model to compare treatment groups. The model will fit a random intercept and slope for each subject and will include fixed effects for treatment group, time, randomization strata, and treatment group × time interaction. Time will be expressed in weeks as a continuous variable and will include all scheduled time points including baseline. An unstructured covariance structure will be used to model the within-subject errors. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR (1)], AR(1), heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance

structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. The null hypothesis of no difference in slopes between the treatment groups will be determined by testing the significance of the treatment group by time interaction term.

Estimates of the slope will be presented by treatment group along with corresponding 95% CIs. The estimate of the difference between slopes (Rodatristat ethyl -Placebo) and the 95% CI of the difference between slopes will also be presented. Appropriate contrasts for pairwise differences in coefficients at time points of interest between rodatristat ethyl and placebo with corresponding 95% CIs will be estimated from the model and tested for significance.

7.4. Additional/Exploratory Efficacy Analyses

7.4.1. Change from Baseline in Cardiac Index, mPAP, mRAP, SvO2 at rest, and PAC

Cardiopulmonary hemodynamics are being assessed by right heart catheterization (RHC). All required RHC parameters are being collected using the same methods at Screening/Randomization and Week 24.

Table 10 lists the RHC parameters collected on the CRF, which will be manually adjudicated by blinded medical monitors.

Table 10: Collected RHC Parameters

SDTM Test Code (FTTESTCD)	SDTM Test Name (FTTEST)
DPAP	Diastolic Pulmonary Artery Pressure
SPAP	Systolic Pulmonary Artery Pressure
MRAP	Central Venous/Mean Right Atrial Pressure
PCWP	Pulmonary Capillary Wedge Pressure
LVEDP	Left Ventricular-end Diastolic Pressure
MEAN THERMCO	Thermodilution CO (Mean)
FICKCO	Fick CO
VO2MEAS	Measured VO2
CARDFIO2	FiO2 at measurement
ASSUMVO2	Assumed VO2
CARDART	Arterial Oxygen Saturation SaO2

SDTM Test Code (FTTESTCD)	SDTM Test Name (FTTEST)
CARDHEMO	Hemoglobin Concentration
SVO2	Mixed Venous Oxygen Saturation

Table 11 lists the RHC parameters derived in the EDC based on investigator assessed parameters above and all to be derived based on adjudicated values where applicable.

Table 11: Derived RHC Parameters

SDTM Test Code (FTTESTCD)	SDTM Test (FTTEST)	Derivation Formula
CI	Cardiac Index	CI = CO ÷ BSA *CO=THERMCO, if THERMCO not used then CO= FICKCO
FICKCO	Fick CO (will not be summarized due to small sample sizes)	FICKCO= VO2 (VO2MEAS or ASSUMVO2[+])/ [(CARDART – SVO2) x CARDHEMO × 0.134) [+] If VO2 not measured Bergstra Equation used to determine assumed VO2 (ASSUMVO2). *FICKCO is measured when THERMCO was not available
MPAP	Mean Pulmonary Artery Pressure	mPAP = (2 × dPAP + sPAP)/3
PAC	Pulmonary Artery Compliance	PAC = SV/ (sPAP – dPAP)
PVR	Pulmonary Vascular Resistance	PVR= [(MPAP – PCWP) ÷CO] × 80 or if PCWP missing then PVR=[(MPAP – LVEDP) ÷ CO] × 80 *CO=THERMCO, if THERMCO not used then CO= FICKCO
PVRI	Pulmonary Vascular Resistance Index	PVRI = ((mPAP – PCWP)/CI) × 80 or If LVEDP was provided instead of PCWP use LVEDP in the formula instead of PCWP. PVRI = ((mPAP – LVEDP)/CI) × 80

SDTM Test Code (FTTESTCD)	SDTM Test (FTTEST)	Derivation Formula
SV	Stroke Volume	SV = CO ÷ HR × 1000 *CO=THERMCO, if THERMCO not used, then CO= FICKCO
SVR	Systemic Vascular Resistance	SVR= [(MAP – MRAP) ÷CO] × 80 *CO=THERMCO, if THERMCO not used, then CO= FICKCO
MAP	Mean Arterial Pressure	MAP=(2 × dBP + sBP)/3
SVRI	Systemic Vascular Resistance Index	SVRI=80 × (MAP – MRAP)/CI

Thermodilution and Fick Cardiac Output will be combined for summary purposes, where Thermodilution will be used primarily and Fick if Thermodilution is not available. PVR and LVEDP will be combined for summary purposes, where PVR will be used primarily and LVEDP if PVR is not available.

Primary analyses of hemodynamic parameters will be based on adjudicated data, where applicable, using the ITT and Treatment Completer populations, and sensitivity analyses will be based on investigator assessment as collected on the CRF. The change from baseline will be analyzed using the same ANCOVA model as specified in Section 7.2.

7.4.2. Time to Clinical Worsening (TTCW)

A clinical worsening event is defined using two definitions (a composite endpoint):

Protocol Definition

1. Death from any cause
2. Hospitalization for worsening PAH (any hospitalization for worsening PAH, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanoid)
3. Disease progression, defined as a decrease of more than 15% from baseline in the 6MWD combined with WHO FC III or IV symptoms at 2 consecutive visits separated by at least 14 days. The time of disease progression is at the time of initial visit.

Additional Definition

1. Death from any cause
2. Hospitalization for worsening PAH (any hospitalization for worsening PAH, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanoid therapy)

3. Disease progression defined as a decrease of more than 15% from Baseline in the 6-minute walk distance (6MWD) (2 consecutive visits separated by at least 14 days), combined with World Health Organization (WHO) Functional Class (FC) III or IV symptoms at 2 consecutive visits separated by at least 14 days. Also requires the absence of a clinical rationale (e.g., an intercurrent event that would be expected to worsen the walk and functional class independent of pulmonary hypertension progression).
4. Addition of parenteral prostanoid therapy or increase of greater than 10% of any prostanoid
5. Appearance of worsening signs and symptoms of right heart failure

TTCW will be adjudicated separately for each definition of clinical worsening. TTCW is defined as the first occurrence of any of the above events (separately for each definition).

The CEAC adjudicated CWEs include the date and reason will be incorporated into the clinical database. Adjudicated TTCW is defined as the number of days from randomization date to the date of the first adjudicated CWE. Subjects who do not have an adjudicated CWE during the 24 weeks of the main study will be censored at the first OLE dose date if enrolled into OLE or if not enrolled into OLE, the minimum of last dose of study drug + 30 days or date of last contact in the main study.

Sensitivity analysis for TTCW will be performed based on investigator assessed CWE. Investigator assessed TTCW is defined as the number of days from randomization date to the first investigator assessed CWE. Subjects who do not have an investigator assessed CWE during the 24 weeks of the main study will be censored at the date of last contact in the main study.

For a subject with CWE (adjudicated or investigator assessed) due to disease progression and the initial assessment was on-treatment during the main study, and the confirmation assessment was off treatment or post Week 24, the subject will be counted as on-treatment CWE for the main study. The date of CW is the date of the initial assessment.

The time from randomization to the adjudicated clinical worsening event will be summarized using Kaplan-Meier estimates and compared between each active treatment and placebo treatment group using the stratified log-rank test stratified by the randomization strata. Kaplan-Meier (KM) estimates of the survival distributions of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians, 25^{th} and 75^{th} quartiles, and corresponding 95% CIs, if they can be estimated. The tabular and graphical summaries will include the at-risk counts for every visit. The number and percent of subjects censored, reason for censoring, and with events will be presented overall and for each visit, using last day of the visit window by treatment group. The hazard ratio and 95% CI a will be determined based on the semi-parametric Cox regression model stratified by randomization strata to estimate the magnitude of the effect. In order to test assess the effects of the stratification factors, the unadjusted/not stratified hazard ratio with associated 95% CI will be presented. KM plots will also be presented for each stratification factor by treatment group.

Sensitivity analysis on TTCW will be performed based on investigator reported clinical worsening.

The CEACP adjudicated and investigator reported CWE data will be listed.

7.4.3. Change from Baseline in ECHO Parameters

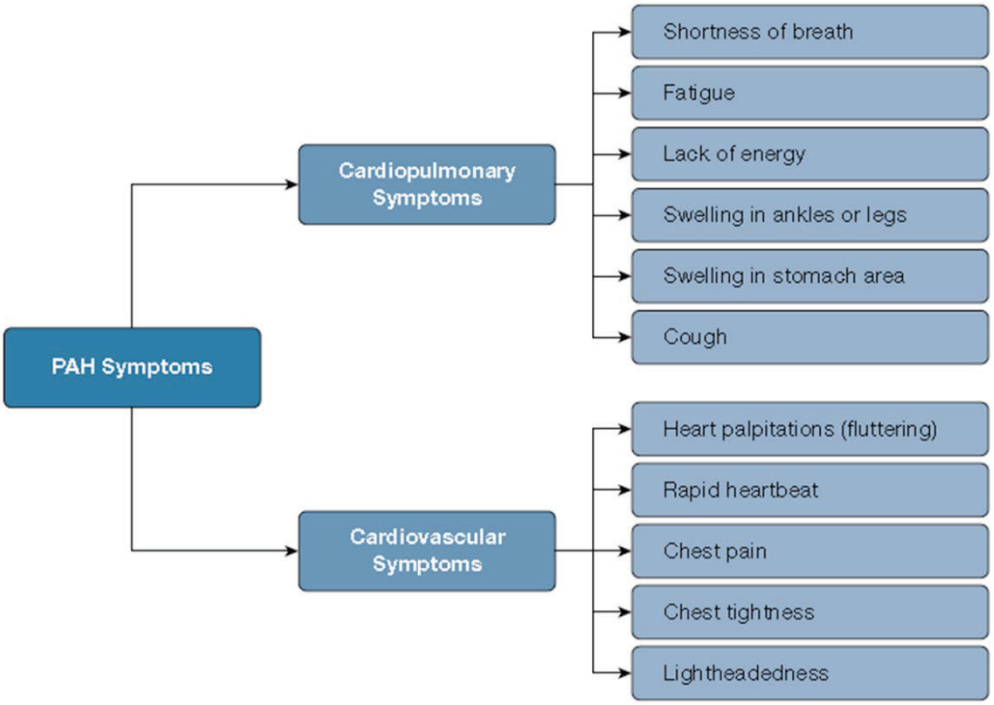
The following ECHO parameters will be summarized: Right Atrium area (cm^2), Tricuspid annular plane systole excursion [TAPSE] (cm), Tricuspid annular peak systolic myocardial velocity (m/sec), Right ventricular fractional area change [RVFAC] (%), Right ventricular end diastolic area [RVEDA] (cm^2), Right ventricular end systolic area [RVESA] (cm^2), Right Ventricular Pulmonary Artery contractile-pressure coupling (RV-PA coupling = TAPSE/SPAP [from RHC]), Right Ventricle free-wall thickness, Peak Tricuspid regurgitation velocity (m/sec), and Pericardial effusion (cm). The RHC and ECHO should be from the same visit, not necessarily the same date.

The change from baseline will be analyzed using the same ANCOVA model as specified in Section 7.2.

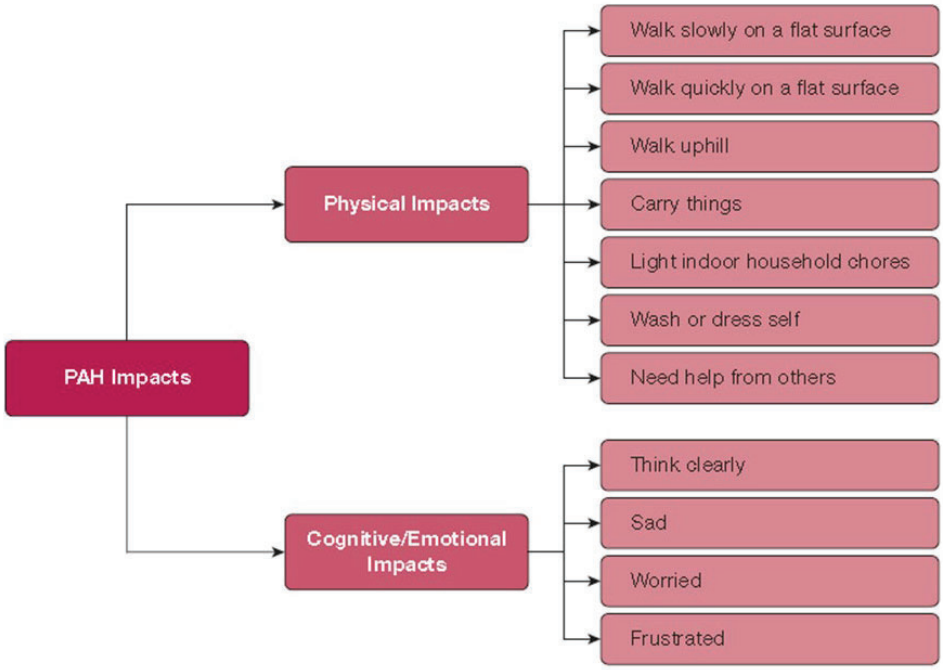
7.4.4. Change from Baseline in PAH-SYMPACT

The PAH SYMPACT Questionnaire is an instrument for quantifying PAH symptoms and impacts. It is a brief, disease specific subject reported outcome (PRO) instrument possessing good psychometric properties.

PAH Symptoms Questionnaire is collected for 7 days at each scheduled visit.



PAH Impacts questionnaire are collected once each visit (on the day of the visit):



Scores for the individual items and domains ranged from 0 to 4, with higher scores indicating greater symptom severity or worse impact. Symptoms Domains include Cardiopulmonary Symptoms and Cardiovascular Symptoms. Impacts Domains include Physical Impacts and Cognitive/Emotional Impacts. The domain score derivations are as follows:

Symptoms Domain Score Derivation:

Mean weekly symptom item scores are calculated as an average of the daily item scores. At least 4 days must be available within 14 days prior to the visit to calculate an average. Day 7 must also be available to calculate the average. The days closest to the visit with non-missing data will be used for analyses.

Symptom domain score is then calculated as the average of the mean weekly scores for its included items.

Impacts Domain Score Derivation

Impact domain score is calculated as the average of the mean impact item scores for its included items.

Analysis

In cases where the tablets were not working, the data was recorded on paper and transcribed into the EDC. The primary analysis will use all available data (paper and tablet together). Paper ePROs were data entered in Unscheduled Visits in the EDC. Sensitivity analyses may be conducted using only tablet data.

PAH-SYMPACT domain scores will be analyzed using observed data and the same REML based MMRM model as specified in Section 7.3.3.

Sensitivity analyses will be conducted using the single score at the scheduled visit (Day 7) instead of the mean weekly scores.

7.4.5. Change from Baseline REVEAL Lite 2 Score

REVEAL Lite 2 includes 6 non-invasive variables: FC, vital signs (SBP and HR), 6MWD, NT-proBNP, and renal insufficiency (by eGFR). Individual component scores are defined as follows:

1. New York Heart Association (NYHA) or WHO functional class (FC):

FC Class	REVEAL2 FC Component Score
I	-1
II	0
III	+1
IV	+2

2. Systolic BP:

Systolic BP (mmHg)	BP Component Score
< 110	+1
≥ 110	0

3. Heart Rate

Heart Rate (bpm)	Heart Rate Component Score
> 96	+1
≤ 96	0

4. 6-min walk distance (6MWD);

6MWD (meters)	6MWD Component Score
> 440	-2
320 - 440	-1
165 – <320	0
<165	+1

5. N-terminal prohormone of brain natriuretic peptide (NT-proBNP);

NT-proBNP	REVEAL2 FC Component Score
<35.4 pmol/L <300 pg/mL	-2
≥35.4 and <129.8 pmol/L ≥300 and <1100 pg/mL	0
≥129.8 pmol/L ≥ 1100 pg/mL	+2

6. Renal insufficiency:

eGFR (mL/min/1.73 m^2)	Renal Component Score
< 60 or reported AE of Renal Insufficiency	+1
≥ 60	0

REVEAL Lite 2 Score= Sum of 6 component scores + 6 (with scores ranging from 1 to 14).

For subjects with missing component score(s) for #2 (SBP), #3 (HR), or #6 (eGFR), the REVEAL Lite 2 score will still be calculated as the sum of the 3 remaining component scores. Otherwise, if any other components are missing, the REVEAL Lite 2 score will be set as missing.

The REVEAL Lite 2 score will be analyzed using observed data and the same REML based MMRM model as specified in Section 7.3.3.

7.4.6. Time to Clinical Improvement (TTCI)

Subjects are considered as having clinical improvement on-treatment during the 24 weeks of the main study if they meet the following criteria:

- 10% increase in 6MWD or 30 meters increase AND
- improvement to WHO FC II or I, or maintenance of WHO FC II
- absence of a deterioration in clinical condition or death (defined as without an adjudicated clinical worsening event during the 24 weeks [see Section 7.4.2])

On-treatment is defined as randomization date through last dose of study drug + 30 days. TTCI is the number of days from the randomization date to the minimum of (date of the first assessment of 6MWD increase of 10% or 30 meters, first date improved WHO FC, last post-baseline date WHO FC II was maintained from baseline, censor date from an adjudicated TTCW). Subjects who do not improve during the 24 weeks of the main study will be censored at the first OLE dose date if enrolled into OLE or if not enrolled into OLE, the minimum of last dose of study drug + 30 days or date of last contact in the main study.

TTCI will be summarized using the same methods as specified above in Section 7.4.2.

7.4.7. Actigraphy

Actigraphy analyses will be described separately.

8. SAFETY ANALYSES

Safety analyses will be conducted using the Safety population.

No inferential comparison of safety endpoints will be performed.

8.1. Extent of Exposure and Treatment Compliance

Total duration of exposure will be calculated in weeks as (the last date study drug administration – the first date study drug administration + 1)/7, regardless of dose interruptions. In addition, duration of exposure accounting for dose interruptions will be calculated as [(last date study drug administration – the first date study drug administration + 1) – sum of (end date of dose interruption – start date of dose interruption + 1)]/7. The dates of interruption are from the Dose Adjustment CRF. Total exposure will be calculated as the total duration of exposure (in days) multiplied by the dose level (mg) during those days. Each duration of exposure and total exposure will be summarized descriptively by treatment for the Safety population. A cumulative summary of the number and percentage of subjects with the following duration of exposure categories will also be provided by treatment (≥1 day, ≥4 weeks, ≥12 weeks, ≥24 weeks). In addition, a swim lane figure by treatment will present each subject's time on each dose, accounting for dose interruptions and dose reductions, with the reason for each annotated on the figure.

Randomized treatment compliance during the main study is defined based on the randomized treatment, not accounting for any dose reductions:

Randomized Treatment Compliance (%) = [Total number of randomized dose tablets taken/Total number of randomized dose tablets expected] ×100, where

- Total number of randomized dose tablets taken=Total number of randomized dose tablets dispensed (sum of bottles A, B, C, D from each visit) – Total number of planned dose tablets returned (sum of bottles A, B, C, D from each visit).
- Total number of randomized dose tablets expected= treatment duration ×4 (tablets per day)

  where treatment duration is calculated as the number of days between the first dose date and last dose date of study drug, without accounting for any drug interruptions.

Actual treatment compliance during the main study including accounting for any dose reductions or dose interruptions and is defined as:

Actual Treatment Compliance (%) = [Total number of dose tablets taken/Total number of dose tablets expected] ×100, where

- Total number of dose tablets taken=Total number of dose tablets dispensed – Total number of dose tablets returned.

- Total number of dose tablets expected= [dose reduction treatment duration ×2 (tablets per day)] + [treatment duration without reduction or interruption ×4 (tablets per day)]

  where dose reduction treatment duration is calculated as the sum from all dose adjustments of the number of days between the dose adjustment start date and dose adjustment end date and the treatment duration without any dose reduction or dose interruption is the sum of these durations number of days from start to end dates.

Dose interruptions resulting drug withdrawal will have a missing end date, and the date of last dose will be used. Subjects who continue into the OLE on a dose reduction may have a missing end date, the day before the first OLE dose will be used.

Treatment compliance will be summarized using descriptive statistics for the Safety population. In addition, the overall treatment compliance will be further categorized as < 80%, 80% – 100% and > 100%, and the number and percentage of subjects with compliance in each category will be presented.

Study drug administration including drug interruptions, dose reductions, overdoses, and study drug dispensing and accountability, calculated durations of exposure, and calculated compliances will be presented in by-subject data listings.

8.2. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) each verbatim term coded to a lower level term (LLT) which is mapped to a preferred term (PT), high level term (HLT), high level group term (HLGT), and a system organ class (SOC). AE severity and intensity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5) are recorded on the eCRF. Both will be presented in listings, CTCAE grade will be used in summaries and analyses.

Adverse event summaries will summarize only treatment-emergent AEs (TEAEs), which are defined as AEs not present prior to the start of study medication, or AEs present before study medication that worsened after starting study medication. If a partially missing date or time of onset allows the possibility that an AE may be a TEAE it will be assumed that it is a TEAE. Each AE will be assigned to the most recent treatment received AEs with a start on or after the first OLE dose will be assigned to the OLE treatment phase and not included in the main study AE analyses. For subjects who discontinued study without going to the open label extension, AEs started after first dose and within the 28 days of last dose will be counted as TEAEs. If it cannot be determined whether an AE is treatment emergent due to a partial onset date, then it will be counted as such. Methodology for imputation of partial AE start and stop dates is described in Appendix 1. Each summary will be displayed by treatment group, including Total Rodatristat ethyl and Overall.

8.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined in Table 12. The AESI checkbox on the CRF will not be considered or presented in summaries or data listings. AESIs are defined based on the FDA Medical Queries (FMQ) or Standardized MedDRA Queries (SMQ).

Table 12: Adverse Events of Special Interest

AESI	MedDRA Terms	Grades
Severe constipation (and/or severe, persistent, or worsening abdominal pain)	FMQ = Constipation FMQ = Abdominal Pain	Grade 3+
Diarrhea	FMQ = Diarrhea	Any Grade
Nausea and Vomiting	FMQ = Nausea FMQ = Vomiting	Grade 3+
Depression/other significant mood related disturbance (active suicidal ideation or behavior, severe depressive and/or anxious symptoms, other severe psychiatric TEAE)	FMQ = Depression FMQ = Anxiety FMQ = Psychosis	Grade 2+
Elevations in hepatic enzymes	SMQ = Liver related investigations, signs and symptoms (SMQ)	Grade 2+
Cardiac arrhythmia, related to an increase in QT/QTc interval.	SMQ = Torsade de pointes/QT prolongation (SMQ)	Any Grade

Other adverse events to be evaluated include Grade 3+ events of:

- Abdominal pain (FMQ) or Abdominal distension (HLT=Flatulence, bloating and distension)
- Elevations in INR defined by the MedDRA HLT = Coagulation and bleeding analyses

These adverse events are not defined as adverse events of special interest in the protocol but will be included in summaries of AESIs.

8.2.2. Overall Summary of Adverse Events

The number and percentage of subjects who experience at least one of the following:

- Any TEAE, All CTCAE grades
- Any TE AESI
- Grade 3+ TEAE
- TEAE by Maximum CTCAE Grade
- Serious TEAE
- TEAE leading to death

- Treatment-related TEAE, All CTCAE grades
- TEAE by highest relationship
- Treatment-related Grade 3+ TEAE
- Treatment-related serious TEAE
- TEAE leading to dose modification
  - TEAE leading to dose reduction
  - TEAE leading to study drug interruption
  - TEAE leading to study drug discontinued
- TEAE leading to discontinuation from the study

As subjects were allowed to dose reduce and hold, this summary will be repeated where the adverse event is assigned to the dose the subject was taking at the time of the adverse event. AEs will be determined to have occurred on a dose (0 mg/placebo, 300 mg, 600 mg) based on the adverse event start date. For example, if the adverse event starts on or after the start of the first dose, before any dose reduction, the adverse event will be counted as occurring during the first dose. If a subject dose reduces (0 mg/placebo or 300 mg) and the adverse event starts after the dose reduction/start of the second dose, the adverse event will be counted as occurring on the second dose. If the AE occurred after the last dose, the AE will be assigned to the last dose taken. The denominator for percentages is the number of subjects who ever took the specified dose.

8.2.3. Subject Incidence of Adverse Events

Summaries will be displayed by SOC and PT, and will be ordered by descending order of overall incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Subject incidence of TEAEs by MedDRA SOC and PT.
- Subject incidence of TEAEs by MedDRA PT.
- Subject incidence of TE AESIs by AESI Category MedDRA PT.
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity (CTCAE grade). At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for this summary.
- Subject incidence of CTCAE Grade 3 or higher TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for this summary.
- Subject incidence of treatment-related TEAEs by MedDRA SOC and PT. Related AEs are those with relationships reported as “Related” or “Possibly Related”. At each level of subject summarization, a subject is classified according to the closest

relationship to study drug if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.

- Subject incidence of treatment-related CTCAE Grade 3 or higher TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for this summary. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs by MedDRA SOC and PT.
- Subject incidence of serious TEAEs by MedDRA PT.
- Subject incidence of TEAEs leading to any study drug modification (reduced, interrupted, discontinued) by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as "Drug Withdrawn.", "Dose Reduced", or "Drug Interrupted".
  - Subject incidence of TEAEs leading to study drug discontinued by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as "Drug Withdrawn."
  - Subject incidence of TEAEs leading to dose reduction by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as "Dose Reduced."
  - Subject incidence of TEAEs leading to study drug interruption by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as "Drug Interrupted."

The above summaries will be repeated where the adverse event is assigned to the dose the subject was taking at the time of the adverse event.

The following listings will be presented by treatment group and subject, include study day event started and the duration of event:

- All adverse events.
- AESIs (subset of the AEs where AE of Special Interest is marked as "Yes" or the AE meets the criteria specified in Section 8.2.1).
- Serious adverse events (subset of the AEs where serious is marked as "Yes").
- CTCAE Grade 3 or higher adverse events (subset of AEs where severity is marked as CTCAE Grade 3, 4, or 5 or missing [to be presented as missing on the listing]).
- Related adverse events (subset of the AEs where relationship marked as "Related" or "Possibly Related" or missing relationship [to be presented as missing on the listing]).
- Adverse events leading to dose reduction (subset of the AEs where Action Taken with Study Drug is checked as "Dose Reduced").

- Adverse events leading to study drug interruption (subset of the AEs where Action Taken with Study Drug is checked as "Drug Interrupted").
- Adverse events leading to study drug discontinued (subset of the AEs where Action Taken with Study Drug is checked as "Drug Withdrawn").
- Adverse events leading to discontinuation from the study (subset of the AEs where "Did the adverse event cause the subject to be discontinued from the study?" is "Yes")
- Adverse events leading to death (subset of the AEs where outcome is indicated as "Fatal" or the CTCAE grade is 5 or seriousness criteria is Death).

8.3. Clinical Safety Laboratory Evaluations

Hematology, clinical chemistry, coagulation, urinalysis, and additional laboratory parameters to be tested are provided in section 9.2.5 of the protocol. All clinical laboratory data will be presented in by-subject data listings using standard international (SI) system of units.

In general, clinical safety laboratory evaluations were assessed via a central laboratory. However, in some cases, a local laboratory was used for repeat assessments or when the appropriate central lab kit was not available. Local labs are recorded on an Unscheduled CRF and will be windowed according to Section 4.7.1. For the purposes of summaries, if a central laboratory result is available in the analysis visit window (Section 4.7.1), it will be used for analyses, If not central laboratory result is available, and a local laboratory result is available within the visit window, it will be used for summaries. Local labs without a unit will be excluded.

The following laboratory tests will be presented in listings only: Direct Bilirubin, Lipase, Urinalysis, FSH, Pregnancy testing (hCG), and drugs of abuse. Estimated glomerular filtration rate (eGFR) will be summarized with the chemistry panel.

Continuous laboratory results and changes from baseline will be summarized descriptively. All clinical laboratory data will be presented in by-subject data listings with local laboratory results flagged. Values outside of the laboratory's reference range (ie, those with high or low values) will be flagged in the laboratory listings. The CTCAE grade will also be included in the listings. A separate listing for laboratory normal ranges, by lab category, lab test, sex, and age, will be presented.

8.3.1. Treatment Emergent Abnormalities

Quantitative laboratory values will be assigned grades according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, where applicable.

For each applicable laboratory test, a treatment emergent abnormality will be defined as a post-baseline, through Follow-Up (Week 28) or prior to first dose in the OLE phase, CTCAE grade increase of ≥2 grades and any CTCAE grade 3 or 4.

The number and percentage of subjects overall and by laboratory test, with any treatment emergent laboratory abnormality, CTCAE increase of ≥2 grades, will be presented.

A separate data listing of treatment emergent Grade 3 and Grade 4 laboratory abnormalities or increase of ≥2 grades will also be provided.

8.3.2. Shifts in CTCAE Grade

Shifts in CTCAE grade of laboratory tests will be presented from baseline to worst post-baseline value and at each post-baseline visit. Summaries will present the number and percentage of subjects with shifts in laboratory grade by treatment group. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

Some lab tests include additional clinical criteria which cannot be determined programmatically. Table 13 below specifies the grade with clinical criteria in italics. The text in italics will not be considered when assigning grades programmatically.

Table 13: CTCAE Laboratory Tests with Clinical Criteria

Amylase (serum amylase increase) • Grade 1: >ULN - 1.5×ULN • Grade 2: >1.5×ULN - 2.0×ULN; *>2.0 – 5.0×ULN and asymptomatic* • Grade 3: >2.0 – 5.0×ULN *with signs or symptoms; >5.0×ULN and asymptomatic* • Grade 4: >5.0×ULN *and with signs or symptoms*
Bicarbonate (Blood bicarbonate decreased): • Grade 1: <LLN *and no intervention initiated*.
Prothrombin Time (PT)/International Normalized Ratio (INR) (INR increased): • Grade 1: >1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated* • Grade 2: >1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated* • Grade 3: >2.5; *>2.5 x baseline if on anticoagulation; bleeding*
eGFR (Chronic Kidney Disease): • Grade 4: <15 ml/min/1.73m^2; *dialysis or renal transplant indicated*
Glucose (Hypoglycemia): • Grade 4: <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*.
Potassium (Hypokalemia) • *Grade 2: Symptomatic with <LLN - 3.0 mmol/L; intervention indicated* • Grade 3: <3.0 - 2.5 mmol/L; *hospitalization indicated* • Grade 4: <2.5 mmol/L; *life-threatening consequences*
Potassium (Hyperkalemia)

• Grade 2: >5.5 - 6.0 mmol/L; *intervention initiated* • Grade 3: >6.0 - 7.0 mmol/L; *hospitalization indicated* • Grade 4: >7.0 mmol/L; *life-threatening consequences*
Sodium (Hyponatremia) • Grade 2: 125-129 mmol/L *and asymptomatic* • Grade 3: *125-129 mmol/L symptomatic;* 120-124 mmol/L regardless of symptoms • Grade 4: <120 mmol/L; *life-threatening consequences*
Sodium (Hypernatremia) • Grade 2: >150 - 155 mmol/L; *intervention initiated* • Grade 3: >155 - 160 mmol/L; *hospitalization indicated* • Grade 4: >160 mmol/L; *life-threatening consequences*
Albumin (Hypoalbuminemia) • *Grade 4: Life-threatening consequences; urgent intervention indicated.*

8.3.3. Special Assessments of Potential Hepatoxicity

The number and percentage of subjects who met the criteria in Table 14, based on their maximum post-baseline value, will be presented to assess any potential for drug-induced hepatotoxicity or liver injury per Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation, CDER, FDA (2009).

Table 14: Hy's Rule Laboratory Abnormalities

Hepatocellular Injury and Liver Function Tests	Range of Test Values
AST	3 to <5 × ULN
	5 to <10 × ULN
	10 to <20 × ULN
	≥20 × ULN
	>2 × Baseline
ALT	3 to <5 × ULN
	5 to <10 × ULN
	10 to <20 × ULN
	≥20 × ULN
	>2 × Baseline
AST or ALT	3 to <5 × ULN

Hepatocellular Injury and Liver Function Tests	Range of Test Values
	5 to <10 × ULN
	10 to <20 ×ULN
	≥20 × ULN
	>2 × Baseline
Total bilirubin	> ULN
	>1.5 × ULN
	>2 × ULN
Alkaline phosphatase	>1.5 × ULN
	>2 × ULN
AST or ALT plus total bilirubin	>3 × ULN (AST or ALT) plus >1.5 × ULN Total Bilirubin, and ALP<2 × ULN
AST or ALT plus total bilirubin	>3 × ULN (AST or ALT) plus >2 × ULN (Total Bilirubin, and ALP<2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plots will be provided for the maximum AST/ALT post baseline vs the maximum total bilirubin post baseline. Similarly eDISH plots for the maximum AST/ALT post baseline vs the maximum GGT post baseline will be provided.

The mean values and mean change from baseline in GGT, AST, and ALT will be plotted by treatment group over time. The same plots will be generated in units of ULN.

8.3.4. Evaluation of Labs of Special Interest

Liver enzymes (ALT, AST, GGT, ALP) will be evaluated in terms of upper limits of normal (ULN). The result will be divided by the ULN, and summarized using descriptive statistics. In addition, the number and percentage of subjects with GGT or ALP increases >2×, 3×, 5×, 8×, 10×, 15×, and 20× ULN will be presented based on their maximum post-baseline value, by treatment group.

Summaries of coagulation parameters will be presented by treatment group for the subset of subjects concomitantly taking drugs included in the WHO Drug Dictionary Standardized Drug Grouping “Antithrombotic drugs”.

8.4. Vital Signs

Vital sign results will be listed by treatment, subject, and time point. Vital signs will be summarized using descriptive statistics over time including changes from baseline at each scheduled time point.

8.5. Electrocardiograms

Electrocardiogram results (including heart rate (HR), RR interval, PR interval, QRS duration, QT interval, and QTcF interval will be listed by treatment, subject, and time point. As QTcF could not be calculated on all machines, QTcF will be programmatically derived as $QT/RR^{(1/3)}$ and used in all summary tables. .All data provided on the CRF and derived will be listed.

Electrocardiogram results will be summarized using descriptive statistics over time including changes from baseline at each scheduled time point.

A categorical summary of maximum post baseline QTcF values will be summarized by treatment, in accordance with ICH E14 (Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, CHMP/ICH/2/04). The number and percentage of subject with values >450 msec, >480 msec, and >500 msec and increase from baseline values >30 msec and >60 msec.

For any subjects with a QT/QTc/QTcF >500 msec, or QTcF change from baseline of >60 msec, a separate listing of all ECG data for these subjects will be provided.

Abnormal ECG findings will also be listed separately.

8.6. Other Safety Measures

For all of the below ePRO, in cases where the tablets were not working, the data was recorded on paper and transcribed into the EDC. The primary analysis will use all available data (paper and tablet together).

8.6.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is provided in protocol Appendix 10. Table 15 describes how to score the C-SSRS and the scoring is done on the CRF. Missing data will not be imputed.

Table 15: C-SSRS Scoring

C-SSRS Item	Derivation
Suicidal Ideation	A "yes" answer to any one of the following five questions from suicidal ideation section on the C-SSRS. 1. Wish to be dead 2. Non-specific active suicidal thoughts 3. Active suicidal ideation with any methods (not plan) without intent to act 4. Active suicidal ideation with some intent to act, without specific plan 5. Active suicidal ideation with specific plan and intent If a subject answer "yes" to more than one suicidal ideation question within a visit window as an analysis time point, the worst-case response (i.e. the highest) will be used in any summaries.
Suicidal Behavior	A "yes" answer to any one of the following five questions from suicidal behavior section on the C-SSRS. 6. Preparatory acts or behavior 7. Aborted attempt 8. Interrupted attempt 9. Actual attempt 10. Completed suicide If a subject answer "yes" to more than one suicidal ideation question within a visit window as an analysis time point, the worst-case response (i.e. the highest) will be used in any summaries.
Suicidal Ideation or Behavior	A "yes" answer to any one of the above ten suicidal ideation or behavior questions on the C-SSRS.

C-SSRS Item	Derivation
Self-Injurious Behavior without Suicidal Intent	A "yes" answer to the following question from suicidal behavior section on the C-SSRS: "Has subject engaged in Non-Suicidal Self-Injurious Behavior?"

C-SSRS data will be listed by treatment, subject and visit. Subjects who reported any suicidal ideation and behavior during the main study will also be listed separately.

8.6.2. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Score (HADS) is provided in protocol Appendix 11. The HADS is a self-report rating scale of 14 items on a 4-point Likert scale (range 0–3). It is designed to measure anxiety and depression (7 items for each subscale), each item is scored between zero (no impairment) and three (severe impairment). The total score is the sum of the 14 items, and for each subscale the score is the sum of the respective seven items (ranging from 0–21).

The individual Hospital Anxiety and Depression Scale (HADS) items and domain (anxiety and depression) scores will be listed by treatment, subject and visit.

The domain scores and their changes from baseline to maximum post-baseline score will be summarized by treatment group. Domain scores will be categorized as Normal (0-7), Mild Depression (8-10), Moderate Depression (11-15), and Severe Depression (16-21). Summaries will present the number and percentage of subjects with shifts in categories from baseline to maximum post-baseline score by treatment group. Denominators for percentages will be the number of subjects with non-missing data post-baseline and baseline.

8.6.3. Quick Inventory of Depressive Symptomatology (QIDS)

The clinician-rated Quick Inventory of Depressive Symptomatology (QIDS) is provided in protocol Appendix 12. Total QIDS scores range from 0 to 27 (Rush et al., 2003), with scores of 5 or lower indicative of no depression, scores from 6 to 10 indicating mild depression, 11 to 15 indicating moderate depression, 16 to 20 reflecting severe depression, and total scores greater than 21 indicating very severe depression. The total score is the sum of all item scores. The sleep domain score is the highest score on any one of the four sleep items. The appetite/weight domain score is the highest score on any one of the four appetite/weight items. The psychomotor domain score is the highest score on any one of the two psychomotor items.

The Clinician-Rated Quick Inventory of Depression (QIDS-C) individual items, total and domain scores will be listed by treatment, subject and visit.

The results and change from baseline to maximum post-baseline score in QIDS-C total and domain scores will be summarized by treatment group.

The total score will be categorized as No Depression (0-5), Mild Depression (6-10), Moderate Depression (11-15), Severe Depression (16-20), and Very Severe Depression (21+). Summaries will present the number and percentage of subjects with shifts in categories by treatment group.

Denominators for percentages will be the number of subjects with non-missing data at the specific visit and baseline.

9. PK, PD, AND PK/PD ANALYSES

The details of the Population PK and PK/PD analyses will be presented in a separate statistical analysis plan.

Descriptive statistics of rodatristat ethyl and its metabolite PK concentrations, selexipag and ACT 333679 trough PK concentrations, plasma and urine 5-HIAA concentrations will be presented as the timepoints collected. All data will be provided in data listings.

10. OTHER ASSESSMENTS

Other assessments will be provided in by-subject data listings only; no summary tables will be provided, including but not limited to the following:

- Eligibility details including unmet eligibility criteria
- Informed consent and re-consents
- Randomization schema
- Physical examination
- Serology
- Pregnancy testing and Reproductive Health
- FSH test
- Urine drug screen
- Urinalysis and Urine Microscopic Examination
- Collection information for pharmacogenetic and future research samples

11. CHANGES TO PROTOCOL PLANNED ANALYSES

- The exploratory objective “To evaluate the effect of rodatristat ethyl on the plasma concentration of selexipag and ACT333679” was reclassified as a PK/PD objective given it is assessing the drug concentrations.
- The Enrolled analysis set was relabeled to the “Screened” analysis set for clarity.
- The Safety analysis set was modified to include all subjects who received IP, regardless of randomization or not, to align with ICH E9 principles.
- The mITT analysis set was updated to specify at least one post-baseline PVR assessment (primary endpoint), instead of general efficacy assessment.
- The PP analysis set was updated to specify “who have completed treatment with ≥80% treatment compliance” instead of general “complete Week 24”.

- The Treatment Completer analysis set was added.
- For primary endpoint analysis, missing data imputation was updated from LOCF to using multiple imputation for data MAR and worst observation for data NMAR.
- Analysis of WHO FC was updated from an ANCOVA model to ordinal logistic regression as it is a categorical endpoint.
- Analysis of 6MWT was updated from non parametric analysis of covariance within the framework of the extended Cochran Mantel-Haenszel test to aligned rank stratified Wilcoxon test with Hodges-Lehman estimates for consistency with drugs with similar indications.
- Physical examinations will be listed only.
- An additional definition of the TTCW endpoint was added.
- Additional exploratory endpoints added to specify all visits will be analyzed for secondary, additional, and exploratory endpoints where appropriate.
- Additional safety analyses were added to further characterize the risk profile.

12. REFERENCES

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13. APPENDICES

APPENDIX 1. IMPUTATION RULES FOR MISSING OR PARTIAL DATES FOR ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

Date	Situation	Imputation Rule
Start Date	Only month and year are known and month and year are prior to first dose date	Use the last day of the month
	Only month and year are known and month and year are the same as first dose date	Use the first study drug administration date
	Only month and year are known and month and year are after first dose date	Use the first day of the month
	Only year is known and year is before first dose date	Use Dec 31 of that year
	Only year is known and year is same as first dose date	Use the first study drug administration date
	Only year is known and year is after first dose date	Use Jan 1 of that year
	Entire date is missing	Use the first study drug administration date
	The estimated start date is after a complete or imputed AE stop date	Use the first day of the month of the AE/CM stop date
Stop/End Date	Only month and year are known and month and year are prior to last dose date	Use the last day of the month
	Only month and year are known and month and year are the same as last dose date	Use the last dose date
	Only month and year are known and month and year are after last dose date	Use the last day of the month
	Only year is known and year is before last dose date	Use Dec 31 of that year
	Only year is known and year is same as last dose date	Use the last study drug administration date
	Only year is known and year is after last dose date	Use Dec 31 of that year
	Entire date is missing	Use the last study drug administration date
	The estimated stop date is before a complete or imputed AE start date	Use the last day of the month of the AE/CM start date

AE = adverse event, Dec = December, Jan = January

APPENDIX 2. ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CFR	Code of Federal Regulations
CHD	congenital heart defects
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standard of Reporting Trials
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBP	diastolic blood pressure
DM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FC	functional class
FDA	United States Food and Drug Administration
FEV_1	forced expiratory volume one second
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HADS	Hospital Anxiety and Depression Scale
hCG	human chorionic gonadotropin
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin (5-hydroxytryptamine)
5-HTP	5-hydroxytryptophan
HIV	human immunodeficiency virus
HR	heart rate
HRCT	high-resolution computed tomography
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IMP	investigational medicinal product
IP	investigational product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
LQTS	long QT syndrome
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
MAOIs	monoamine oxidase inhibitors
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCT	monocrotaline
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	modified intent-to-treat
mPAP	mean pulmonary artery pressure
mRAP	mean right arterial pressure
ms	millisecond
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
OLE	open-label extension
PAC	pulmonary artery compliance
PAH	pulmonary arterial hypertension
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic
PFT	Pulmonary Function Test
P-gp	P-glycoprotein
PH	pulmonary hypertension
PK	Pharmacokinetic
PP	per protocol
PR	PR interval of the ECG
PRO	patient-reported outcome
PT	prothrombin time
PVG	pharmacovigilance
PVR	pulmonary vascular resistance
QD	once daily
QIDS-C, -SR	Quick Inventory of Depressive Symptomatology, -Clinician Rated, -Self Reported
QRS	QRS interval of the ECG
QT	QT interval of the ECG
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAP	right arterial pressure
RBC	red blood cell

Abbreviation or Specialist Term	Explanation
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
RHC	right heart catheterization
RR	RR interval of the ECG or Respiratory Rate
ROW	rest of world
RV	right ventricular
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SDS	safety data sheet
6MWT/6MWD	six-minute walk test / six-minute walk distance
SoA	schedule of assessment
SOC	standard of care
SU5416, SUGEN	semaxanib
SUSARs	suspected unexpected serious adverse reactions
SV	stroke volume
SvO_2	Mixed venous oxygen saturation
TAPSE	tricuspid annular plane systolic excursion
TBL	total bilirubin level
TEAEs	treatment-emergent adverse events
TLC	total lung capacity
TPH	tryptophan hydroxylase
TTCI	time to clinical improvement
TTCW	time to clinical worsening
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

APPENDIX 3. DOCUMENT HISTORY

Version	Date	Author	Description
1.0	22 June 2023	[redacted]	Initial Final Version
2.0	28 June 2023	[redacted]	Update title page to remove Draft for Final Versions Update time to event analyses to be from randomization instead of first dose Correct typographical errors

APPENDIX 4. APPROVAL PAGE

I confirm that I have reviewed this document and agree with the content.

APPROVALS		
[redacted]		6/28/2023
[redacted]		**Date** **(dd-mmm-yyyy)** 6/29/2023
[redacted]		**Date** **(dd-mmm-yyyy)** 6/28/2023
[redacted]		**Date** **(dd-mmm-yyyy)**