CLINICAL STUDY PROTOCOL

Protocol Title	A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Rodatristat Ethyl in Patients with Pulmonary Arterial Hypertension	
Protocol Name/Number	ELEVATE 2 / RVT-1201-2002, Version 4.0 (Amendment 3)	
Approval Date	19JAN2022	
Compound Name/Number	Rodatristat ethyl / RVT-1201	
Indication	Treatment of Pulmonary Arterial Hypertension	
Study Phase	Phase 2b	
Sponsor Name	Altavant Sciences GmbH	
Legal Registered Address	Sponsor: Altavant Sciences GmbH Viaduktstrasse 8 CH-4051 Basel Switzerland	U.S. Agent: Altavant Sciences, Inc. 6501 Weston Parkway Suite 330 Cary, North Carolina 27513 United States of America
Study Region(s)	United States, Canada, Poland, United Kingdom, France, Spain, Germany, Italy, Belgium, Bulgaria, Ukraine, Latvia, Austria, Republic of Moldova, Bosnia and Herzegovina, Serbia, and Czech Republic	
Regulatory Agency Identifier Number(s)	IND: 126945	File Number: HC6-24-c223565 EudraCT: 2020-004971-42

1: All sites outside the United States are subject to the requirements of 21 CFR 312.120 and not under the IND 126945

CONFIDENTIALITY STATEMENT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 3, Version 4.0	19JAN2022
Amendment 2, Version 3.0	21DEC2021
Amendment 1.9, Version 2.9 (Serbia Specific Amendment)	21DEC2021
Amendment 1.8, Version 2.8 (Germany Specific Amendment)	07SEP2021
Amendment 1.7, Version 2.7 (Poland Specific Amendment)	23AUG2021
Amendment 1.6, Version 2.6 (France Specific Amendment)	20JUL2021
Amendment 1.5, Version 2.5 (Czech Republic Specific Amendment)	14JUL2021
Amendment 1.4, Version 2.4 (Poland Specific Amendment)	14JUL2021
Amendment 1.3, Version 2.3 (France Specific Amendment)	22JUN2021
Amendment 1.2, Version 2.2 (Italy and Germany Specific Amendment)	17JUN2021
Amendment 1.1, Version 2.1 (UK and Bulgaria Specific Amendment)	28MAY2021
Amendment 1, Version 2.0	19NOV2020
Original Protocol	18SEP2020

Amendment 3 (19JAN2022)

Section# and Name	Description of Change	Brief Rationale
1.3 Schedule of Assessments (Main Study) 1.4 Schedule of Assessments (First 24 Weeks of OLE)	Week 8 of the Main Study and OLE have been changed from a telephone/telemed visit to a clinic visit. Weight, vital signs, ECG and collection of safety laboratories are being added to Week 8 of both the Main Study and the OLE.	Assessments are being added to Week 8 as an additional safety measure so there is not 8 weeks between visits.
1.3 Schedule of Assessments (Main Study) 1.4 Schedule of Assessments (First 24 Weeks of OLE)	Additional unscheduled safety assessments may be conducted at any time during the study if the Investigator or Sponsor deems it necessary for the safety of the patient.	Additional wording added to clarify unscheduled visits.
3.0 Objectives and Endpoints	Deletion of the following from additional objectives: o Peptide (NT-proBNP)	This is a discrepancy – this objective is under Secondary endpoints already and so deleted here.
9.2.5.5 Other Tests	Additional wording added to end of section: Additional unscheduled laboratory assessments may be conducted at any time during the study if the Investigator or Sponsor deems it necessary for the safety of the patient.	Additional wording added to clarify unscheduled visits.

Amendment 2 (21DEC2021)

Section# and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.2 Number of Patients	Addition of Serbia, Republic of Moldova, Austria, Bosnia Addition of new sites from the original 45-50 sites, approximately 68 sites.	Additional countries and sites added for enrollment

	Ex-US clinical sites are subject to 21 CFR 312.120 (acceptance of foreign data) and are non-IND sites	Clarify ex-US sites are not under the US IND
1.1 Synopsis 3.0 Objectives and Endpoints	Objectives and Endpoints subheadings were added (safety, additional and PK/PD). No changes to actual Objectives or Endpoints were done.	Clarification of type of objectives and endpoints. Included in Amendment 1.9 (Serbia, RA request)
1.1 Synopsis	In synopsis only: title change from Primary and Secondary Endpoints to Primary and Secondary **Objectives** and update to Exploratory Objectives	Change to reflect the synopsis wording is all Objectives rather than Endpoints. Both Main Study Objectives and End Points are found in Section 3 of the Protocol.
1.1 Synopsis 5.1 Inclusion Criteria	Change to #7 Inclusion criteria *From (changes in italics):* a. Forced expiratory volume in one second (FEV_1) ≥ 60% of predicted normal, and *b. FEV1:Forced Vital Capacity (FVC) ratio ≥ 0.70, and* c. Total lung capacity (TLC) ≥ 70% of predicted normal (high-resolution computed tomography [HRCT] *required for* TLC ≥ 60% and < 70%) **To (changes in bold):** a. Forced expiratory volume in one second (FEV_1) ≥ 60% of predicted normal, and **b.** Total lung capacity (TLC) ≥ 70% of predicted normal **or FVC ≥ 70% predicted if TLC is not available; For subjects with CTD associated PAH, if TLC is ≥ 60% of**	Change in wording to clear up ambiguity.

	predicted but < 70**% of predicted or if FVC ≥ 60% of predicted but < 70% of predicted, high resolution computed tomography [HRCT] obtained within 6 months of screening may be utilized to demonstrate limited interstitial lung disease**	
1.1 Synopsis 5.1 Inclusion Criteria	*From:* 3. Body mass index (BMI) ≥ 18 kg/m^2 and ≤ *38* kg/m^2 **To:** 3. Body mass index (BMI) ≥ 18 kg/m^2 and ≤ **40** kg/m^2	Increase in BMI to be more inclusive of patient population.
1.1.Synopsis 5.1 Inclusion Criteria	*From (changes in italics):* 5. Confirmed diagnosis of PAH and meet ALL the following hemodynamic criteria by means of a screening RHC completed prior to randomization: a. mPAP of ≥ *20* mmHg b. PVR ≥ *400* dyne•sec/cm^5 c. Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) of ≤ 12 mmHg if PVR ≥ 400 and < 500 dyne•sec/cm^5, or PCWP/LVEDP ≤ 15 mmHg if PVR ≥ 500 dyne•sec/cm^5 *d. 6MWD of 100 to 550 meters at Screening* **To (changes in bold):** 5. Confirmed diagnosis of PAH and meet ALL the following hemodynamic criteria by means of a screening RHC completed prior to randomization: a. mPAP of **> 20** mmHg b. PVR ≥ **350** dyne•sec/cm^5 c. Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) of ≤ 12 mmHg if PVR ≥ **350** and < 500 dyne•sec/cm^5, or PCWP/LVEDP ≤ 15 mmHg if PVR ≥ 500 dyne•sec/cm^5	Updated guidelines for pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg, confirmed by right-sided heart catheterization, therefore this update is being made. The selection of a minimal PVR of 400 dyn.sec.cm-5 was selected for the ELEVATE-2 study based upon precedent of recent phase 2 clinical trials of other agents, given the

	Below criteria was separated out from Inclusion #5 6. 6MWD of 100 to 550 meters at Screening	mechanism of action of rodatristat ethyl, there is no scientific evidence to suggest that subjects with lower, yet substantial pulmonary vascular disease will not demonstrate a treatment response, thus the lower limit of PVR is changed to greater than or equal to 350 dyn.sec.cm-5. 6MWD is not a hemodynamic criteria and therefore now a stand alone inclusion criteria.
1.1 Synopsis 5.2 Exclusion Criteria	**Bolded** wording added: 4. Three or more of the following risk factors for left ventricular disease: a. BMI $\geq$ 30 kg/m^2 b. Diagnosis of essential hypertension that is actively treated c. Diabetes mellitus	Alternative diagnostic criterion if LAVi not available.

	d. History of significant coronary artery disease (e.g., chronic stable angina, history of coronary intervention within the last 3 months, or a stenosis > 70% at coronary angiography) e. Atrial fibrillation **f.** Left atrial volume index > 41 mL/m^2 **[or left atrial diameter (LA) > 4 cm if LAVi unavailable]**	
1.1 Synopsis 5.2 Exclusion Criteria	Exclusion criteria changed from (in *italics*) to (in **bold**) 15. Patients with: *Uncontrolled arterial hypertension (Systolic Blood Pressure [SBP] > 180 mmHg and/or Diastolic Blood Pressure [DBP] > 110 mmHg), or hypotension (SBP < 90 mmHg and/or DBP < 50 mmHg)* **15. Patients with (during Screening):** **a. Severe hypertension (SBP > 180 mmHg and/or Diastolic Blood Pressure [DBP] > 110 mmHg), and patients with severe hypotension (SBP < 90 mmHg and/or DBP < 50 mmHg)** **b. Hypertension or hypotension considered not controlled in line with clinical standards**	Updated to clarify 'uncontrolled' Included in Amendment 1.8 (Germany, RA request)
1 Synopsis 5.2 Exclusion Criteria	Added wording in **bold**: **26.** Use of any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to Screening or 90 days if an investigational drug for PAH, unless local health authority guidelines mandate a longer period**, or in consultation with the medical monitor, will not interfere with the safety or efficacy of the study**	Added wording to allow for flexibility.
1.1 Synopsis 5.2 Exclusion Criteria	Addition of exclusion criteria #27. Any history of hypersensitivity to rodatristat ethyl, any of its components, or any components in the placebo preparation.	Exclusion criteria missed in original protocol Included in Amendment 1.2 (Germany, Italy and Czech

		Republic RA request)
1.1 Synopsis 5.2 Exclusion Criteria	The following exclusion criteria has been added: 28. Patient is deprived of their liberty by a judicial or administrative decision, or is receiving psychiatric care, and is admitted to a health or social institution 29. Patient is subject to legal protection or is unable to express consent	Criteria was added at request of Regulatory Authority. Included in Amendment 1.3 (France RA request)
Schedule of Assessments (Main Study) 9. Study Assessments and Procedures 9.1.6 Pulmonary Function Tests (PFTs)	Addition of Assessment: Pulmonary Function Tests (PFTs) (unless completed in last 24 weeks) Wording added in **bold:** Once all screening procedures are complete and the Investigator determines that the patient is eligible, the site must upload/send the required supporting documentation for approval by the Sponsor. The required information will include the RHC report (including tracings), PFTs obtained **(may use PFTs completed within the 24 week period prior to screening or obtained at Screening)**, the screening echocardiogram, as well as specific information about the patient's medical history and disease state to further ensure the appropriateness of each patient being enrolled into this study. Approval from the Sponsor must be obtained prior to randomization. **9.1.6. Pulmonary Function Tests (PFTs)** **PFTs (performed with or without bronchodilation) should be completed at Screening if there are no historical results from tests completed within 24 weeks prior to Screening.**	PFTs were already part of the Inclusion Criteria but were not in the Schedule of Assessments or described in Study Assessments and Procedures section.
1.3 Schedule of Assessments (Main Study)	Dispensing IP via IRT deleted from Week 8 and 18. Echocardiogram assessment moved from Day 1 to Screening	Enough IP will be dispensed at Week 4 and Week 12 to enable dosing

	Plasma NT-proBNP level has been deleted from Screening. **New wording in bold:** Rodatristat Ethyl and Rodatristat PK: At Day 1 and Week 4, a predose PK sample will be collected (patients will take study medication in the clinic). At Week 12, a postdose PK sample will be collected between 1 to 8 hours after the morning dose **(patients will take the morning dose in the clinic and the time of dose will be recorded – all other assessments can be done pre or post dose).** At Week 24, no study medication will be taken prior to the clinic visit **(the last dose in the Main Study will be the evening before the Week 24 visit)** and a PK sample will be collected. If the subject enrolls in the OLE, this PK sample will be collected prior to the first dose of study treatment in the OLE.	through to Week 12 and Week 24. Echocardiogram is needed as a Screening tool. Plasma NT-proBNP level only needs to be performed on patients who are eligible for the study, not at Screening. Clarification on when to take dose at Week 12 visit and when the last dose for the Main Study is completed.
1.3 Schedule of Assessments (Main Study) 9.2.6 Pharmacogenetic Testing	Additional wording in **Bold**/addition to Schedule of Assessment table: A separate and specific informed consent form will be provided to patients to allow the sponsor to obtain and test a patient's blood sample taken at the Baseline/Day1 **and the Week 24 visits** for pharmacogenetic markers that may be predictive of the natural history of the disease, response to therapy and tolerability of therapy.	Addition of a pharmacogenetic blood draw at Week 24.
1.1 Schedule of Assessments (Main Study) 9.1.10 Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management	REVEAL Lite 2.0 has been deleted from the table. Added wording in **bold**: REVEAL Lite 2 includes 6 non-invasive variables: FC, vital signs (SBP and HR), 6MWD, NT-proBNP, and renal insufficiency (by eGFR). **REVEAL Lite 2 will be a calculated parameter (by statistician) at Baseline and Week 24 of the Main Study and Week 24 of the OLE (this score will not be in the eCRF).**	This is a calculation that will be performed by the Statistician. This is not an assessment that the site performs and therefore

Lite 2 Risk Assessment Calculator		does not need to be in the table.
1.4 Schedule of Assessments – Open-Label Extension – (First 24 weeks of Open Label Extension)	First 24 weeks of OLE has been updated to mirror the Main Study (with the exception of PK, PD, and actigraphy)	Up to one-third of the patients will receive rodatristat ethyl for the first time in the OLE. Safety and efficacy procedures have been updated to ensure patient safety. Included in Amendment 1.1 (UK and Bulgaria RA request) Included in Amendment 1.8 (Germany RA request)
1.3 Schedule of Assessments – Main Study 1.4 Schedule of Assessments – First 24 Weeks of Open-Label Extension 1.5 Schedule of Assessments – Open-Label Extension Post 24 Weeks 5.4.1 Contraception 9.2.1 Pregnancy Testing	Insertion of requirement for additional pregnancy testing in women whose menstruation is delayed or who have infrequent or irregular menstrual cycles. Wording added in **bold:** Serum pregnancy tests will be obtained for all female patients of childbearing potential at Screening **and every 4 weeks while on IP.** Pregnancy tests will be completed in women of child-bearing potential **every 4 weeks** while on study. **Weeks 8, 16 and 20 will be performed at home (with a kit given to the subject by the site) and the results will be confirmed with the subject by a phone call.**	Adding instructions for sites to perform pregnancy testing per CTFG Guideline, contraception and pregnancy testing recommendation. Included in Amendment 1.7 (Poland RA request)

		Included in Amendment 1.4 (Czech Republic RA request) Included in Amendment 1.8 (Germany RA request)
2.1 Background 9.5 Pharmacokinetics	Addition to background: Rodatristat ethyl is a prodrug for the active tryptophan hydroxylase 1 (TPH1) inhibitor rodatristat. In vitro, nonclinical, and human pharmacokinetic (PK) studies to date have provided valuable information on the PK properties of rodatristat ethyl and its active moiety, rodatristat. Rodatristat ethyl has low to moderate oral bioavailability in nonclinical species and is rapidly converted to rodatristat in vivo. Both rodatristat ethyl and rodatristat are highly protein bound and little is excreted in the urine. Biliary excretion predominates in rats and no further metabolism of rodatristat has been detected in human hepatocyte preparations. However, preliminary investigations have also identified a metabolite, M15, in the plasma of dogs and humans after administration of rodatristat ethyl. After single-dose administration, the half-life of rodatristat ethyl and rodatristat are approximately 5 and 12 hours, respectively, reaching steady-state exposure, according to trough concentrations, by Day 5. The highest exposures achieved in healthy subjects to date were reached on Day 7 following 800 mg twice daily (BID) doses of rodatristat ethyl. Addition of M15 metabolite in PK section.	A metabolite profiling study performed in dogs led to the identification of an additional major metabolite, M15, in plasma after the start of this study. Blood for PK samples will analyze for M15 in addition to rodatristat ethyl and rodatristat.
4.5 Criteria for Study Termination	Additional wording in Section 4.5: **The study may resume once concerns about safety, protocol compliance, and data quality are addressed and the IRBs/ECs and competent authorities are satisfied. The study will only resume after prior submission and approval of the substantial amendment (if required) by the competent authority.**	Clarification of procedures Included in Amendment 1.1 (UK and Bulgaria RA request)

4.8 End of Study Definition	New wording in bold: A patient is considered to have completed the study if he/she completed 24 weeks of treatment including the Week 24 visit and the Follow-up Visit (for patients that complete the study through Week 24 but decide not to rollover to the OLE), or the last scheduled procedure shown in the Schedule of Assessments(SoA; Section 1.3). **If the patient decides to continue into the OLE, subject must not participate in another interventional study until completing the final follow-up visit (4 weeks after the last dose of study drug) according to the Schedule of Assessments OLE (Section 1.4 or 1.5).**	Sentence added to define end of study for patient participating in OLE. Included in Amendment 1.3 France RA request
5.3 Other Eligibility Criteria	Wording updated to reflect change in process: *From* To determine patient eligibility at Screening, a single repeat of certain tests such as laboratory values, vital signs, or ECGs *may be* allowed, *with consultation of the Medical Monitor.* **To:** To determine patient eligibility at Screening, a single repeat of certain tests such as laboratory values, vital signs, or ECGs **will be allowed**.	Clarification on updated procedure for single repeat Screening procedures.
5.4.1 Contraception	Correction of inconsistencies in the protocol. -Inclusion 1a has contraception beginning 4 weeks prior to first dose of IP and Section 5.4.1 has contraception starting at Screening. Correction of Inclusion 1a to match Section 5.4.1., contraception should start at Screening. -Inclusion 1a and 1b have contraception ending for women 4 weeks after the last dose of IP and for men 100 days after the last dose of IP and Section 5.4.1 has contraception ending for women 4 weeks after the last study visit and for men 100 days after the last visit. The protocol now has contraception ending for both women and men 4 weeks and 100 days after the last dose of IP, respectively.	Correction of inconsistency

5.4.1 Contraception	Addition of contraception method: Sexual abstinence – (refraining from heterosexual intercourse). If study patient chooses this option, site staff must follow-up to reconfirm throughout the study. If patient becomes sexually active, one of the above choices must be utilized and documented.	Clarification on highly effective method of birth control Included in Amendment 1.2 (Germany, Italy and Czech Republic RA request) Included in Amendment 1.4 (Poland and Austria RA request) Included in Amendment 1.6 (France RA request)
5.4.1 Contraception	Deletion of contraception method: *Cervical cap or diaphragm (double barrier) plus spermicide*	Cervical cap or diaphragm with a condom and spermicide is not a method that can achieve a failure rate of less than 1% per year Included in Amendment 1.1 (UK and Bulgaria RA request) Included in Amendment 1.2 (Germany, Italy and Czech Republic RA request) Included in Amendment 1.4 (Poland and

		Austria RA request) Included in Amendment 1.6 (France RA request)
6.1 Table 3 Footnote	* 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	Clarifying statement Included in Amendment 1.2 (Germany, Italy and Czech Republic RA request)
6.4 Measures to Minimize bias: Randomization and Blinding	Added wording in **bold:** This is a double-blind study. The Sponsor, Investigator, patient, 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 patient, **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.** **At the time of Screening for entry into the OLE, all patients will be re-randomized to receive either 300 mg BID or 600 mg BID rodatristat ethyl in an open-label fashion. Patients will not know what they received in the Main Study until all patients have completed the Main Study and the database is locked.** **At the time of re-randomization in the OLE, patients will be assigned a new randomization number. Once this number has been assigned, it cannot be reused/reassigned.**	Additions to paragraph to reduce ambiguity. Wording added to section to make clear the process for randomization and dose level in the OLE.
6.5 Investigational Product Compliance	Statement added:	Statement added to clarify what is considered IP

	Full compliance with the IP regimen, per subject, will be considered to be >80%.	compliance in this study.
1.1 Synopsis 4.1 Overall Design 7.1.4 Open-Label Extension Design	Wording added in **bold**: Patients who participate in the OLE **will <u>continue to receive rodatristat ethyl for 6.5 years</u>,** until the Investigator or patient chooses to stop the IP, any stopping criteria in the Main Study are met, IP becomes commercially available, <u>or</u> the Sponsor stops the study for lack of efficacy or a safety signal **(<u>whichever preceding criteria comes first). In no case will a patient be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.</u>** <u>Deletion of:</u> *Investigator or patient chooses to stop the IP, any stopping criterion in the Main Study is met, IP becomes commercially available, or the Sponsor stops the study for lack of efficacy or a safety signal.* <u>Addition to Overall Design section:</u> **Female patients 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, starting at Screening, during the course of the study and for at least 4 weeks following the last dose of rodatristat ethyl.** **If there is not a clinic visit, a urine pregnancy test will be sent home with the patient and results will be followed up with a phone call.**	A stop date for the total time a subject can be on rodatristat ethyl has been established and added to the protocol. Included in Amendment 1.2 (Germany, Italy, and Czech Republic RA request)
8.1. Discontinuation of Investigatrional Product	Wording added in **bold:** The Investigator must also discontinue/withdraw a patient's participation in the study if any of the following criteria apply:	Updated to define stopping criteria for IP non-compliance.

	• Pregnancy • Significant protocol violation/lack of compliance with the study and/or study procedures - **non-compliance with IP for discontinuation of patient is defined as < 50%.** • Severe constipation (e.g., obstipation with manual evacuation indicated) and/or severe, persistent, or worsening abdominal pain • Any significant worsening on postdose C-SSRS indicative of active suicidal ideation with intent to act (defined as C-SSRS Suicidal Ideation category score of 4 or 5) or behavior (either preparatory acts/behavior, aborted attempt, interrupted attempt, or actual attempt) • Severe depression or anxiety based on a HADS Depression or Anxiety score ≥ 15, or a QIDS-C Total Score ≥ 16. • Any severe psychiatric or CNS AE as determined by the Investigator.	
9.2.1 Pregnancy Testing	Clarification that if FSH does not confirm postmenopausal status, in addition to pregnancy testing, patients must use approved contraception	Clarification of pregnancy testing and use of contraception in patients where post-menopausal status is not confirmed by FSH. Included in Amendment 1.1 (UK and Bulgaria RA request)
9.2.8 Suicidal Ideation and Behavior Risk Monitoring	Wording updated to reflect the immediate discontinuation of investigational product in any patient who experiences suicidal ideation or behavior, following a risk assessment.	Updated wording to be consistent with Section 8.1 and reflect the procedures to be taken if patient

		exhibits suicidal ideation or behavior while on investigational product. Included in Amendment 1.1 (UK and Bulgaria RA request)
9.3.2 Time Period and Frequency for Collecting Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events	Wording added: Adverse events of special interest should be reported to the sponsor should they meet the definition of an SAE, and all timelines for reporting of SAEs should be adhered to.	Clarification of reporting of Adverse of Special Interest Included in Amendment 1.1 (UK and Bulgaria RA request)
9.1.1 Right Heart Catheterization	All of the following wording has been deleted from this section: Parameters measured during the RHC: • Heart rate (HR) - HR should be determined at the time of the cardiac output measure preferably by thermodilution. HR should be measured until 2 consecutive values do not differ by more than 10%; the last value will be recorded in the eCRF. • Cardiac Output by the Thermodilution or Fick (if thermodilution is not available) Method - Thermodilution is the preferred method for the estimation of cardiac output. At least 3 determinations that are within 10% variability of one another must be measured. Measurements must be repeated until this reliability is met. The mean cardiac output will be defined as the average of these 3 measurements and used for the calculation of PVR. The mean value will be recorded in the eCRF. Investigators must ensure	There is a Right Hearth Catheterization Manual sites should be referring to, so this list of parameters is being deleted so there are no discrepancies. There will not be a core imaging laboratory for adjudication of the RHC endpoints.

	that the individual values and the calculation of the mean are recorded in the source documents. If the mean cardiac output is auto-generated, investigators must ensure that the measurements used to calculate the mean are within the 10% variability and are available to be recorded in the source documents and in the eCRF. The last value will be recorded in the eCRF. • Systemic arterial pressure (systolic, diastolic, and mean) - Systemic arterial pressures should be taken just prior to entry of the catheter and should be measured until 2 consecutive mean values do not differ by more than 10%. The last value will be recorded in the eCRF. All values should be available in the source documents. • PAP (systolic, diastolic, and mean) - Pulmonary arterial pressures should be measured at end expiration and should be measured until 2 consecutive mean values do not differ by more than 10%. The last value will be recorded in the eCRF. All values should be available in the source documents. Mean PAP as determined by the site's medical instrument (automatically generated) will be entered into the EDC system. If the site's medical instrument does not automatically generate the mPAP, it should then be calculated manually using the following equation: mPAP = ([diastolic PAP × 2] + systolic PAP) ÷ 3. • Mean right atrial pressure (RAP) - Mean RAP should be measured until 2 consecutive values do not differ by more than 10%. If mean RAP values are less than 10 mmHg, the 2 consecutive values must not differ by more than 1 mmHg. The last value will be recorded in the eCRF. All values should be available in the source documents. • PCWP or LVEDP - The PCWP or LVEDP should be recorded as the mean of 3 separate measurements taken at end-expiration, involving balloon deflation and re-wedging of the balloon	

	for these separate measurements. It is strongly preferred that the same assessment (PCWP or LVEDP) be performed for both RHC assessments. In situations where this is not possible, the Investigator should provide an explanation in the eCRF. All values should be available in the source documents. • SvO_2 - Blood gas by pulmonary artery mixed venous blood sample should be measured and recorded in the eCRF. All values should be available in the source documents. • Calculated parameters: o PVR (dyne•sec/cm^5) = [(mPAP – PCWP) ÷ mean CO] × 80 or [(mPAP – LVEDP) ÷ mean CO] × 80 o Cardiac Index = CO ÷ BSA o Stroke Volume (SV) = CO ÷ HR o PAC = ratio of SV to pulmonary artery pulse pressure o (Weight) kg0.425 x (Height) cm0.725 x 0.007184 = BSA in M^2	
9.1.9 Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire	Deleted wording in *italics*: Prior to departing the study site *at the Day 1 Baseline Visit,* patients will be instructed and trained on how to complete the questionnaire. Added wording in *bold*: Prior to departing the study site **at the Screening Visit,** patients will be instructed and trained on how to complete the questionnaire. **Patients will start the PAH-SYMPACT questionnaire 6 days prior to the visit for which PAH-SYMPACT is collected, with the Day 7 being completed on the day of the visit.**	Clarity on how the PAH-Sympact questionnaire is being administered.
1.3 Schedule of Assessments (Main Study)	Deleted wording in *italics*: Coagulation testing will be done at *Baseline***,** Week 12, and Week 24 for all patients on the Main Study and every clinic visit post 24 weeks in the OLE.	Clarification of when coagulation test will be

1.4 Schedule of Assessent (OLE – First 24 Weeks) 9.2.5.2 Coagulation	Added wording in **bold:** Coagulation testing will be done at **Screening,** Week 12, and Week 24 for all patients on the Main Study **and at Week 12 and Week 24 of the OLE in the first 24 weeks** and every clinic visit post 24 weeks in the OLE.	completed under the new design.
9.2.5.5 Other tests	Urine Creatinine (for calculation of 5-HIAA) at each 5-HIAA collection time	Addition of urine creatinine for clarification.
Appendix 1. Concomitant and Prohibited Medications	Marketed drugs known to prolong QT/QTc AND which are also clearly associated with a known risk of Torsades de Pointe source: www.CredibleMeds.org (Woosley, 2021)	An update to the list of marketed drugs known to prolong QT/QTc AND which are also clearly associated with a known risk of Torsades de Pointe was made in 2021. Amendment 1 of the protocol included the 2019 version. This protocol has been updated with the new list.
Appendix 1 6.6.1. Rodatristat Drug Interaction Potential	Amodiaquine, Pimozide, and Quinidine were deleted from the Narrow Therapeutic Drug table as acceptable concomitant medications.	Amodiaquine, pimozide, and quinidine are drugs that are known to prolong QTcF and therefore not allowed in this study.

Amendment 1 (19NOV2020)

Section# and Name	Description of Change	Brief Rationale
1.1 Synopsis	Words deleted in *italics* and added in **bold**: **Study center(s):** United States, Canada, Poland, United Kingdom, France, Spain, Germany, Italy, Belgium, Bulgaria, Russia, Ukraine, *Netherlands,* **Czech Republic, Latvia**	Final country list completed
1.1 Synopsis	Addition of Objective and Endpoint to evaluate the effect of rodatristat ethyl on selexipag/ACT-333679 PK	Additional PK assessments to further evaluate interaction between rodatristat ethyl and selexipag/ACT-333679
1.1 Synopsis 5.1 Inclusion Criteria	2. Added wording in **bold**: 3. Male and female patients must be **at least** 18 years of age at the time of signing the informed consent.	Clarification of age of patient who can be enrolled.
1.1 Synopsis 5.1 Inclusion Criteria	Deleted wording in *italics*: *A male patient is eligible to participate if he does not have a female partner who is pregnant or who intends to become pregnant during the study.*	Wording deleted as conflicting with intent and contraception wording.
1.1 Synopsis 4.1 Overall Design 6.4 Methods to Reduce Measures to Minimize Bias: Randomization and Blinding	Additional wording in **Bold** added: Eligible patients will be stratified during the randomization process based on the number of background PAH therapies they are receiving (1, 2 or 3) **and use of selexipag (yes/no).** The	The results of a drug interaction with rodatristat ethyl and selexipag in healthy volunteers is available. The new criteria in stratification and capping of patients on selexipag are due to the results of this study.

	number of patients who are receiving a prostanoid infusion will be capped at 50% of the total number of patients enrolled. **The number of patients who are receiving selexipag will be capped at 20% of the total enrolled.**	
1.2 Study Schematic	Figure 1 updated to reflect accurate study visits	Figure 1 Study Schematic was not aligned with correct study visits
1.3 Schedule of Assessments – Main Study	Week 18 (Day 140) changed to Week 18 (Day 126)	The number of days for Week 18 was wrong in original protocol
1.3 Schedule of Assessments – Main Study	Physical exam will not be conducted at Follow-up Visit	Change is being made to accommodate a home visit, if needed.
1.3 Schedule of Assessments – Main Study and Section 9.2.7, Optional Sample for Future Research	Optional Sample for Future Research was added to the protocol	The addition of this optional future research sample will be used to increase our knowledge and understanding of the biology, pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the process of drug absorption and disposition.
1.3 Schedule of Assessments – Main Study Footnote #5	Amendment 1 wording (wording in italics are deleted) Weight only (no height or BMI) will be performed at Weeks 4, 12, ~~18,~~ 24, and 28	Weight does not need to be collected at Week 18. This change in the footnote reflects what is in the table.
1.3 Schedule of Assessments – Main Study Footnote #9 and Morning Dose Taken in Clinic with Food in the Table	Amendment 1 wording (additions in **bold**): IP must be taken daily, morning and evening **until the night before the Week 24 visit**. Patients must be told not to take a dose the morning of the Week 24 visit. Doses should be taken	Updated language provides more clarity of process for IP and when to take the dose on clinic visit days

	with food. During visits at the clinic or home, all assessments should be done predose, **except where otherwise indicated.** Patients should bring their IP with them for each visit **(including any empty bottles).**	
1.3 Schedule of Assessments – Main Study Footnote #12	Amendment 1 wording (additions in **bold**): Three 12 lead ECGs (**at least** 1 minute apart) will be collected on Day 1 after at least 5 minutes of rest. Single 12-lead ECGs will be collected at all other time points.	Updated language provides more guidance for collection of ECGs.
1.3 Schedule of Assessments – Main Study Footnote #14 9.1.1 Right Heart Catherization	Additional wording added at beginning of footnote #14: RHC results from 4 weeks prior to the Screening visit may be used for entry provided the historical RHC includes all required information and provided that changes to the patient's PAH regimen were not made.	New criteria allow for hemodynamics obtained during a recent RHC to be considered when determining a patient's eligibility for participation in the study.
1.3 Schedule of Assessments – Main Study Footnote #17	**Original protocol wording:** At Day 1 and Weeks 4 and 24, a predose PK sample will be collected (patients will take study medication in the clinic). At Week 12, a postdose PK sample will be collected between 1 to 8 hours after the morning dose (patients will take the	Clarification of collection of PK and PD samples

	morning dose at home before the clinic visit). **Amendment 1 new wording:** **At Day 1 and Week 4, a predose PK sample will be collected (patients will take study medication in the clinic). At Week 12, a postdose PK sample will be collected between 1 to 8 hours after the morning dose (patients will take the morning dose at home before the clinic visit). At Week 24, no study medication will be taken prior to the clinic visit and a PK sample will be collected. If the subject enrolls in the OLE, this PK sample will be collected prior to the first dose of study treatment in the OLE.** Blood and spot urine samples for 5-HIAA (and urine samples for creatinine) will be collected **pre-dose** on Day 1 and at Weeks 4, 12, and 24.	
1.3 Schedule of Assessments – PK Sampling and Main Study Footnote #18	Additional of PK sample for selexipag/ACT-333679 at Baseline and Week 4	Additional PK assessments to further evaluate interaction between rodatristat ethyl and selexipag/ACT-333679
1.4 Schedule of Assessments – OLE first 24 Weeks	Addition of PK sample for selexipag/ACT-33679 at Week 4 of OLE	Additional PK assessments to further evaluate interaction between rodatristat ethyl and selexipag/ACT-333679

1.4 Schedule of Assessments – OLE first 24 Weeks	Wording in *italics* will be deleted. Footnote 4: Placebo subjects from the Main Study will be re-randomized to active IP. *As necessary, a 6month supply of IP will be dispensed.* IP must be taken daily morning and evening.	Removing wording to allow for flexibility of dispensing IP.
3 Objectives and Endpoints	Addition of Objective and Endpoint to evaluate the effect of rodatristat ethyl on selexipag/ACT-333679 PK	Additional PK assessments to further evaluate interaction between rodatristat ethyl and selexipag/ACT-333679
6.1Description of IP, Table 3	Updated wording in **bold** for the Physical Appearance of the IP: **White to off-white modified oval shaped tablet, debossed with "2E8" on one side**	Updated to reflect the new tablet appearance.
6.2 Dose Regimen	Additional wording added to section in bold: **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).**	Clarification of dosing and timing.
6.4 Measures to Minimize the Bias: Randomization and Blinding	Added words in **bold**: **The Investigator will have the ability, in the IRT system, to unblind a patient unless it will cause an unacceptable safety delay in the care of the patient, the Investigator should contact and discuss with the Medical Monitor first.**	Clarification of who can unblind a patient and how.

6.6 Concomitant Medications	New wording in bold: **(Note: Vaccines, including potential Covid-19 vaccine, are allowed but must be documented in the eCRF).**	Updated for clarity.
6.6.1 Rodatristat Drug Interaction Potential	Addition of data from rodatristat-selexipag interaction study and additional listing of narrow therapeutic substrates of CYP2C8	Provide data from rodatristat-selexipag interaction study and guidance to investigator regarding CYP2C8 substrates.
7.1.7 Exclusion Criteria	OLE exclusion criteria #6 is deleted in Amendment 1 *6. Elevated ALT, AST, or TBL > 2X ULN*	Criteria is being taken out of Amendment as there is already stopping criteria for ALT/AST that is being followed
7.1.9 Open-Label Extension Treatment Assignment	Additional wording added to the Amendment: **The first dose of IP in the OLE will be considered the first dose after all Week 24 assessments in the Main Study are completed and all entry criteria are met.**	Clarification of dosing and timing in the OLE.
9.2.2.5 Other Tests	Pharmacogenetics and Optional Blood Sample for Future Research added to 'Other Tests' Table	Add lab samples to appropriate table
9.2.6 Pharmacogenetic Sampling	Wording is being added to the amendment to clarify the pharmacogenetic sample collection: **A separate and specific informed consent form will be provided to patients to allow the sponsor to obtain and test a patient's blood**	Pharmacogenetic sampling wording added for clarification.

	sample taken at the Baseline/Day1 visit for pharmacogenetic markers that may be predictive of the natural history of the disease, response to therapy and tolerability of therapy. If it is not collected at the Baseline/Day 1 visit, it may be collected at any time during the treatment period. Providing this blood sample is optional and not required for participation in the study.	
9.2.8 Suicidal Ideation and Behavior Risk Monitoring	Wording added in **Bold**: Screening and Baseline assessments **(within 1 month)** of suicidal ideation and behavior as well as potential treatment emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS.	Clarifying the timeframe for Baseline collection of the C-SSRS
9.5 Pharmacokinetics	Addition of selexipag/ACT-33679 Pharmacokinetic Sampling	Additional PK assessments to further evaluate interaction between rodatristat ethyl and selexipag/ACT-333679
Appendix 1 – Concomitant and Prohibited Medications	Renaming of Section, clarified wording, and additional listing of narrow therapeutic substrates of CYP2C8	Provide guidance to investigator regarding CYP2C8 substrates.
Appendix 12 REVEAL Lite 2.0 Risk Calculator	Added the scoring and formula for REVEAL Lite 2.0 risk calculator	Added the scoring and calculator for REVEAL Lite 2.0 for calculations

SIGNATURE PAGE

Protocol RVT-1201-2002

A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Rodatristat Ethyl in Patients with Pulmonary Arterial Hypertension

Sponsor's Approval

This protocol has been approved by Altavant Sciences GmbH, as indicated by the signature below.

[redacted]

1/20/2022 | 15:00:42 EST

Company/Sponsor Signatory **Date**

[redacted]

INVESTIGATOR'S AGREEMENT

Protocol RVT-1201-2002

A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Rodatristat Ethyl in Patients with Pulmonary Arterial Hypertension

I, the undersigned, have received and read the Investigator's Brochure for Rodatristat Ethyl. I have read the RVT1201-2002 protocol and agree to conduct the study as outlined in this protocol and in accordance with the ethical principles set forth in the Declaration of Helsinki, current Good Clinical Practice, and all applicable local laws and requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

MEDICAL CONTACT INFORMATION

Table 1: Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader	[redacted]	[redacted]
Responsible Physician	[redacted]	[redacted]
North American Emergency Contact	[redacted]	[redacted]
Rest of the World Emergency Contact	[redacted]	[redacted]
Drug Safety Physician/ Serious Adverse Event Reporting	Pharmacovigilance (PVG)	On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to SPONSOR or Sponsors' safety vendor by filling out the SAE form in the eCRF.

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LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

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

Abbreviation or Specialist Term	Explanation
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
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

Abbreviation or Specialist Term	**Explanation**
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAP	right arterial pressure
RBC	red blood cell
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

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:
Altavant Sciences GmbH

Name of Investigational Product:
Rodatristat ethyl

Name of Active Ingredient:
Rodatristat ethyl

Protocol Number/Study Name:
RVT-1201-2002 / ELEVATE 2

Title of Study:
A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Rodatristat Ethyl in Patients with Pulmonary Arterial Hypertension

Study region(s):

United States, Canada, Poland, United Kingdom, France, Spain, Germany, Italy, Belgium, Bulgaria, Ukraine, Czech Republic, Latvia, Austria, Bosnia and Herzegovina, Republic of Moldova, and Serbia

Ex-US sites are non-IND sites

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: March 2021 Estimated date last patient completed: October 2022	2b

Rationale:

Rodatristat ethyl is an orally bioavailable prodrug that is rapidly converted to the active tryptophan hydroxylase (TPH) inhibitor rodatristat in the systemic circulation of multiple nonclinical species and humans. The clinical doses and regimens selected for this study have been selected with the goal to achieve optimal rodatristat exposure and serotonin (5 HT) lowering targets associated with efficacy in nonclinical models of pulmonary arterial hypertension (PAH) and pharmacokinetic (PK) and pharmacodynamic (PD) data in healthy subjects.

Objectives

Primary Objective:

- 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

Secondary Objectives:

- To evaluate the effect of rodatristat ethyl on change from baseline on the following:
  - WHO FC
  - 6MWD
  - N-terminal pro-Brain Natriuretic Peptide (NT-proBNP)

Safety Objectives:

- To assess safety and tolerability of rodatristat ethyl in patients with PAH

Additional Objectives:

- To evaluate the effect of rodatristat ethyl on change from baseline on the following:
  - Cardiopulmonary hemodynamics (cardiac index, mean pulmonary artery pressure [mPAP], mean right atrial pressure [mRAP], mean mixed venous oxygen saturation [SvO_2], 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 World Health Organization (WHO) Functional Class (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 & right ventricular (RV) function (tricuspid annular plan systolic excursion [TAPSE], tricuspid annular systolic velocity, and RV fractional area change)
  - Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire (PAH-SYMPACT)
  - Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 score

PK/PD Objectives:

- To assess the PK of rodatristat ethyl and metabolites using population PK
- To assess the effect of rodatristat ethyl on plasma and urine 5-hydroxyindoleacetic acid (5-HIAA)

Exploratory Objectives:

- Time to Clinical Improvement (TTCI)
- Actigraphy
- To evaluate the effect of rodatristat ethyl on the plasma concentration of selexipag and ACT-333679

See protocol Section 3 for Endpoints.

Open-Label Extension Objectives:

The objective of the OLE is to evaluate the long-term safety, tolerability, and efficacy of rodatristat ethyl in patients with PAH.

See protocol Section 7.3 for Open-Label Extension Endpoints.

Methodology/Overall Study Design:

This double-blind study will compare the efficacy, safety, and tolerability of 2 doses of rodatristat ethyl to placebo in patients with PAH. Eligible patients will be stratified during the randomization process based on the number of background PAH therapies they are receiving (1, 2 or 3) and use of selexipag

(yes/no). The number of patients who are receiving a prostanoid infusion will be capped at 50% of the total number of patients enrolled. The number of patients who are receiving selexipag will be capped at 20% of the total enrolled. Patients will be randomized 1:1:1 to placebo, 300 mg BID, or 600 mg BID of rodatristat ethyl.

Patients who complete the Main Study will have the option to enroll into the 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 patient 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 patient be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.

Disclosure Statement:

This is a parallel group treatment study with 3 arms that is participant, Sponsor, and Investigator blinded.

Number of participants (planned):

Approximately 90 patients with PAH are expected to be enrolled at approximately 68study sites in the U.S., Canada, and Rest of World (ROW).

Inclusion Criteria:

Patients are eligible to be included in the study only if all the following criteria apply:

1. Male and female patients must be at least 18 years of age at the time of signing the informed consent.
    a. Male patients and female partners must agree to use contraception as detailed in Section 5.4.1 of the protocol starting at Screening, during the treatment period, and for at least 100 days after the last dose of IP. Male patients must refrain from donating sperm during this period.
    b. Female patients of childbearing potential must agree to use contraception as detailed in Section 5.4.1 starting at Screening, during the treatment period, and for at least 4 weeks after the last dose of IP.
2. Body mass index (BMI) $\geq$ 18 kg/m^2 and $\leq$ 40 kg/m^2
3. Patients with symptomatic PAH belonging to one of the following 2018 Clinical Group 1 Sub-types:
    a. Idiopathic PAH
    b. Heritable PAH
    c. Drug- or toxin- induced
    d. PAH associated with:
        1. Connective tissue disease
        2. Congenital systemic to pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) repaired at least one year prior to Screening
        3. Human Immunodeficiency Virus (HIV) infection - if diagnosed with HIV, must have stable disease status defined as follows:
            a. stable treatment with HIV medications for at least 8 weeks prior to Screening
            b. no active opportunistic infection during the Screening Period
            c. no hospitalizations due to HIV for at least 4 weeks prior to Screening

4. WHO FC II or III
5. Confirmed diagnosis of PAH and meet **all** the following hemodynamic criteria by means of a screening RHC completed prior to randomization:
    a. mPAP of > 20 mmHg
    b. PVR ≥ 350 dyne•sec/cm^5
    c. Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) of ≤ 12 mmHg if PVR ≥ 350 and < 500 dyne•sec/cm^5, or PCWP/LVEDP ≤ 15 mmHg if PVR ≥ 500 dyne•sec/cm^5
6. 6MWD of 100 to 550 meters at Screening
7. Currently on a stable treatment regimen with one or more treatments approved for PAH. Stable therapy is defined as receiving the same medication(s) for ≥ 12 weeks prior to the screening RHC and at a stable dose level for each for ≥ 8 weeks prior to the screening RHC (see Protocol Section 6.6.2 for approved PAH medications). Any instances where doses of a medication have been missed prior to RHC must be discussed with the Medical Monitor prior to performing the RHC.
8. Meet the following criteria determined by pulmonary function tests (PFTs) completed no more than 24 weeks prior to Screening (performed with or without bronchodilation):
    a. Forced expiratory volume in one second (FEV_1) ≥ 60% of predicted normal
    b. Total lung capacity (TLC) ≥ 70% of predicted normal or FVC ≥ 70% predicted if TLC is not available; For subjects with CTD associated PAH, if TLC is ≥ 60% of predicted but < 70% of predicted or if FVC ≥ 60% of predicted but < 70% of predicted, high resolution computed tomography [HRCT] obtained within 6 months of screening may be utilized to demonstrate limited interstitial lung disease
9. If participating in an exercise program for pulmonary rehabilitation, the program must have been initiated ≥ 12 weeks prior to Screening, and patient must agree to maintain the current level of rehabilitation for the first 24 weeks of IP. If not participating in an exercise training program for pulmonary rehabilitation, must agree not to enroll in an exercise training program for pulmonary rehabilitation during the Screening Period and the first 24 weeks of IP.
10. Willing and able to give written informed consent and to comply with the requirements of the study for its duration.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Women of childbearing potential who are pregnant, planning to become pregnant, or lactating or female/male patients unwilling to use effective contraception as defined in Section 5.4.1.

Medical Conditions

2. WHO Pulmonary Hypertension (PH) Group 1 PAH associated with portal hypertension or schistosomiasis; PH due to left heart disease (WHO PH Group 2), lung diseases and/or hypoxia (WHO PH Group 3), chronic thromboembolic pulmonary hypertension (WHO PH Group 4), or PH with unclear multifactorial mechanisms (WHO PH Group 5).
3. PH associated with significant venous or capillary involvement (PCWP > 15 mmHg), pulmonary capillary hemangiomatosis, portal hypertension, or unrepaired congenital heart defects (CHD).

4. Three or more of the following risk factors for left ventricular disease:
   a. BMI $\geq$ 30 kg/m^2
   b. Diagnosis of essential hypertension that is actively treated
   c. Diabetes mellitus
   d. History of significant coronary artery disease (e.g., chronic stable angina, history of coronary intervention within the last 3 months, or a stenosis > 70% at coronary angiography)
   e. Atrial fibrillation
   f. Left atrial volume index (LAVi) > 41 mL/m^2 [or left atrial diameter (LA) > 4 cm if LAVi unavailable]
5. Known genetic hypertrophic cardiomyopathy.
6. Known cardiac sarcoidosis or amyloidosis.
7. The patient has a history of, or currently has, a constrictive cardiomyopathy.
8. Known history of any LVEF < 40% by echocardiogram within 3 years of randomization (**Note**: a transient decline in LVEF below 40% that occurred and recovered more than 6 months before the start of Screening and was associated with an acute intercurrent condition [e.g., atrial fibrillation] is allowed).
9. Hemodynamically significant valvular heart disease as determined by the Investigator, including:
   a. greater than mild aortic and/or mitral stenosis and/or
   b. severe mitral and/or aortic regurgitation (> Grade 3)
10. Severe arthritis, musculoskeletal problems, or morbid obesity that, in the opinion of the Investigator, is the cause of the patient's functional limitation and would affect the patient's ability to perform or complete the 6MWT.
11. Planned major surgery within the next 3 months, including lung transplantation, major abdominal or major intestinal surgery.
12. End stage renal disease defined as receiving peritoneal dialysis, hemodialysis, or status after renal transplantation; or severe liver disease defined as Child-Pugh Class C, with or without cirrhosis
13. Known congenital long QT syndrome (LQTS) or known family history of LQTS
14. Depression that is currently rated as severe (defined as a score of $\geq$ 16 on the QIDS-C and/or Hospital Anxiety and Depression Scale [HADS] Depression and/or Anxiety score $\geq$ 15), recent suicidal behavior (either preparatory acts/behavior, aborted attempt, interrupted attempt, or actual attempt in the past 3 months per the Screening Columbia Suicide Severity Rating Scale [C-SSRS], or active suicidal ideation with intent to act (defined as C-SSRS category score of 4 or 5 in the past month)
15. Patients with (during Screening):
    a. Severe hypertension (SBP > 180 mmHg and/or Diastolic Blood Pressure [DBP] > 110 mmHg), and patients with severe hypotension (SBP < 90 mmHg and/or DBP < 50 mmHg)
    b. Hypertension or hypotension considered not controlled in line with clinical standards
16. Clinically significant electrolyte abnormality (e.g., hypokalemia, hypomagnesemia, or hypocalcemia) in the judgement of the Investigator.

17. Current or prior history within the last 5 years of neoplasm (except for treated basal cell or squamous small cell carcinoma of the skin with no evidence of recurrence).
18. Any concurrent clinically significant medical condition/disorder which in the Investigator's opinion would interfere with the patient's ability to comply with or complete the study or could affect the interpretation of the efficacy and safety variables.

Prior/Concomitant Therapy

19. Use of any of the following medications or supplements within 30 days prior to Screening:
    a. Monoamine oxidase inhibitors (MAOIs; Refer to Appendix 1)
    b. 5-Hydroxytryptophan (5-HTP) or L-tryptophan
    c. Telotristat ethyl
20. Patients currently taking one or more drugs known to prolong the QT interval and which are clearly associated with a known risk of Torsades de Pointe (see Appendix 1).

Diagnostic Assessments

21. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at Screening as determined by central laboratory.
22. 12-Lead electrocardiogram (ECG) results at Screening demonstrating QTcF interval > 450 ms for males or > 470 ms for females.
23. Elevated alanine transaminase (ALT), aspartate transaminase (AST)), or total bilirubin (TBL) > 2X upper limit of normal (ULN).
24. Any ECG or clinical laboratory abnormality which precludes safe participation in the study in the opinion of the Investigator.

Lifestyle

25. History of active substance use disorder (including alcohol) within the past 2 years which, in the option of the Investigator, would limit the ability of the patient to provide adequate informed consent or to comply with study requirements
26. Use of any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to Screening or 90 days if an investigational drug for PAH or anytime while on IP (including during OLE), unless local health authority guidelines mandate a longer period**,** or in consultation with the medical monitor, will not interfere with the safety or efficacy of the study**.**
27. Any history of hypersensitivity to rodatristat ethyl, any of its components, or any components in the placebo preparation (refer to Rodatristat Ethyl IB, 2021).
28. Patient is deprived of their liberty by a judicial or administrative decision, or is receiving psychiatric care, and is admitted to a health or social institution.
29. Patient is subject to legal protection or is unable to express consent.

Duration of Treatment and Length of Study:

The treatment duration will be 24 weeks. The study will last up to 32 weeks in duration for patients completing the study that do not enroll into the OLE:

- Screening period: up to 28 days
- Fixed dose treatment period (including Baseline): 24 weeks
- Safety Follow-Up Visit: 4 weeks after the end of dosing if the patient does not enroll into the OLE

OLE will continue for 6.5 years, until the Investigator or patient 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 patient be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.

Investigational Product, Dosage, and Mode of Administration:

Patients will be enrolled into 1 of 3 treatment arms in a 1:1:1 randomization, with 30 patients per arm, receiving placebo or IP, taken with food for 24 weeks as follows:

- Rodatristat ethyl 300 mg + matching placebo BID (1 x 300 mg + 1 x placebo BID)
- Rodatristat ethyl 600 mg BID (2 x 300 mg BID)
- Matching placebo BID (2 x placebo BID)

In order to maintain the study blind, all patients will receive 2 tablets of either rodatristat ethyl and/or placebo in the morning and in the evening in one of the combinations noted above.

Temporary dosage reductions or discontinuations will be allowed to manage adverse events (AEs)/Adverse events of special interest (AESIs), including gastrointestinal AEs (e.g., diarrhea, nausea, or vomiting) and liver enzyme elevations occurring during the 24-week treatment period. Use of antidiarrheal and/or anti-emetic medications will be permitted as directed by the Investigator.

Patients randomized to a rodatristat ethyl arm in the Main Study may continue at the dose level given during the Main Study in the OLE. Patients randomized to placebo in the Main Study will be re-randomized to one of the active rodatristat ethyl treatment arms (300 mg BID or 600 mg BID) during the OLE. Changing of treatment for all patients in the OLE, to receive either 300 mg BID or 600 mg BID, could depend on the timing and outcome of the 24-week analysis from the Main Study. Tolerability and all accumulated safety and efficacy data will be reviewed by the Independent Data Monitoring Committee (IDMC) at regular intervals.

Non-Investigational Therapies:

Patients will remain on their prescribed, pre-existing background PAH medications; doses of these medications should remain stable during the study. All treatment modifications (changes in dose or regimen) will be documented.

Any changes to background PAH therapy during the study should be based on clear medical need and should be first discussed with the Medical Monitor whenever possible.

Statistical methods:

A detailed description of statistical methods will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized prior to database lock.

Sample Size Justification:

The planned sample size is 90 patients with 30 patients to be randomized into 1 of the 3 treatment arms in a 1:1:1 randomization. A sample size of 30 per group 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 of PVR from baseline between an active arm and the placebo arm. For example, if the SD for PVR percent change from baseline is 24%, the study has 80% power to detect a difference of 18% between an active arm and the placebo arm.

Analysis Populations:

Intent-to-Treat (ITT): All patients randomized into the study. For all summaries based on the ITT population, patients will be assigned to the treatment arm to which they were randomized.

Safety: The Safety Population will consist of all patients who are randomized and received at least one dose of study medication. For all summaries based on the safety population, patients will be assigned to the treatment arm corresponding to the dose they had received.

Modified Intent-to-Treat (m-ITT): All Safety population patients that had an evaluable baseline and at least 1 post-baseline PVR measurement.

Per Protocol (PP): All m-ITT population patients who had no major protocol deviations.

Pharmacokinetic:

All Safety Population patients with rodatristat ethyl or rodatristat concentration data.

Efficacy Analysis:

Primary efficacy analyses will be performed using the m-ITT and PP populations.

Percent change from baseline in PVR will be analyzed using an analysis of covariance (ANCOVA) with baseline PVR as the covariate. Additional baseline characteristics may also be evaluated as covariates in the model. The estimated between-treatment differences, 95% confidence intervals (CIs) and p-values will be presented. For patients who discontinue from the study early, the last observation carried forward method will be used to impute the PVR at Week 24.

Secondary efficacy analyses will be performed using the m-ITT and PP populations:

- Change in cardiac index, mPAP, mRAP, SvO2 at rest and PAC from baseline
- Time to Clinical Worsening
- Death from any cause
- Change in WHO FC from baseline
- Change in 6MWD from baseline
- Change in NT-proBNP from baseline
- Changes in right atrial size & RV function: TAPSE, tricuspid annular systolic velocity, and RV fractional area change from baseline
- Change in PAH-SYMPACT from baseline
- Change in the REVEAL Lite 2 score
- Change in 5-HIAA (plasma and spot urine concentration)

The change from baseline endpoints will be analyzed using an ANCOVA model with treatment as a fixed effect, randomization stratum and baseline assessment as covariates. The estimated between treatment differences, 95% CIs and p-values will be presented.

The change in 6MWD from baseline will also be compared between groups using non-parametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel Test. For endpoints measured over time, a mixed effect of repeated measure model may be used as sensitivity analyses. Details of statistical methods will be provided in the SAP. The time from the first dose of IP until to the first clinical worsening event will be summarized using Kaplan-Meier estimates, and compared between treatment groups using the log-rank test.

Safety Analysis:

A summary of rodatristat exposure will be performed using the safety population. The safety and tolerability of rodatristat ethyl will be evaluated by assessment of AE incidences and changes in clinical laboratory tests, vital signs measurements, ECG tracings, and the use of concomitant medication during the study. Adverse events (AEs) will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA)-preferred term and system organ classification. The occurrence of treatment-emergent AEs (TEAEs) will be summarized by treatment group using MedDRA preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events (SAEs) and AEs considered to be related to IP will be generated. All AEs will be listed for individual patients showing both verbatim and preferred terms. Descriptive summaries of vital signs, ECG parameters, and clinical laboratory results will be presented by study visit and treatment group.

Pharmacokinetic Analysis

Population Pharmacokinetic Analysis:

A population PK approach will be utilized to characterize the PK of rodatristat ethyl and rodatristat. A detailed description of the PK and any PK/PD analysis methods used will be provided in the separate analysis plan.

Demographic and Baseline Characteristics:

Demographic and baseline characteristics for the ITT population will be summarized using descriptive statistics.

Other Analyses:

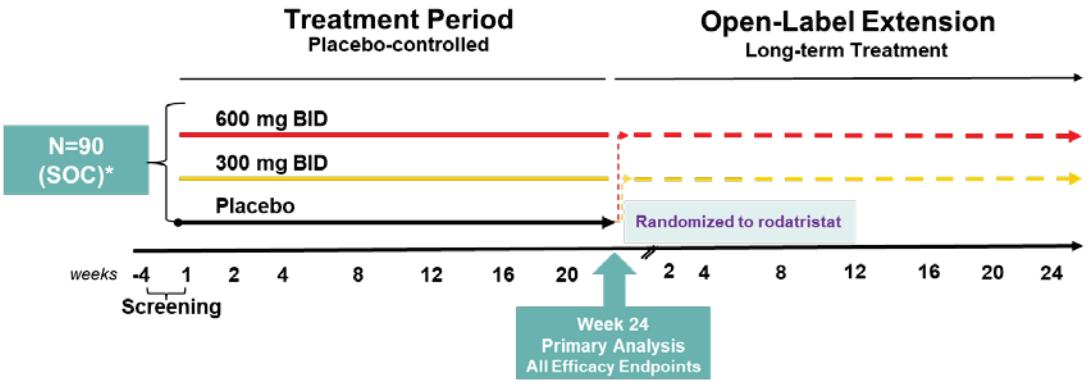
Patient Reported Outcomes (C-SSRS, HADS and QIDS-C), PK concentration data, PD, and exploratory descriptive analyses will be described in the SAP finalized before database lock.

Independent Data Monitoring Committee:

The primary role of the IDMC which consists of independent physicians with experience in the care of patients with PAH and the conduct of randomized controlled trials, and one non-voting biostatistician, is to ensure the safety of the patients enrolled in the study/OLE. A detailed description of IDMC procedures is provided in a separate data monitoring committee charter maintained by the Sponsor.

1.2. Study Schematic

Figure 1: Study Schematic



*Standard of Care
Patients who participate in the OLE will continue to receive rodatristat ethyl for 6.5 years, until the Investigator or patient 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 patient be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.

Abbreviations: BID = twice daily; IP = investigational product

1.3. Schedule of Assessments – Main Study

	Screening	Baseline	Treatment						Follow-Up
Visit No.	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Study Week[1] (Days)	**-4 Wks**[2] (D-28 to D-1) Clinic	**D1** Clinic	**Wk 2** (D14) Telemed/ Phone Call	**Wk 4** (D28) Clinic	**Wk 8** (D56) Clinic or Home	**Wk 12** (D84) Clinic	**Wk 18** (D126) Clinic or Home	**Wk 24** (D168) Clinic	**Wk 28** (D196) **FU**[3]/ **ET**[3,4] Clinic or Home
Screening/ Demography/ Baseline									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Demographics	X								
Height/Weight/BMI	X	X[5]		X[5]	X[5]	X[5]		X[5]	X[5]
Medical History Including Cardiac and Pulmonary History/Current Conditions[6]	X	X							
PAH Medication History[7]	X	X							
Pulmonary Function Tests (PFTs) (unless completed in last 24 weeks)	X								
FSH[8]	X								
Urinary Screen for Drugs of Abuse	X								
Register Patient in IRT Screening/Randomization	X	X							
Treatment									
Concomitant Medications	X	X	X	X	X	X	X	X	X
Dispensing IP via IRT		X		X		X			
Administer Rodatristat Ethyl or Placebo[9]		X	X	X	X	X	X		
Morning Dose Taken in Clinic with Food[9]		X		X					
Investigational Product Compliance/ Accountability				X		X	X	X	
Safety/Tolerability Assessments									
Adverse Events[10]	← X →								
Pregnancy Test (Serum/urine)[11]	X	X		X	X	X		X	X
Physical Examination	X	X		X		X		X	

	Screening	Baseline	Treatment						Follow-Up
Visit No.	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Study Week[1] (Days)	**-4 Wks**[2] (D-28 to D-1) Clinic	**D1** Clinic	**Wk 2** (D14) Telemed/ Phone Call	**Wk 4** (D28) Clinic	**Wk 8** (D56) Clinic or Home	**Wk 12** (D84) Clinic	**Wk 18** (D126) Clinic or Home	**Wk 24** (D168) Clinic	**Wk 28** (D196) **FU**[3]/ **ET**[3,4] Clinic or Home
Vital Signs (BP, HR, RR, temp, oxygen saturation)	X	X		X	X	X	X	X	X
12-Lead ECG[12]	X	X		X	X	X	X	X	X
Laboratory – Hematology, Coagulation[13], Chemistry, urinalysis,	X	X		X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X		X		X	X	X	X
Hospital Anxiety and Depression Scale (HADS)	X	X		X		X	X	X	X
Quick Inventory of Depressive Symptoms (QIDS-C)	X	X		X		X	X	X	X
Efficacy-Related Assessments									
6MWT	X	X		X		X		X	
Right Heart Catheterization (RHC)[14]	X							X	X[14]
Echocardiography[15]	X					X		X	
WHO FC	X	X		X		X		X	
Plasma NT-proBNP level		X		X		X		X	
PAH Symptoms and Impact Questionnaire (PAH-SYMPACT)		X				X		X	
Actigraphy[16]		← X →							
Pharmacokinetics									
Rodatristat PK Sampling[17]		X		X		X		X	
Selexipag PK sampling[18]		X		X					
Pharmacodynamics									
Urine 5-HIAA[17]		X		X		X		X	
Urine Creatinine[17]		X		X		X		X	
Plasma 5-HIAA[17]		X		X		X		X	
Other									
Optional Blood for Future Research Sample		X						X	
Pharmacogenetic Samples		X						X	

[1] Visits at Week 2 (Telemed/Phone Call) and Week 4 (clinic visit) can occur within +/-2 days from the randomization date; Visits at Weeks 8 (Telemed/Phone call), 12 (clinic), 18 (clinic or home visit), 24 and 28/Follow Up (clinic) can occur within +/-5 days from the randomization date.

[2] Screening may be broken up into more than 1 visit, if necessary. Once all screening procedures are complete and the Investigator determines that the patient is eligible, the site must upload/send the required supporting documentation for approval by the Sponsor.

[3] Patients who early terminate from the IP should be asked to return for visits as scheduled for ongoing assessments through the Week 28 Visit. Patients who withdraw consent should be asked to complete the Week 28 Visit for safety. Patients who have not completed the study as planned (through Week 24) cannot participate in OLE. Patients who withdraw consent will continue to be followed for vital status from public records such as government vital statistics or obituaries, as allowed by local law, or periodic contact (about every 6 to 12months).

[4] Patients that complete the study (defined as completing all visits through Week 24) have the option to enroll into the OLE (See Section 1.4). Patients who complete through Week 24 but decide not to enroll into the OLE, should complete the Week 28 Follow-Up Visit.

[5] Weight only (no height or BMI) will be performed at Day 1 and Weeks 4, 8, 12, 24, and 28.

[6] Must have a confirmed diagnosis of PAH in patients' medical history

[7] Background PAH therapy dose regimens must be stabilized for > 12 weeks prior to the screening RHC and on stable dose(s) > 8 weeks prior to the screening RHC to be eligible. All changes and dose adjustments in background PAH therapy must be documented.

[8] Pregnancy tests not required for women who are surgically sterile. FSH required for women with amenorrhea < 2 years at the Screening Visit only to confirm postmenopausal status.

[9] IP must be taken daily, morning and evening until the night before the Week 24 visit. Patients must be told not to take a dose the morning of the Week 24 visit. Doses should be taken with food. During visits at the clinic or home, all assessments should be done predose, except where otherwise indicated. Patients should bring their IP with them for each visit (including any empty bottles).

[10] SAEs will be collected starting at informed consent form signing. AEs will be collected starting at first dosing.

[11] Serum pregnancy tests will be performed at Screening and urine pregnancy tests over the rest of the study. A negative urine pregnancy test must be completed before Day 1 procedures. If a positive result on a urine test, a serum pregnancy test should be completed to confirm. Pregnancy tests will be completed in women of child-bearing potential every 4 weeks while on study. Weeks 8, 16 and 20 will be performed at home (with a kit given to the subject by the site) and the results will be confirmed with the subject by a phone call. Additional pregnancy tests should be completed anytime menstruation is delayed and in women with infrequent or irregular menstrual cycles.

[12] Three 12-lead ECGs (at least 1 minute apart) will be collected on Day 1 after at least 5 minutes of rest. Single 12-lead ECGs will be collected at all other time points.

[13] Coagulation testing will be done at Screening, Weeks 12 and 24.

[14] RHC results from 4 weeks prior to the Screening visit may be used for entry provided the RHC includes all required information and provided that changes to the patient's PAH regimen were not made. If prior approval is obtained from the Sponsor, the screening RHC may be performed on the same day as the randomization procedures, provided that all blood draws and other efficacy assessments are conducted prior to the RHC procedure, and the RHC is performed prior to randomization and IP dosing. Week 24 RHC may occur up to 7 days prior to or on the Week 24 Visit. If a patient terminates early, and at or after the Week 12 Visit, an RHC should be performed at the Early Termination Visit.

[15] Echocardiography should be done in supine position after at least 5 minutes of rest.

[16] Patients will wear a wrist device for the entire duration of the study, but for endpoint assessments, focus will be on the 3 following periods: Day 1 to Week 4, Week 12 to Week 16, and Week 20 to Week 24. All details of collection will be provided in the study manual.

[17] Rodatristat Ethyl and Rodatristat PK: At Day 1 and Week 4, a predose PK sample will be collected (patients will take study medication in the clinic). At Week 12, a postdose PK sample will be collected between 1 to 8 hours after the morning dose (patients will take the morning dose in the clinic and the time of dose will be recorded – all other assessments can be done pre or post dose). At Week 24, no study medication will be taken prior to the clinic visit (the last dose in the Main Study will be the evening before the Week 24 visit) and a PK sample will be collected. If the subject enrolls in the OLE, this PK sample will be collected prior to the first dose of study treatment in the OLE. Blood and spot urine samples for 5-HIAA (and urine samples for creatinine) will be collected pre-dose on Day 1 and at Weeks 4, 12, and 24.

[18] Selexipag and ACT-333679 PK (for subjects using selexipag at baseline only): At Day 1 and Week 4, a predose PK sample will be collected (patients will take selexipag in the clinic at these visits, and the PK samples will be collected approximately 12 h after the prior dose)

Additional unscheduled safety assessments may be conducted at any time during the study if the Investigator or Sponsor deems it necessary for the safety of the patient.

Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid; 6MWT = 6-minute walk test; AEs = adverse events; BMI = body mass index; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; FU = follow up; HADS = Hospital Anxiety and Depression Scale; HR = heart rate; IP = investigational product; IRT = interactive response technology; LFTs = liver function tests; mo = months; NT-proBNP = N-terminal pro-brain natriuretic peptide; OLE = Open-Label Extension; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire; QIDS-C = Quick Inventory of Depressive System-Clinician Rated; RHC = right heart catheterization; RR = respiratory rate; SAE = serious adverse event; temp = temperature; WHO FC = World Health Organization Functional Class; Wk = week

1.4. Schedule of Assessments – Open-Label Extension – (First 24 weeks of Open-Label Extension)

Study Week[1] (following Week 24 in Main Study)	**D1** Clinic (Week 24 Main Study)	**Wk 2** (D14) Telemed/ Phone Call	**Wk 4**(D28) Clinic	**Wk 8** (D56) Clinic or Home	**Wk 12** (D84) Clinic	**Wk 18** (D126) Clinic or Home	**Wk 24** (D168) Clinic	**ET**[2] Clinic or Home
Screening/ Demography/ Baseline								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Weight			X[3]	X[3]	X[3]		X[3]	X[3]
Treatment								
Concomitant Medications	X	X	X	X	X	X	X	X
Re-Randomization in IRT	X							
Dispensing IP via IRT	X		X		X			
Administer Rodatristat Ethyl	X	X	X	X	X	X	X	
Morning Dose Taken in Clinic with Food[4]	X		X					
Investigational Product Compliance/ Accountability			X		X	X	X	X
Safety/Tolerability Assessments								
Adverse Events	← X →							
Pregnancy Test (Serum/urine)[5]			X	X	X		X	X
Physical Examination			X		X		X	
Vital Signs (BP, HR, RR, temp, oxygen saturation)			X	X	X	X	X	X
12-Lead ECG[6]			X	X	X	X	X	X
Laboratory – Hematology, Coagulation[7], Chemistry, urinalysis,			X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)			X		X	X	X	X
Hospital Anxiety and Depression Scale (HADS)			X		X	X	X	X
Quick Inventory of Depressive Symptoms (QIDS-C)			X		X	X	X	X

Study Week[1] (following Week 24 in Main Study)	**D1** Clinic (Week 24 Main Study)	**Wk 2** (D14) Telemed/ Phone Call	**Wk 4**(D28) Clinic	**Wk 8** (D56) Clinic or Home	**Wk 12** (D84) Clinic	**Wk 18** (D126) Clinic or Home	**Wk 24** (D168) Clinic	**ET**[2] Clinic or Home
Efficacy-Related Assessments								
6MWT			X		X		X	
Right Heart Catheterization (RHC)[8]							X	X
Echocardiography[9]					X		X	
WHO FC			X		X		X	
Plasma NT-proBNP level			X		X		X	
PAH Symptoms and Impact Questionnaire (PAH-SYMPACT)					X		X	
Selexipag PK Sampling[10]	X		X					

[1] Visits at Week 2 (Telemed/Phone Call) and Week 4 (clinic visit) can occur within +/-2 days from the randomization date; Visits at Weeks 8 (Telemed/Phone call), 12 (clinic), 18 (clinic or home visit), 24 and 28/Follow Up (clinic) can occur within +/-5 days from the randomization date.

[2] Patients who withdraw consent should be asked to complete the ET Visit for safety. Patients who withdraw consent will continue to be followed for vital status from public records such as government vital statistics or obituaries, as allowed by local law, or periodic contact (about every 6 to 12months).

[3] Weight only (no height or BMI) will be performed at Weeks 4, 8, 12, 24, and 28.

[4] IP must be taken daily, morning and evening. Doses should be taken with food. During visits at the clinic or home, all assessments should be done predose, except where otherwise indicated. Patients should bring their IP with them for each visit (including any empty bottles).

[5]Pregnancy tests not required for women who are surgically sterile. Pregnancy tests will be completed in women of child-bearing potential every 4 weeks while on study. Weeks 8, 16 and 20 will be performed at home (with a kit given to the subject by the site) and the results will be confirmed with the subject by a phone call. Additional pregnancy tests should be completed anytime menstruation is delayed and in women with infrequent or irregular menstrual cycles.

[6] Single 12-lead ECGs will be collected at all time points.

[7] Coagulation testing will be done at Weeks 12 and 24.

[8] Week 24 RHC may occur up to 7 days prior to or on the Week 24 Visit. If a patient terminates early, and at or after the Week 12 Visit, an RHC should be performed at the Early Termination Visit.

[9] Echocardiography should be done in supine position after at least 5 minutes of rest.

[10] Selexipag and ACT-333679 PK (for subjects using selexipag at baseline only): At Day 1 and Week 4, a predose PK sample will be collected (patients will take selexipag in the clinic at these visits, and the PK samples will be collected approximately 12 h after the prior dose)

Additional unscheduled safety assessments may be conducted at any time during the study if the Investigator or Sponsor deems it necessary for the safety of the patient.

Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid; 6MWT = 6-minute walk test; AEs = adverse events; BMI = body mass index; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; FU = follow up; HADS = Hospital Anxiety and Depression Scale; HR = heart rate; IP = investigational product; IRT = interactive response technology; LFTs = liver function tests; mo = months; NT-proBNP = N-terminal pro-brain natriuretic peptide; OLE = Open-Label Extension; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire; QIDS-C = Quick Inventory of Depressive System-Clinician Rated; RHC = right heart catheterization; RR = respiratory rate; SAE = serious adverse event; temp = temperature; WHO FC = World Health Organization Functional Class; Wk = week

1.5. Schedule of Assessments – Open-Label Extension – (Post 24 Weeks of the Open-Label Extension)

	Pregnancy Test	**Clinic Visits[4]**	**Follow Up[4] (4 weeks after last dose of IP)**
Week	**Every 4 Weeks (+/- 2 days)**	**Every 24 Weeks (+/- 4 days)**	
IP Dispensing via IRT[1]		X	
IP Compliance/ Accountability[2]		X	
Concomitant medications	X	X	
Vital Signs (BP, HR, RR, temp, oxygen saturation)		X	X
Pregnancy Test (serum/urine)[3]	X	X	X
Laboratory – Hematology, Coagulation, Chemistry (including LFTs)		X	X
Adverse Events	X	X	X

[1] As necessary, 6-month supply of IP will be dispensed.

[2] Patients should be instructed to bring their used, partial, and unused IP containers with them to every Clinic Visit to assess compliance and IP accountability.

[3] Pregnancy test will be required every 4 weeks, in women of childbearing potential only. Urine pregnancy kits will be provided to the patient. Completion of the pregnancy test, and collection of adverse events and concomitant medications will be documented via telephone contact. Serum pregnancy test to be done to confirm a positive urine test. Additional pregnancy tests should be completed anytime menstruation is delayed and in women with infrequent or irregular menstrual cycles.

[4] If a patient discontinues IP for any reason a follow-up visit must be performed 4 weeks after the last dose of IP.

Abbreviations: BP = blood pressure; HR = heart rate; IP = investigational product; RT = interactive response technology; LFTs = liver function tests; RR = respiratory rate; temp = temperature

Additional unscheduled safety assessments may be conducted at any time during the study if the Investigator or Sponsor deems it necessary for the safety of the patient.

2. INTRODUCTION

2.1. Background

Pulmonary arterial hypertension (PAH) is a severe, incurable disease characterized by remodeling of the pulmonary arterial bed, leading to elevations in resting mean pulmonary artery pressures, subsequent right ventricular hypertrophy, and eventually, right heart failure and (Agarwal & Gomberg-Maitland, 2011). Current standard-of-care therapies for PAH target 3 different pathways – namely, the endothelin-1 pathway, the nitric oxide pathway, and the prostacyclin pathway – and act primarily as vasodilators. They reduce PAH symptoms and may slow disease progression, but they lack compelling disease-modifying properties.

Several lines of evidence implicate serotonin (5-hydroxytryptamine [5-HT]) in the pathophysiology of PAH where there are findings that 5-HT plasma levels are markedly elevated in PAH (Humbert et al., 2002); tryptophan hydroxylase (TPH) 1, the key rate-limiting enzyme in the biosynthesis of systemic 5-HT, is overexpressed in lung tissue of PAH patients (Eddahibi, 2006), and 5-HT acts on pulmonary artery smooth muscle cells to induce vasoconstriction and proliferation (MacLean & Dempsie, 2010). In addition, 5-HT acts at the 5-HT1B receptor and the 5-HT transporter to mediate constriction and proliferation of pulmonary artery smooth muscle cells (MacLean & Dempsie, 2010). Finally, genetic deletion and pharmacological inhibition of TPH1 protects against the development of experimentally induced PAH (Abid et al., 2012; Izikki et al., 2007) in nonclinical pharmacology models. In aggregate, these findings indicate that modulation of the 5-HT pathway by TPH1 inhibition is a novel approach that differentiates itself mechanistically from current therapeutic options and offers the potential to modify the underlying disease pathophysiology and progression of PAH (Aiello et al., 2016; MacLean, 2018).

A therapeutic strategy is needed to safely and effectively inhibit TPH1 activity in peripheral tissues, without unwanted central nervous system (CNS) effects that result from inhibition of TPH2, the predominant TPH isoform in the CNS.

Rodatristat ethyl is a peripherally restricted TPH1/TPH2 inhibitor with little CNS penetration. Nonclinical data indicate that neither rodatristat ethyl nor rodatristat cross the blood brain barrier to a pharmacologically relevant level and do not lower brain levels of 5-HT in nonclinical pharmacodynamic studies in rats. By limiting inhibition to TPH1 in the periphery, rodatristat ethyl may avoid potential untoward CNS effects that could otherwise be a consequence of inhibiting TPH2-mediated CNS 5-HT production (Kim et al., 2015; Shi et al., 2008).

Rodatristat ethyl is a prodrug that is rapidly hydrolyzed to rodatristat, a potent TPH inhibitor that reduces peripheral 5-HT levels in the gut mucosa, lung, and serum in animal models of PAH. In vitro, nonclinical, and human pharmacokinetic (PK) studies to date have provided valuable information on the PK properties of rodatristat ethyl and its active moiety, rodatristat. Rodatristat ethyl has low to moderate oral bioavailability in nonclinical species and is rapidly converted to rodatristat in vivo. Both rodatristat ethyl and rodatristat are highly protein bound and little is excreted in the urine. Biliary excretion predominates in rats and no further metabolism of rodatristat has been detected in human hepatocyte preparations. However, preliminary investigations have also identified a metabolite, M15, in the plasma of dogs and humans after

administration of rodatristat ethyl. After single-dose administration, the half-life of rodatristat ethyl and rodatristat are approximately 5 and 12 hours, respectively, reaching steady-state exposure, according to trough concentrations, by Day 5. The highest exposures achieved in healthy subjects to date were reached on Day 7 following 800 mg twice daily (BID) doses of rodatristat ethyl.

Rodatristat ethyl was selected for development in the treatment of PAH based on a range of criteria, including achieving efficacy endpoints in nonclinical in vivo models of PAH, pharmacokinetic (PK) parameters, and biomarker endpoints related to both changes in systemic 5-HT levels and PAH pathology.

Reductions in biomarkers indicative of decreased 5-HT biosynthesis were observed in healthy subjects receiving repeat twice daily (BID) oral doses (range 100 to 800 mg BID) of rodatristat ethyl over 14 days. Rodatristat ethyl doses of either 400 or 800 mg BID achieved reductions in 5-HT by Day 14 comparable to those associated with efficacy in the rodent models of PAH.

2.2. Study Rationale

Rodatristat ethyl is expected to have efficacy for PAH. Results from nonclinical pharmacology studies demonstrate that rodatristat ethyl is a potent and selective inhibitor of TPH1 with the potential to ameliorate disease by halting or reversing the pulmonary vascular remodeling characteristically observed. Through inhibition of TPH1, rodatristat ethyl is expected to improve cardiopulmonary hemodynamics, functional capacity, PAH symptoms, and right ventricular (RV) function via its novel antiproliferative and anti-remodeling mechanism of action.

This study will evaluate rodatristat ethyl doses of 300 mg BID and 600 mg BID. Dose selection was guided by the goal of demonstrating a dose/exposure efficacy relationship and was supported by nonclinical pharmacology, toxicology, and animal model efficacy data. Results from Phase 1 human studies suggest that these dosing regimens should be safe and generally well tolerated with dose-proportional differences in systemic drug exposure. Further details regarding the dose rationale can be found in Section 4.7.

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with rodatristat ethyl as well as more detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of rodatristat ethyl may be found in the Investigator's Brochure. This section outlines the potential adverse events of special interest (AESI; based either on preclinical or clinical data generated to date, the mechanism of action of rodatristat ethyl, or the prescribing information for telotristat ethyl [a TPH inhibitor previously approved for the treatment of carcinoid syndrome-related diarrhea] and mitigation strategies for this protocol. The potential risk for QTc prolongation (described in the Investigator's Brochure) will be further evaluated in a definitive thorough QT study in the future. Until further data are available in that regard, cardiac arrhythmia, related to an increase in QT/QTc interval, will be treated as a potential AESI and has therefore also been included in the table of potential risks below.

Although any potential benefits to patients with PAH will not be known until the study is completed, the development of a drug with disease-modifying potential will certainly be of value to patients with this diagnosis.

Potential Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria OR Management Criteria**
Severe constipation	None	Severe constipation (e.g., obstipation with manual evacuation indicated) and/or severe, persistent, or worsening abdominal pain would warrant withdrawal from the study.
Depression/other mood-related disturbance due to central depletion	• Exclusion of patients with active suicidal thinking or behavior at Screening/Baseline based on the Columbia-Suicide Severity Rating Scale (C-SSRS) • Exclusion of patients with severe depression at Screening/Baseline based on the Quick Inventory of Depressive Symptoms Clinician-Rated (QIDS-C) or the Hospital Anxiety and Depression Scale (HADS)	Withdrawal of patients with: • Any significant worsening on postdose C-SSRS indicative of active suicidal ideation with intent to act or suicidal behavior • Severe depression or anxiety based on a HADS Depression or Anxiety Score ≥ 15 or a QIDS-C Total Score ≥ 16. • Any severe psychiatric or CNS AE as determined by the Investigator.

Potential Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Stopping Criteria OR Management Criteria**
Hepatic enzyme elevations	Exclude patients with alanine aminotransferase (ALT) / aspartate aminotransferase (AST) / gamma-glutamyl transferase (GGT) results greater than 2X upper limit of normal (ULN) and/or TBL ≥ 2X ULN	Withdrawal criteria for abnormal liver function tests set at: • ALT or AST > 3X ULN **and** TBL > 2X ULN (or international normalized ratio (INR) > 1.5) • ALT or AST > 3X ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%) • ALT or AST > 5X ULN for > 2 weeks • ALT or AST > 8X ULN
Cardiac arrhythmia, related to an increase in QT/QTc interval	Exclude patients with: • QTcF > 450 ms (males) or > 470 ms (females) • Known congenital Long QT Syndrome (LQTS), or known family history of LQTS • Clinically significant electrolyte abnormality (i.e., hypokalemia, hypocalcemia, hypomagnesemia) • Concomitant use of QT-prolonging drugs clearly associated with a risk of Torsades de Pointe (see Appendix 1)	Withdrawal criteria for abnormal/worsening QT interval prolongation: • QTcF interval > 500 ms • QTcF interval > 480 ms AND increase from baseline ≥ 60 ms • QTcF interval > 480 ms associated with syncope, life-threatening arrhythmias, resuscitated cardiac arrest, or seizure

3. OBJECTIVES AND 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	**Primary** • 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)	**Secondary** 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
To evaluate the effect of rodatristat ethyl from baseline to Week 24 on the following: • **Safety** o To assess safety & tolerability of rodatristat ethyl in patients with PAH • **Additional** o Hemodynamics (cardiac index, mean pulmonary artery pressure [mPAP], mean right atrial pressure [mRAP], mixed venous oxygen saturation [SvO2], and pulmonary artery compliance [PAC]) o 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). o Death from any cause	To evaluate the effect of rodatristat ethyl from baseline to Week 24 on the following: • **Safety** o Change in safety parameters including AEs, vital signs, laboratory values, and electrocardiogram (ECG) assessments • **Additional** o Change from baseline in cardiac index, mPAP, mRAP, SvO2 at rest and PAC o Change from baseline in TTCW o Death from any cause o Change from baseline in right atrial size & RV function (TAPSE, tricuspid annular systolic velocity, & RV fractional area change) o Change from baseline in PAH-SYMPACT o Change from baseline in REVEAL Lite 2.0 Score • **PK/PD** o Population PK parameters of rodatristat ethyl, active metabolite rodatristat, M15, and other metabolites

Objectives	Endpoints/Criteria for Evaluation
○ 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 • **PK/PD** ○ To assess the PK of rodatristat ethyl and metabolites ○ To assess the effect of rodatristat ethyl on plasma and urinary 5-HIAA	○ Change from baseline in 5-hydroxyindoleacetic acid (5-HIAA; plasma and spot urine concentration)
Exploratory To evaluate the effect of rodatristat ethyl from baseline to Week 24 on the following: • Time to Clinical Improvement (TTCI) • Actigraphy • To evaluate the effect of rodatristat ethyl on the plasma concentration of selexipag and ACT-333679	**Exploratory** To evaluate the effect of rodatristat ethyl from baseline to Week 24 on the following: • 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: ○ Light to vigorous activity/day ○ Moderate to vigorous activity/day ○ Total movement/day ○ Best 6-minute walk effort • Plasma selexipag and ACT-333679 trough concentration at baseline and Week 4

4. STUDY DESIGN

4.1. Overall Design

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

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

Eligible patients 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 patients who are on a prostanoid infusion will be capped at 50% of the total enrolled. The number of patients 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 patients 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.

Patients 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 patient 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 patient be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.

All participating patients 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 patients 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 Weeks 2 and 8, patients will return to the study center for safety, tolerability and efficacy-related assessments at Weeks 4, 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 patients 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.

Further details for the OLE are found in Section 7.

4.2. Number of Patients

Approximately ninety (90) patients with PAH are expected to be enrolled at approximately 68 study sites in the United States, Canada, and Rest of World (ROW).

4.3. Treatment Assignment

Patients will be randomized to IP according to a computer-generated allocation schedule, prepared prior to the start of the study.

At the Baseline Visit, eligible patients will be randomly allocated (1:1:1) to one of the following 3 treatment groups:

Treatment Arm Name	Treatment Description
Rodatristat ethyl 300 mg BID	1 x 300 mg tablet + 1 x matching placebo BID
Rodatristat ethyl 600 mg BID	2 x 300 mg tablets BID
Placebo	2 x matching placebo tablets BID

In order to maintain the study blind, patients will take 2 tablets in the morning and 2 tablets in the evening in one of the combinations noted above.

4.4. Dose Adjustment Criteria

4.4.1. Dose Reduction

All determinations of rodatristat ethyl dose reduction should be discussed with the Medical Monitor prior to implementing unless time does not allow for safety.

Temporary dosage reductions or discontinuations will be allowed to manage AEs/AESIs (or other instances to be discussed with the Medical Monitor), including gastrointestinal AEs (e.g., diarrhea, nausea, or vomiting) or liver enzyme increase occurring during the 24 weeks of the study. Judicious use of antidiarrheal and/or anti-emetic medications will be permitted. One level of dose reduction is available.

To reduce the IP, the patient will be instructed to take one tablet in the morning and one tablet in the evening from the appropriate dispensed bottles during the dose reduction period per dosing instructions supplied in a separate document. If AEs continue, the patient may stop taking the IP completely for up to 7 days before restarting.

4.4.1.1. Diarrhea

In the event the patient experiences diarrhea, the dose may be reduced. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading will be used to grade the severity of all AEs and serious adverse events (SAEs) of diarrhea. Management recommendations for diarrhea are based on the CTCAE grades and are detailed in Appendix 2. In general, the patient should be treated with anti-diarrheal drugs such as loperamide as clinically indicated. In addition to directly treating any diarrhea, possible intermittent or permanent interruption of IP and dose reduction will be possible, depending upon the frequency and severity of diarrhea.

4.4.1.2. Aminotransferase (Alanine aminotransferase or Aspartate Aminotransferase) Elevation

Management recommendations for ALT or AST elevations are based on U.S. Food and Drug Administration (FDA) Guidance for Liver Toxicity.

In general, all baseline or treatment-emergent ALT or AST elevations > 3X ULN should be confirmed within 48 to 72 hours with repeat assessments of ALT and AST as well as TBL, alkaline phosphatase (ALP), prothrombin time/INR, and complete blood count for eosinophil levels. Further details for managing IP reduction, restart, and discontinuation can be found in Appendix 3.

If at any time, the criteria as outlined in Section 8 are met, the IP must be permanently discontinued.

4.5. Criteria for Study Termination

This study (including OLE) may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party, to the Investigators, Institutional Review Boards (IRB)/Ethics Committees (EC), regulatory authorities. If the study is prematurely terminated or suspended, the Investigators will promptly inform the IRB/ECs and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and the IRBs/ECs and competent authorities are satisfied. The study will only resume after prior submission and approval of the substantial amendment (if required) by the competent authority.

4.6. Scientific Rationale for Study Design

The design of this study will provide efficacy, safety, and dosing information to support proof of concept. Two rodatristat ethyl doses will be studied. Patients with idiopathic PAH and other Group 1 PAH sub-types will be included in this study.

Placebo-controlled randomized studies provide the most robust results and are thus considered the most appropriate design. However, approved therapies for PAH are available, making a placebo-controlled rodatristat ethyl *monotherapy* study unethical. Therefore, rodatristat ethyl (or placebo) will be evaluated in addition to standard of care (SOC) PAH-specific treatments, i.e., this study will only include patients on stable, approved, and available treatments at baseline.

Patients on prior monotherapy and combination regimens to include up to 3 agents will be permitted to participate. Treatment with oral, inhaled, or parenteral prostanoids will be permitted. Any changes to background PAH therapy during the study should be based on clear medical need.

In prior studies of patients treated with PAH therapies, up to 24 weeks of treatment with study medication were considered necessary to demonstrate efficacy based on potential impact on pulmonary hemodynamics. This duration of exposure will also allow for assessment of safety, tolerability, and possible effects on exercise ability, patient reported outcomes, and biomarkers.

The OLE will provide long term safety, tolerability, and efficacy of rodatristat ethyl in patients with PAH. In order to minimize bias during the OLE, patients will remain blinded to original treatment assignment in the Main Study. Patients receiving active rodatristat ethyl during main treatment period will continue at their originally randomized dose to generate additional long-term safety and efficacy data. Patients originally randomized to placebo will also have the opportunity to receive active rodatristat ethyl during the OLE, providing additional patient exposures for further assessment of safety and efficacy.

4.7. Justification for Dose

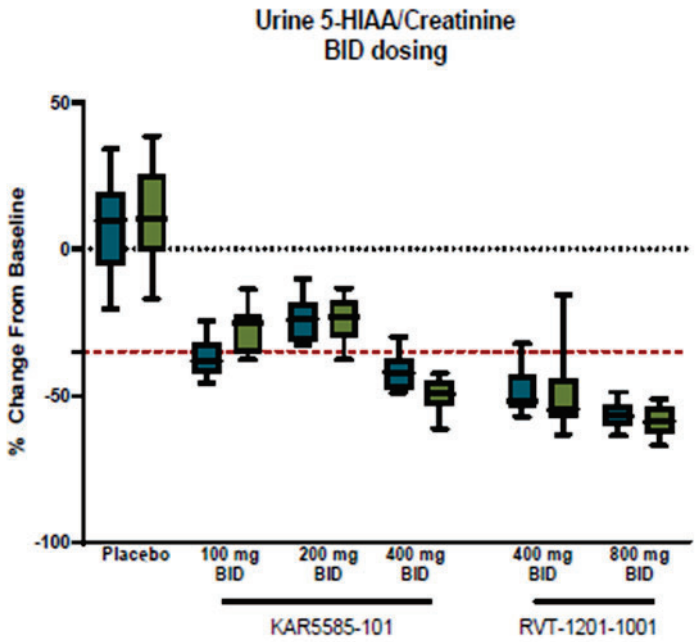
The dose levels selected are based on prior pharmacodynamic (PD) observations in nonclinical models of PAH and PK, PD, safety, and tolerability data in healthy subjects receiving rodatristat ethyl for up to 14 days.

Disease-modifying effects of rodatristat ethyl were demonstrated in the semaxanib (SU5416, SUGEN) hypoxia and the monocrotaline (MCT) injury rat models of PAH. In the MCT rat model, rodatristat ethyl decreased serum and lung 5-HT levels and reduced the extent of vascular remodeling. In the SU5416 hypoxia rat model, rodatristat ethyl significantly reduced RV systolic pressure, RV hypertrophy, the biomarker brain natriuretic peptide (BNP), and pulmonary vessel wall thickness and occlusions as measured by histological analysis, without impacting systolic blood pressure (SBP). These benefits were observed at doses of $\geq$ 100 mg/kg, which results in approximately a 40% reduction in 5-HT biosynthesis (IB, 2020). Based on these data, a target reduction in 5-HT (as determined by urinary 5-HIAA excretion rate) of at least 40% was the basis for the doses selected in the current study.

After 14 day BID administration to healthy subjects, rodatristat ethyl at doses of 400 to 800 mg BID resulted in 50 to 60% reductions in urinary 5-HIAA. Dose-dependent increases in gastrointestinal treatment-emergent AEs (TEAEs; notably nausea and diarrhea) were noted with rodatristat ethyl, including an event of moderate diarrhea and an overall incidence rate of 44% after administration of 800 mg BID (IB, 2020). Therefore, the highest dose regimen selected for the current study is rodatristat ethyl 600 mg BID which is expected the maintain the majority of the 5-HT lowering effect while minimizing potential of gastrointestinal TEAEs.

The lower dose regimen of rodatristat ethyl of 300 mg BID was selected to evaluate a lower dose to aid in defining potential dose-response relationships and is expected to result in approximately 40% reduction in 5-HIAA, equivalent to the reductions observed at efficacious doses in nonclinical models (IB, 2020).

Figure 2: Percentage Change from Baseline of Urine 5-HIAA: Creatinine Ratio 5-HIAA on Days 7 and 14 following Twice Daily Repeat Oral Administration of Rodatristat Ethyl in Studies KAR5585-101 and RVT-1201-1001



Note: Blue boxes and green boxes represent data from Day 7 and Day 14, respectively. Data for subjects receiving placebo represent totality of data across BID cohorts.
Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid; BID = twice daily

Aside from the dose-dependent gastrointestinal TEAEs observed in healthy subjects receiving higher doses for 14 days, which have all been considered mild with the exception of 1 event of moderate diarrhea, no other safety concerns were identified following single doses ranging up to 2000 mg or following repeat dosing over 14 days of up to 800 mg administered BID to healthy subjects. The majority of TEAEs for all dose regimens evaluated to date have been mild and have resolved without requiring intervention or discontinuation of the IP. There have been no SAEs reported nor any dose-limiting toxicities identified. Mild, transient elevations in ALT were reported in 5 subjects who received either single or multiple doses of rodatristat ethyl (5 of 136 subjects [3.7%]). Further information can be found in the Investigator's Brochure.

With respect to nonclinical toxicology studies, rodatristat ethyl and rodatristat exposures at the no observed adverse effect level (NOAEL) in the 26-week rat (female only) or 39-week dog toxicology studies are > 4-fold higher than the expected exposure after at the higher dose regimen of 600 mg BID (IB, 2020). Due to adverse decreases in mean body weight gain (20 to -41.7% relative to controls) and food consumption at all dose levels in the 26-week study in male rats, the NOAEL could not be established. Exposure at the lowest dose tested in this study was 4-fold higher than that anticipated at the higher dose regimen of 600 mg BID. The major toxicities associated with oral rodatristat ethyl administration included mortality in rats preceded by clinical signs of toxicity and body weight loss occurring at exposures > 4-fold the highest exposure expected in the current study. Findings in both species were indicative of gastrointestinal changes including decreased body weight and/or decreased rate of weight gain, decreased food consumption, diarrhea/fecal change, dehydration, distended abdomen (rats only),

intestinal dilation with mucosal thickening and macrophage vacuolation (rats only), histopathologic findings of intestinal dilation with vacuolated macrophages, and increased mucosal thickness with regeneration in the duodenum. Observed liver enzyme elevations were not associated with adverse histopathology (hepatocellular necrosis) and are considered monitorable.

Prior studies have demonstrated coadministration of rodatristat ethyl with food can increase systemic exposure of rodatristat ethyl and rodatristat from 1.1- to 1.8-fold. Thus, the prior Phase 1 studies in healthy subjects evaluated rodatristat ethyl administered with a standard meal (IB, 2020). To maintain consistency with these studies and therefore the expected PD effects, IP will be administered BID with a standard meal.

Taken together, the nonclinical pharmacology and safety data, and prior clinical experience with rodatristat ethyl support the low and high BID dose regimens (300 mg and 600 mg) to be evaluated in patients with PAH over the 24-week treatment period.

4.8. End of Study Definition

A patient is considered to have completed the study if he/she has completed 24 weeks of treatment including the Week 24 visit and the Follow-up Visit (for patients that complete the study through Week 24 but decide not to rollover to the OLE), or the last scheduled procedure shown in the Schedule of Assessments(SoA; Section 1.3). If the patient decides to continue into the OLE, subject must not participate in another interventional study until completing the ET/final follow-up visit (4 weeks after the last dose of study drug) according to the Schedule of Assessments OLE (Section 1.4 or 1.5).

The end of the study for assessment of the primary endpoint is defined as the date of the last visit of the last patient in the Main Study or last scheduled procedure in the Main Study shown in the SoA for the last patient in the study globally, regardless of duration of participation in the OLE.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria are met:

1. Male and female patients must be at least 18 years of age at the time of signing the informed consent.
    a. Male patients and female partners of childbearing potential must agree to use contraception as detailed in a Section 5.4.1 to the protocol starting at Screening, during the treatment period, and for at least 100 days after the last dose of IP. Male patients must refrain from donating sperm during this period.
    b. Female patients of childbearing potential must agree to use contraception as detailed in Section 5.4.1 starting at Screening, during the treatment period, and for at least 4 weeks after the last dose of IP.
2. Body mass index (BMI) ≥ 18 kg/m^2 and ≤ 40 kg/m^2
3. Patients with symptomatic PAH belonging to one of the following 2018 Clinical Group 1 sub-types:
    a. Idiopathic PAH
    b. Heritable PAH
    c. Drug- or toxin-induced
    d. PAH associated with:
        1. Connective tissue disease
        2. Congenital systemic to pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) repaired at least one year prior to Screening
        3. Human immunodeficiency virus (HIV) infection - if diagnosed with HIV, must have stable disease status defined as follows:
            a. stable treatment with HIV medications for at least 8 weeks prior to Screening
            b. no active opportunistic infection during the Screening Period
            c. no hospitalizations due to HIV for at least 4 weeks prior to Screening
4. WHO FC II or III
5. Confirmed diagnosis of PAH and meet **all** the following hemodynamic criteria by means of a screening RHC completed prior to randomization:
    a. mPAP of >20 mmHg
    b. PVR ≥ 350 dyne•sec/cm^5
    c. Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) of ≤ 12 mmHg if PVR ≥ 350 and < 500 dyne•sec/cm^5, or PCWP/LVEDP ≤ 15 mmHg if PVR ≥ 500 dyne•sec/cm^5
6. 6MWD of 100 to 550 meters at Screening

7. Currently on a stable treatment regimen with one or more treatments approved for PAH. Stable therapy is defined as receiving the same medication(s) for ≥ 12 weeks prior to the screening RHC and at a stable dose level for each for ≥ 8 weeks prior to the screening RHC (see Protocol Section 6.6.2 for approved PAH medications). Any instances where doses of a medication have been missed prior to RHC must be discussed with the Medical Monitor prior to performing the RHC.
8. Meet all of the following criteria determined by pulmonary function tests completed no more than 24 weeks prior to Screening (performed with or without bronchodilation):
    a. Forced expiratory volume in one second (FEV_1) ≥ 60% of predicted normal, and
    b. Total lung capacity (TLC) ≥ 70% of predicted normal or FVC ≥ 70% predicted if TLC is not available; For subjects with CTD associated PAH, if TLC is ≥ 60% of predicted but < 70% of predicted of if FVC ≥ 60% or predicted but < 70% of predicted, high resolution computed tomography [HRCT] obtained within 6 months of screening may be utilized to demonstrate limited interstitial lung disease
9. If participating in an exercise program for pulmonary rehabilitation, the program must have been initiated ≥ 12 weeks prior to Screening, and patient must agree to maintain the current level of rehabilitation for the first 24 weeks of receiving IP. If not participating in an exercise training program for pulmonary rehabilitation, patient must agree not to enroll in an exercise training program for pulmonary rehabilitation during the Screening Period and the first 24 weeks of receiving IP.
10. Willing and able to give written informed consent and to comply with the requirements of the study for its duration

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met:

1. Women of childbearing potential who are pregnant, planning to become pregnant, or lactating or female/male patients unwilling to use effective contraception as defined in Section 5.4.1

Medical Conditions

2. WHO pulmonary hypertension (PH) Group 1 PAH associated with portal hypertension or schistosomiasis; PH due to left heart disease (WHO PH Group 2), lung diseases and/or hypoxia (WHO PH Group 3), chronic thromboembolic PH (WHO PH Group 4), or PH with unclear multifactorial mechanisms (WHO PH Group 5)
3. PH associated with significant venous or capillary involvement (PCWP > 15 mmHg), pulmonary capillary hemangiomatosis, portal hypertension, or unrepaired congenital heart defects (CHD)
4. Three or more of the following risk factors for left ventricular disease:
    a. BMI ≥ 30 kg/m^2
    b. Diagnosis of essential hypertension that is actively treated
    c. Diabetes mellitus

   d. History of significant coronary artery disease (e.g., chronic stable angina, history of coronary intervention within the last 3 months, or a stenosis > 70% at coronary angiography)
   e. Atrial fibrillation
   f. Left atrial volume index > 41 mL/m^2 [or left atrial diameter (LA) > 4 cm if LAVi unavailable]
5. Known genetic hypertrophic cardiomyopathy
6. Known cardiac sarcoidosis or amyloidosis
7. The patient has a history of, or currently has, a constrictive cardiomyopathy.
8. Known history of any left ventricular ejection fraction (LVEF) < 40% by echocardiogram within 3 years of randomization (**Note:** a transient decline in LVEF below 40% that occurred and recovered more than 6 months before the start of Screening and was associated with an acute intercurrent condition [e.g., atrial fibrillation] is allowed).
9. Hemodynamically significant valvular heart disease as determined by the Investigator, including:
   a. greater than mild aortic and/or mitral stenosis and/or
   b. severe mitral and/or aortic regurgitation (> Grade 3)
10. Severe arthritis, musculoskeletal problems, or morbid obesity that, in the opinion of the Investigator, is the cause of the patient's functional limitation and would affect the patient's ability to perform or complete the 6MWT.
11. Planned major surgery within the next 3 months, including lung transplantation, major abdominal or major intestinal surgery
12. End stage renal disease defined as receiving peritoneal dialysis, hemodialysis, or status after renal transplantation, or severe liver disease defined as Child-Pugh Class C, with or without cirrhosis
13. Known congenital LQTS or known family history of LQTS
14. Depression that is currently rated as severe (defined as a score of ≥ 16 on the QIDS-C and/or [HADS] Depression and/or Anxiety score ≥ 15), recent suicidal behavior (either preparatory acts/behavior, aborted attempt, interrupted attempt, or actual attempt in the past 3 months per the Screening C-SSRS), or active suicidal ideation with intent to act (defined as C-SSRS category score of 4 or 5 in the past month)
15. Patients with (during Screening):
   a. Severe hypertension (SBP > 180 mmHg and/or Diastolic Blood Pressure [DBP] > 110 mmHg), and patients with severe hypotension (SBP < 90 mmHg and/or DBP < 50 mmHg)
   b. Hypertension or hypotension considered not controlled in line with clinical standards
16. Clinically significant electrolyte abnormality (e.g., hypokalemia, hypomagnesemia, or hypocalcemia) in the judgement of the Investigator
17. Current or prior history within the last 5 years of neoplasm (except for treated basal cell or squamous small cell carcinoma of the skin with no evidence of recurrence)

18. Any concurrent clinically significant medical condition/disorder which in the Investigator's opinion would interfere with the patient's ability to comply with or complete the study or could affect the interpretation of the efficacy and safety variables.

Prior/Concomitant Therapy

19. Use of any of the following medications or supplements within 30 days prior to Screening:
    - monoamine oxidase inhibitors (MAOIs; Appendix 1)
    - 5-hydroxytryptophan (5-HTP) or L-tryptophan
    - telotristat ethyl
20. Patients currently taking one or more drugs known to prolong the QT interval and which are clearly associated with a known risk of Torsades de Pointe (see Appendix 1)

Diagnostic Assessments

21. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at Screening
22. 12-Lead ECG results at Screening demonstrating QTcF interval > 450 ms for males or > 470 ms for females
23. Elevated ALT, AST, or TBL > 2X ULN
24. Any ECG or clinical laboratory abnormality which precludes safe participation in the study in the opinion of the Investigator

Lifestyle

25. History of active substance use disorder (including alcohol) within the past 2 years which, in the option of the Investigator, would limit the ability of the patient to provide adequate informed consent or to comply with study requirements
26. Use of any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to Screening, or 90 days if an investigational drug for PAH, unless local health authority guidelines mandate a longer period, or in consultation with the medical monitor, will not interfere with the safety or efficacy of the study
27. Any history of hypersensitivity to rodatristat ethyl, any of its components, or any components in the placebo preparation (refer to current Rodatristat Ethyl IB).
28. Patient is deprived of their liberty by a judicial or administrative decision, or is receiving psychiatric care, and is admitted to a health or social institution
29. Patient is subject to legal protection or is unable to express consent

5.3. Other Eligibility Criteria Considerations

To determine patient eligibility at Screening, a single repeat of certain tests such as laboratory values, vital signs, or ECGs will be allowed.

To assess any potential impact on patient eligibility with regard to safety, the Investigator must refer to the rodatristat ethyl Investigator's Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the IP being used in this study.

5.4. Lifestyle Considerations

5.4.1. Contraception

Female patients of childbearing potential who have a negative serum pregnancy test at Screening and a negative urine pregnancy test at the randomization visit must agree to use protocol-specified, highly effective contraception starting at Screening and for the duration of the study and for at least 4 weeks following the last dose of IP as follows:

- Use 2 methods of contraception in combination defined as a condom plus an approved method of effective contraception from the following list from the time of informed consent:
  - Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
  - Progestogen-only hormonal contraception: oral, injectable/implantable, intrauterine hormone-releasing system
  - Implantable intrauterine device
  - Bilateral tubal ligation performed less than 6 months prior to randomization
  - Partner with vasectomy
  - Sexual abstinence – (refraining from heterosexual intercourse). If study patient chooses this option, site staff must follow-up to reconfirm throughout the study. If patient becomes sexually active, one of the above choices must be utilized and documented.

Female patients who are considered to have no childbearing potential (surgically sterile defined as bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) for at least 6 months prior to randomization may participate and are not required to use contraception as defined above.

Female patients who are postmenopausal and > 45 years of age with amenorrhea for at least 2 years may participate and are not required to use contraception as defined above.

Postmenopausal women with amenorrhea for less than 2 years must have documented follicle stimulating hormone (FSH) levels > 35 IU/mL and negative pregnancy test at the Screening Visit.

Male patients must agree to the following:

- Not to try to impregnate his partner from the Screening Visit until at least 100 days after the last dose of IP
- If his female partner is of childbearing potential, agree to use 2 methods of contraception in combination defined as a condom plus an approved method of effective contraception from the following list from the time of informed consent until at least 100 days after the last dose of IP:
  - Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
  - Progestogen-only hormonal contraception: oral, injectable/implantable, intrauterine hormone-releasing system
  - Implantable intrauterine device
  - Bilateral tubal ligation performed less than 6 months prior to randomization
  - Vasectomy
  - Sexual abstinence – (refraining from heterosexual intercourse). If study patient chooses this option, site staff must follow-up to reconfirm throughout the study. If patient becomes sexually active, one of the above choices must be utilized and documented.
- Use condoms with partners that are pregnant until at least 100 days after the last dose of IP to ensure that the fetus is not exposed to the IP
- Not donate sperm for the duration of the study until at least 100 days after the last dose of IP

5.4.2. Meals and Dietary Restrictions

5.4.2.1. Tryptophan-Rich Foods

As tryptophan-rich foods may increase 5-HT levels and interfere with biomarker assessments, patients will be asked to abstain from the following foods for 48 hours before study visits on Day 1 and at Weeks 4, 12, and 24:

- Avocado
- Bananas
- Eggplant
- Kiwi fruit
- Tree nuts, tree nut butters and tree nut products (e.g., hickory nuts, pecans, walnuts)
- Pineapple
- Plums
- Tomato and tomato products

5.4.2.2. Food Requirements

IP should be taken with food (at least a snack) at the morning and evening meals.

5.5. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized into the study. After obtaining informed consent, study site personnel will enter the patient into the Interactive Response Technology (IRT), and the patient will be assigned a unique patient number. The IRT should be updated promptly for patients who do not meet the criteria for participation in the study (screen failure) and reason.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information is to be entered into the Electronic Data Capture (EDC), including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened on a case-by-case basis. Approval from the Sponsor must be obtained prior to rescreening.

6. INVESTIGATIONAL PRODUCT

IP is defined as any investigational medicinal product (IMP) or placebo, intended to be administered to a study patient according to the study protocol.

6.1. Description of IP

The IPs to be administered as part of this study are described in Table 3.

Table 3: Investigational Products

Arm 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
Physical Description	White to off-white modified oval shaped tablet, debossed with "2E8" on one side		
Manufacturer	Patheon Pharmaceuticals 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada		
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

6.2. Dose Regimen

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

Each patient 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).

6.3. Preparation/Handling/Storage/Accountability

The Investigator or designee must maintain accurate records of receipt and the condition of the IP supplied for this study including dates of receipt. They must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

2. Only patients enrolled in the study may receive IP. Accurate records must be kept of when and how much IP is dispensed and administered to each patient in the study. Any reason for departure from the instructions provided in the protocol for dispensing of IP must also be recorded. IP may be supplied at the site, from the site to the patient via a Sponsor-approved courier company, or from the depot directly to the patient where allowed by local regulations and approved by the patient.
3. All IP at a study site must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused IP are provided in the Study Reference Manual.
6. A Safety Data Sheet (SDS) describing occupational hazards and recommended handling precautions will be supplied to the Investigator.

6.3.1. Investigational Product Packaging and Labeling

IP will be packaged in an appropriately sized bottle and labeled per local regulations.

6.3.2. Investigational Product Storage

IP is to be stored at 15°C to 25°C (59°F to 77°F) in a dry place and protected from light.

6.3.3. Investigational Product Administration

Once a patient is confirmed as eligible for study participation, the patient will be randomized via the IRT and assigned a kit(s) of IP. For each scheduled visit, the patient will be assigned new IP kit(s).

6.3.4. Investigational Product Accountability

Accountability for the IP is the responsibility of the Investigator. The study site must maintain accurate records including what kits were received and date, to whom the IP was dispensed, and all accounts of IP that is lost/missing or discarded. Additional details will be provided in a pharmacy or study reference manual.

6.3.5. Investigational Product Handling and Disposal

Patients should return all IP (including empty, partial, and full bottles) at their regularly scheduled clinic visits. Reconciliation of all IP that was dispensed, returned, or lost must be accounted for with documentation for any IP that was lost or missing.

Returned IP may be re-issued if the patient is continuing in the study, returned to the drug depot, or destroyed at the site as long as the site has procedures in place for IP destruction where allowed by local regulations. Otherwise, all returned IP will be returned to the depot at increments throughout the study after all IP has been accounted for and verified by the monitor. Additional instructions for IP return and destruction will be found in the pharmacy or study reference manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study. The Sponsor, Investigator, patient, 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 patient, 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 patients 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 patients who are receiving a prostanoid infusion will be capped at 50% of the total number of patients enrolled. The number of patients who are receiving selexipag will be capped at 20% of the total number of patients enrolled. Patients 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 patients will be re-randomized to receive either 300 mg BID or 600 mg BID rodatristat ethyl in an open-label fashion. Patients will not know what they received in the Main Study until all patients have completed the Main Study and the database is locked.

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

At the time of re-randomization in the OLE, patients will be assigned a new randomization number. Once this number has been assigned, it cannot be reused/reassigned.

Blind Break (IVRS/IWRS)	The Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) will be programmed with blind-breaking instructions. Only in case of an emergency, when knowledge of the IP is essential for the clinical management or welfare of a specific patient, may the Investigator unblind a patient's treatment assignment in IVRS/IWRS. The Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind without revealing the patient's study treatment assignment (unless important to the safety of patients in the study) and that the Investigator was unable to contact the Sponsor prior to unblinding. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

6.5. Investigational Product Compliance

Patient compliance with IP will be assessed at each visit by the site/study staff. Compliance will be assessed by direct questioning of the patient and counting returned tablets at each study visit to the study site. Patients will be reminded of the importance of taking their IP as directed at each visit including the Weeks 2 and 8 Phone Calls. Patients will be required to bring their IP supplies with them to each study visit to the study site so that a member of the study staff can check that the doses of IP were taken as directed.

Full compliance with the IP regimen, per subject, will be considered to be >80%.

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient received in the 8 weeks prior to enrollment, is receiving at the time of enrollment, or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

New and existing concomitant therapy(ies) may be considered on a case-by-case basis by the Investigator for treatment of a medical need. Any concomitant medication should be recorded in the study records, including doses administered, the dates and times of administration and the reason for administration.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. (Note: Vaccines, including potential Covid-19 vaccines, are allowed but must be documented in the eCRF).

6.6.1. Rodatristat-Drug Interaction Potential

In vitro experiments and in silico modeling to evaluate the drug-drug interaction potential of rodatristat ethyl and rodatristat have not identified any moderate or high risks for potential drug-drug interactions (IB, 2020). There is the potential for weak interactions with substrates of the drug metabolizing enzymes cytochrome P450 (CYP)2C8 and CYP3A, and drug transporters P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP).

Selexipag, and active metabolite ACT-333679, are substrates of CYP2C8 and preliminary data from a selexipag-rodatristat clinical interaction study in healthy subjects are available. In that study, steady-state rodatristat ethyl 600 mg BID coadministered with single-dose selexipag 400 µg increased selexipag AUC 1.18-fold and reduced ACT-333679 AUC by 40.5%. These data suggest induction of CYP2C8 by rodatristat ethyl/rodatristat. The magnitude of this interaction in PAH patients, and the clinical relevance of these changes in exposure are unknown. PK samples for assessment of selexipag and ACT-333679 trough concentration at baseline and Week 4, in addition to safety and efficacy data, will be collected in this study to further investigate this finding. In the same study, a single-dose of selexipag 400 µg had no relevant impact on the exposure of rodatristat ethyl or rodatristat.

Preliminary safety data from the study show a total of 33 TEAEs-in 8 subjects during the study. There were no SAEs or deaths. Gastrointestinal (GI) TEAEs were the most frequently reported TEAEs over all three periods with 25 GI TEAEs occurring in 6 subjects. All TEAEs were mild to moderate with the exception of one TEAE in one subject of serious diarrhea on Day 6. This same subject was the only subject discontinued from the study. This subject was discontinued by the Investigator due to prolonged GI TEAEs (nausea, vomiting, stomachache, diarrhea) during the rodatristat ethyl alone dosing period (Days 5-9). Nausea was the only TEAE reported in 2 or more subjects when selexipag was given alone. Diarrhea, headache, nausea and stomachache were reported (in ≥ 2 subjects) at approximately the same frequency during both rodatristat ethyl alone period and the selexipag and rodatristat ethyl coadministration period. There were no changes in laboratory parameters, vital signs, or ECGs of clinical significance.

No concomitant medications based on these in vitro and clinical findings are prohibited.

The following information is provided as guidance for the Investigator:

- Patients using systemic narrow therapeutic range substrates of CYP2C8, CYP3A and P-gp should be monitored during coadministration with IP. See Appendix 1 for a list of relevant substrates, for example:
    - Narrow therapeutic range CYP2C8 substrates (induction of CYP2C8 is possible): selexipag, trepostinil, pioglitazone, and torasemide.
    - Narrow therapeutic range CYP3A substrates (weak induction or inhibition of CYP3A is possible): cyclosporine, everolimus, fentanyl, sirolimus, and tacrolimus;
    - Narrow therapeutic range P-gp substrates: digoxin, monitor serum levels approximately 2 weeks after initiation of IP or if patient reports any signs of toxicity;

- Rodatristat was also identified as a substrate of liver uptake transporters OATP1B1/1B3. Strong inhibitors of OATP1B1/1B3 may increase circulating concentrations of rodatristat and may increase adverse effects. Putative strong inhibitors of OATP1B1/1B3 are systemic atanazavir/ritonavir, clarithromycin, cyclosporine, erythromycin, faldaprevir, gemfibrozil, glecaprevir/pibrebtasvir, lopinavir/ritonavir, rifampin, sofosbuvir/velpatasvir/voxilaprevir, and telaprevir. **Note:** Hydroxymethylglutaryl-CoA reductase inhibitors or 'statins' also transported by OATP are not considered strong inhibitors of OATP.

6.6.2. Pulmonary Arterial Hypertension Medications

The target population of patients with PAH will be receiving SOC treatment which can consist of monotherapy, dual, or triple combination therapy that have been taken for at least 12 weeks prior to the Screening RHC. These medications should be prescribed at doses considered therapeutically appropriate (e.g., maximum tolerated) and stable (i.e., no changes in dose or schedule) for at least 8 weeks prior to this RHC. Any instances where doses have been missed for > 2 consecutive days on more than one occasion or other regular lapses in compliance during this 8-week period prior to RHC must be discussed with the Medical Monitor prior to performing the RHC. Changes to these PAH medications must not be anticipated for the duration of the study.

No increases in background oral PAH doses or addition of a new PAH medication(s) will be allowed. Decreases in background oral PAH therapy dosing should only be considered in the event of suspected IP-related adverse effects. The Medical Monitor should be notified of any change to background PAH therapy.

Permissible oral, inhaled, and injectable PAH medications include:

- Tadalafil
- Sildenafil
- Ambrisentan
- Macitentan
- Bosentan
- Riociguat
- Prostanoids
- Prostacyclin receptor agonists (e.g., selexipag)

6.6.3. Prohibited Medications and Supplements

The following drugs are prohibited:

- Drugs which are known to prolong QT and which are also clearly associated with a known risk for Torsades de Pointe (per www.CredibleMeds.org (Woosley, 2019), Refer to Appendix 1).
- MAOIs
- Telotristat ethyl
- 5-HTP or L-tryptophan supplements
- Investigational drugs (other than rodatristat ethyl)

Refer to Appendix 1 for a complete list of concomitant medications that are prohibited in this study.

7. INTERVENTION AFTER THE END OF THE STUDY – OPEN-LABEL EXTENSION

7.1. Rationale for the Open-Label Extension

The purpose of the OLE is to provide continuous, uninterrupted access to rodatristat ethyl for patients who participated in the main part of this study if the patient appears to benefit from the therapy (as determined by Investigator and patient). The OLE will also provide active IP to patients who received placebo in the Main Study.

7.2. Objective

- To evaluate the long-term safety, tolerability, and efficacy of rodatristat ethyl in patients with PAH

7.3. Endpoints

7.3.1. Safety endpoints

- The proportion of patients who discontinue rodatristat ethyl due to an AE
- The proportion of patients with SAEs
- The proportion of patients with AEs
- The proportion of patients with treatment-emergent Grade 3 or 4 AEs
- The proportion of patients with treatment-emergent Grade 3 or 4 laboratory abnormalities

7.3.2. Efficacy endpoints

- Change in PVR
- Change in cardiac index, mPAP, mRAP, SvO2 at rest and PAC from baseline
- Time to Clinical Worsening
- Death from any cause
- Change in WHO FC from baseline
- Change in 6MWD from baseline
- Change in NT-proBNP from baseline
- Changes in right atrial size and RV function: TAPSE, tricuspid annular systolic velocity, and RV fractional area change from baseline

7.4. Open-Label Extension Design

Patients in the Main Study that do not discontinue prematurely and complete up to and including the Week 24 Visit, have the option to rollover into the OLE. Patients who continue into the OLE will be blinded to the treatment they received in the Main Study. Patients who received active IP in the Main Study will remain on their regimen. Patients randomized to placebo in the Main Study will be re-randomized to one of the 2 active rodatristat ethyl treatment arms (300 mg BID or 600 mg BID) in the OLE.

Patients who participate in the OLE will continue to receive rodatristat ethyl for 6.5 years, until the Investigator or patient 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 patient be allowed to exceed 10 years of exposure unless the product is approved for a chronic indication.

During the OLE patients will be followed by the Investigator according to clinical practice, with formal (per protocol) safety assessments. These safety assessments will include AEs, clinical laboratory tests, vital signs, and concomitant medications. Female patients of childbearing potential will be required to use 2 reliable methods of contraception to reduce the risk of pregnancy during the course of the study and for at least 30 days following the last dose of rodatristat ethyl.

During the first 24 weeks of the OLE patients, will also undergo efficacy assessments. These efficacy assessments will include 6MWT, RHC, echocardiogram, WHO FC, and plasma NT-proBNP level. Urine pregnancy tests will be performed every 4 weeks in women of child-bearing potential only, while the patient is on IP and once at 4 weeks post dose. If there is not a clinic visit, a urine pregnancy test will be sent home with the patient and results will be followed up with a phone call. Additional pregnancy testing in women whose menstruation is delayed or who have infrequent or irregular menstrual cycles should be conducted as warranted.

See SoA in Section 1.4 and Section 1.5.

7.5. Number of Patients and Inclusion/Exclusion Criteria

The maximum number of patients enrolled into the OLE will be the number of patients who complete the Main Study (Week 24).

7.6. Inclusion Criteria

1. Patient must have completed study assessments and procedures up to and including Week 24 in the Main Study.
2. Female patients of childbearing potential must have a negative serum or urine pregnancy test at the Week 24 visit and must agree to use contraception as detailed in Section 5.4.1 for at least 4 weeks after the last dose of IP. A female patient of childbearing potential is defined in Appendix 4.

3. Male patients are eligible to participate if they do not have a female partner who is pregnant or who intends to become pregnant during the OLE. Male patients and female partners must agree to use contraception as detailed in Section 5.4.1 of the protocol starting 4 weeks prior to the first dose of IP, during the treatment period, and for at least 100 days after the last dose of IP. Male patients must refrain from donating sperm during this period.
4. Patient must agree not to participate in a clinical study involving another investigational drug or device for PH/PAH while in the OLE (does not include registry or observational studies).
5. Patient must be competent to understand the information given in the IRB- or Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) and must sign the form prior to the initiation of any OLE procedures.

7.7. Exclusion Criteria

1. Patients who have demonstrated noncompliance with study visits or IP in the Main Study.
2. Planned major surgery within the next 3 months, including lung transplantation, major abdominal or major intestinal surgery.
3. New major thrombo-embolic events developed after completion of the Main Study.
4. Time period > 8 weeks between Week 24 of the Main Study and start of treatment in the OLE.
5. A disease or condition which in the opinion of Investigator may put the patient at risk because of participation or limit the patients' ability to participate.
6. Alcohol or drug abuse that in the opinion of the Investigator would interfere with participation.

7.8. Open-Label Extension Procedures

All assessments in the OLE will be performed as explained in the Main Study. SoA for the OLE are in Section 1.4 and Section 1.5.

Patients rolling into the OLE will complete the Screening/Enrollment Visit after their final visit in the Main Study (Week 24). All procedures for Week 24 will be completed including the following for the OLE:

- Obtain informed consent
- Review inclusion/exclusion criteria
- Complete re-randomization procedures for all patients
- Dispense IP and instruct patient to return all used and unused IP containers at next clinic visit
- Instruct Patient to call the clinic or return promptly should an AE occur.

7.9. Open-Label Extension Treatment Assignment

At the Screening/Enrollment Visit of the OLE, eligible patients who received placebo during the main study will be randomly allocated (1:1) to one of the following 2 treatment groups:

Treatment Arm Name	Treatment Description
Rodatristat ethyl 300 mg BID	1 x 300 mg tablet BID
Rodatristat ethyl 600 mg BID	2 x 300 mg tablets BID

Abbreviation: BID = twice daily

Patients who received active IP while in the Main Study may remain on the same active dose in the OLE or may be provided with a new dose of IP to receive either 300 mg BID or 600 mg BID depending on the timing and outcome of the 24-Week analysis from the Main Study.

Tolerability and all accumulated safety and efficacy data will be reviewed by the Independent Data Monitoring Committee (IDMC).

IP will be supplied without placebo. The first dose of IP in the OLE will be considered the first dose after all Week 24 assessments in the Main Study are completed and all entry criteria met.

7.10. Investigational Product Preparation, Handling, Storage, and Accountability

All IP preparation, handling, storage, and accountability will be the same as in the Main Study as in Section 6.

7.11. Dose Adjustment Criteria

Dose adjustment criteria are the same as the Main Study and can be found in Section 6.

7.12. Criteria for Investigational Product/Study Termination

All criteria for IP and study termination are the same as in the Main Study and can be found in Section 8.

8. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND PATIENT DISCONTINUATION/WITHDRAWAL

Unnecessary withdrawal of patients should be avoided, and all efforts should be made to retain patients in the study.

8.1. Discontinuation of Investigational Product

The Medical Monitor should be notified of any change to background PAH therapy to determine any need for withdrawal. See Section 8.2 for study withdrawal procedures.

Patients meeting any of the following liver chemistry criteria must be withdrawn (IP should be discontinued immediately) from the study by the Investigator:

- ALT or AST > 3X ULN **and** TBL > 1.5X ULN or INR > 1.5
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST >8X ULN

If liver chemistry tests meet any of the above criteria, repeat testing should be performed within 48 to 72 hours and the patient followed until resolution.

Patients meeting any of the following confirmed QT/QTc-related criteria must be withdrawn from the study by the Investigator:

- QTcF interval > 500 ms
- QTcF interval > 480 ms AND increase from Baseline ≥ 60 ms
- QTcF interval > 480 ms associated with syncope, life-threatening arrhythmias, resuscitated cardiac arrest, or seizure

The Investigator must also discontinue/withdraw a patient's participation in the study if any of the following criteria apply:

- Pregnancy
- Significant protocol violation/lack of compliance with the study and/or study procedures - non-compliance with IP for discontinuation of patient is defined as < 50%.
- Severe constipation (e.g., obstipation with manual evacuation indicated) and/or severe, persistent, or worsening abdominal pain
- Any significant worsening on postdose C-SSRS indicative of active suicidal ideation with intent to act (defined as C-SSRS Suicidal Ideation category score of 4 or 5) or behavior (either preparatory acts/behavior, aborted attempt, interrupted attempt, or actual attempt)
- Severe depression or anxiety based on a HADS Depression or Anxiety score ≥ 15, or a QIDS-C Total Score ≥ 16.

- Any severe psychiatric or CNS AE as determined by the Investigator.

The Investigator may discontinue/withdraw a study patient's participation in the study if any of the following criteria apply:

- Behavioral or administrative reason

Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient. When applicable, patients should be informed of circumstances under which their participation may be terminated by the Investigator without their consent.

8.1.1. Temporary Discontinuation

Temporary discontinuation of IP of up to 7 days will be allowed for extenuating circumstances or to manage AEs.

8.2. Patient Discontinuation/Withdrawal from the Study

Patients may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Replacement patients may be enrolled in consultation with the Sponsor's Medical Monitor.

8.2.1. Investigational Product Discontinuation

If a patient is permanently discontinued from the IP, but agrees to study visits, the patient will come in for the Early Termination Visit and continue attending clinic visits as scheduled through the 24-week visit (from first dose). A final follow-up visit will not be required.

If a patient prematurely discontinues IP prior to the Week 24 Visit, the Investigator will make every attempt to perform a RHC, as clinically feasible, prior to or within 7 days of IP discontinuation (but after at least 12 weeks of IP), and prior to initiation of any new PAH medications.

8.2.2. Study Discontinuation

If a patient who discontinues IP decides to end all study participation, an Early Termination Visit should be conducted, as shown in the SoA (Section 1.3), if possible.

Patients who withdraw should be asked if they may be contacted by the study site by telephone unless they explicitly withdraw their consent to be followed up.

If a patient withdraws consent, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.3. Lost to Follow up

A patient will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Patients who withdraw consent will continue to be followed for vital status from public records such as government vital statistics or obituaries, as allowed by local law, or periodic contact (about every 6 to 12 months).

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 5.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA in Section 1.3 for the Main Study and in Section 1.4 and Section 1.5 for the OLE.

Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue IP.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Once all screening procedures are complete and the Investigator determines that the patient is eligible, the site must upload/send the required supporting documentation for approval by the Sponsor. The required information will include the RHC report (including tracings), PFTs obtained (may use PFTs completed in the 24 week period prior to screening or obtained at Screening), the screening echocardiogram, as well as specific information about the patient's medical history and disease state to further ensure the appropriateness of each patient being enrolled into this study. Approval from the Sponsor must be obtained prior to randomization.

All assessments should be completed predose unless otherwise stated.

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order whenever possible: ECGs, vital signs, safety blood draws, PK blood draws.
Note: The timing of the assessments should allow the blood draw to occur as close as possible to the nominal time but before dosing.

Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the initial samples.

9.1. Efficacy Assessments

The efficacy-related assessments, as outlined below, will be obtained at time points indicated in the SoA in Section 1.3 and Section 1.4.

9.1.1. Right Heart Catheterization

The RHC is a common procedure used to diagnose PAH.

Cardiopulmonary hemodynamics will be assessed by RHC. All required RHC parameters must be collected using the same methods at Screening/Randomization and Week 24. The Screening/Randomization RHC will be required to confirm the diagnosis of PAH, and data from this RHC will serve as the baseline value for the primary and secondary analyses of cardiopulmonary hemodynamic parameters. Since the study is enrolling treatment-experienced patients, results from a historical RHC conducted prior to the Screening Visit are not expected to reflect the patient's current disease status unless it was performed within 4 weeks of the Screening visit, includes all required information, and provided that changes to the patient's PAH regimen were not made subsequent to that catheterization.

If prior approval is obtained from the Sponsor, the screening RHC may be performed on the same day as the randomization procedures, provided that all blood draws and efficacy assessments are conducted prior to the RHC procedure, and the RHC is performed prior to randomization and IP dosing. The hemodynamic assessment will be conducted in the supine position under resting conditions. The original RHC tracings will be maintained at the site. The RHC tracings will have all personal health information removed and will be labeled with the following: patient number, patient initials, protocol number, and date recorded.

Full details available in RHC manual.

9.1.2. Time to Clinical Improvement

TTCI will be evaluated by a multicomponent improvement score including WHO FC and 6MWT measurements: 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.

9.1.3. Time to Clinical Worsening

TTCW is 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 6MWD combined with WHO FC III or IV symptoms at 2 consecutive visits separated by at least 14 days (adjudicated).

9.1.4. Six-Minute Walk Test/Six-Minute Walk Distance

The 6MWT is a simple, commonly used, standardized measure of functional exercise capacity and endurance. It is a commonly used measure of efficacy in PAH clinical studies. The change from baseline in 6MWD following intervention indicates symptomatic improvement over that time-period. Improvement in 6MWD has been correlated with improvements in quality of life. Refer to Appendix 6.

9.1.5. Echocardiography

Patients will undergo resting cardiac echocardiography at specified visits. Echocardiographic endpoints will include right atrial size and measures of RV function (TAPSE, tricuspid annular systolic velocity, and RV fractional area change). There will be a core imaging laboratory for centralized blinded adjudication of the echocardiographic endpoints.

Full details available in echocardiograph manual.

9.1.6. Pulmonary Function Tests (PFTs)

PFTs (performed with or without bronchodilation) should be completed at Screening if there are no historical results from tests completed within 24 weeks prior to Screening.

9.1.7. World Health Organization Functional Class

PAH functional disease severity is classified according to WHO FC. Patients are classified into 1 of 4 functional classes on the basis of their degree of physical limitation and associated symptoms. Refer to Appendix 7 for full description of each Functional Class.

9.1.8. N-terminal pro-Brain Natriuretic Peptide Level

NT-proBNP is a strong predictor of disease progression and mortality in PAH patients. Current PAH treatment guidelines recommend measurement of NT-proBNP levels for both risk assessment and longitudinal follow up. NT-proBNP levels are also a good marker of response to treatment.

9.1.9. Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire

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

The questionnaire consists of two parts:

- Day 1 to Day 6: The Questionnaire asks 13 questions regarding the patient's PAH symptoms for the past 24 hours. The patient is required to complete these questions each day for Days 1 to 6.
- Day 7: The Questionnaire asks 12 questions regarding the patient's PAH symptoms for the past 24 hours and an additional 11 questions about the "Impacts" that best describes how the patient's life was affected by PAH.

Prior to departing the study site at the Screening Visit, patients will be instructed and trained on how to complete the questionnaire. Patients will start the PAH-SYMPACT questionnaire 6 days prior to the visit for which PAH-SYMPACT is collected, with the Day 7 being completed on the day of the visit.

An example of the PAH SYMPACT Questionnaire can be found in Appendix 9.

9.1.10. Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management Lite 2 Risk Assessment Calculator

REVEAL Lite 2 includes 6 non-invasive variables: FC, vital signs (SBP and HR), 6MWD, NT-proBNP, and renal insufficiency (by eGFR). REVEAL Lite 2 will be a calculated parameter (by statistician) at Baseline and Week 24 of the Main Study and Week 24 of the OLE (this calculation will not be in the eCRF).

9.1.11. Actigraphy

Data on physical activity will be collected using a small wrist-worn physical activity tracker (monitor designed for documenting physical movement) that will transmit all activity through the 24 weeks of the Main Study.

9.2. Safety Assessments

9.2.1. Pregnancy Testing

Serum pregnancy tests will be obtained for all female patients of childbearing potential at Screening and every 4 weeks while on IP. Urine pregnancy tests will be obtained at all subsequent visits and must be confirmed negative at the Baseline Visit before randomization and IP dispensation. Additional pregnancy tests should be completed anytime menstruation is delayed and in women with infrequent or irregular menstrual cycles. A positive urine test will be confirmed by a serum test.

Serum pregnancy test and FSH levels will be obtained at the Screening Visit for any postmenopausal women with amenorrhea for < 2 years to confirm FSH level (must be > 35 IU/mL). If FSH value is confirmed as postmenopausal at Screening, no further pregnancy tests are required. If level does not confirm postmenopausal status, urine pregnancy tests will be required at all scheduled visits and patients must agree to use an approved method of highly effective contraception (refer to Section 5.4.1).

Planned time points for all safety assessments are provided in the SoA (Section 1.3, Section 1.4, and Section 1.5).

9.2.2. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height (only at Screening) and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.2.3. Vital Signs

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, respiration rate and oxygen saturation.

9.2.4. Electrocardiograms

Three 12-lead ECGs, one minute apart, will be obtained after at least 5 minutes of rest at Baseline. Single 12-lead ECGs will be performed at all other time points.

Each ECG performed during the study will be obtained using an ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF intervals.

The corrected QT interval (QTc) using Fridericia's formula (QTcF) will be used for each individual patient to determine study eligibility and for all on-study ECGs. The QTcF interval will be based on the ECG machine's algorithm.

Clinically significant ECG findings that are present prior to initiation of IP, if not exclusionary, must be documented in the Medical History section of the eCRF. Any clinically significant abnormality that represents a change from baseline will be reported as an AE and followed until resolution.

9.2.5. Clinical Safety Laboratory Assessments

A central laboratory will be used for clinical safety laboratory assessments. The details for sample collection, preparation, and shipping to the central laboratory will be provided in a separate lab manual. Reference ranges for all safety parameters will be provided to the site by the central laboratory responsible for the assessments.

See the SoA (Section 1.3, Section 1.4, and Section 1.5) for timing and frequency.

Hematology, clinical chemistry, coagulation, urinalysis, and additional parameters to be tested are listed below:

9.2.5.1. Hematology

Hematology Panel		
Platelet Count	Red Blood Cell (RBC) Indices:	Automated WBC Differential:
RBC Count	Mean Corpuscular Volume (MCV)	Neutrophils
White Blood Cell (WBC) Count (Absolute)	Mean Corpuscular Hemoglobin (MCH)	Lymphocytes
Reticulocyte Count	Mean Corpuscular Hemoglobin Concentration (MCHC)	Monocytes
Hemoglobin	Eosinophils	Basophils
Hematocrit		

9.2.5.2. Coagulation

Coagulation Panel
Prothrombin Time (PT)
INR
Activated Partial Thromboplastin Time (aPTT)

Coagulation testing will be done at Screening, Week 12, and Week 24 for all patients on the Main Study and at Weeks 12 and 24 during the OLE in the first 24 weeks and every clinic visit post 24 weeks in the OLE. In addition, coagulation will be done at an unscheduled visit if there is an ALT result ≥ 3X ULN at any study visits. Refer to Appendix 3 .

9.2.5.3. Clinical Chemistry

Clinical Chemistry Panel			
Blood Urea Nitrogen	Potassium	ALT	Albumin
Creatinine	Chloride	Gamma-Glutamyl Transferase (GGT)	Total Protein
Glucose	Calcium	Alkaline Phosphatase	Urea
Sodium	Bilirubin (Total)	Bilirubin (Direct) (only if Total is elevated)	AST
Bicarbonate	Magnesium	Lipase (reflex if Amylase is > 2X ULN)	Amylase

9.2.5.4. Urinalysis

Urinalysis
Bilirubin, Glucose, Protein, Blood and Ketones, Leukocytes, Nitrites, pH, Specific Gravity and Urobilinogen by dipstick
Microscopic examination (if blood or protein is abnormal)
Microbiology (at discretion of Investigator based on urinalysis results)

9.2.5.5. Other Tests

Other Tests
NT-proBNP
Urine Creatinine (for calculation of 5-HIAA) at each 5-HIAA collection time
Estimated Glomerular Filtration Rate (eGFR)
FSH (as needed at Screening for confirmation of postmenopausal status)
Serum beta-hCG (pregnancy test; only at Screening)
Human Chorionic Gonadotropin (hCG) by urine dipstick
Pharmacogenetic sample
Sample for Future Research sample
Drugs of abuse: amphetamines, barbiturates, benzodiazepines, cocaine metabolites, methadone, opiates, phencyclidine, propoxyphene (only at Screening)

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with abnormal values considered clinically significant during participation in the study or within 4 weeks after the last dose of IP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA (Section 1.3, Section 1.4, and Section 1.5).

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

Additional unscheduled laboratory assessments may be conducted at any time during the study if the Investigator or Sponsor deems it necessary for the safety of the patient.

9.2.6. Pharmacogenetic Testing

A separate and specific informed consent form will be provided to patients to allow the sponsor to obtain and test a patient's blood sample taken at the Baseline/Day1 and the Week 24 visits for pharmacogenetic markers that may be predictive of the natural history of the disease, response to therapy and tolerability of therapy. If it is not collected at the Baseline/Day 1 visit, it may be collected at any time during the treatment period. Providing these blood samples is optional and not required for participation in the study.

9.2.7. Optional Blood Sample for Future Research

In addition to the study-specific informed consent to be signed by each patient participating in the study, a separate, specific signature will be required to document a patient's agreement to provide additional samples or to allow the use of the remainder of their already collected biomarker specimens for optional non-genetic future research, once approved by local authorities as applicable according to specific local regulations. The specimens collected for optional future research will be used to increase our knowledge and understanding of the biology pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the process of drug absorption and disposition.

A plasma sample will be obtained from all patients at the Day 1/Baseline visit and at the end of the treatment or ET (as applicable) visit of the Main Study for future research use. Samples will be collected and archived by the sponsor for up to 10 years.

9.2.8. Suicidal Ideation and Behavior Risk Monitoring

Rodatristat ethyl acts to decrease peripheral 5-HT levels and it was designed to not cross the blood-brain barrier; therefore, CNS 5-HT levels are not expected to be significantly impacted. However, patients being treated with IP should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. IP in patients who experience signs of suicidal ideation or behavior following a risk assessment (see Section 8.1) must be stopped.

Screening and Baseline assessments (within 1 month) of suicidal ideation and behavior as well as potential treatment-emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS.

Suicidal ideation and behavior as well as mood and anxiety assessments, as detailed below, will be obtained at time points indicated in the SoA in (Section 1.3).

9.2.8.1. Columbia Suicide Severity Rating Scale

The C-SSRS is a valid, reliable, evidenced-based suicidal ideation and behavior rating scale, which was developed by multiple institutions, including Columbia University with National Institute of Mental Health support, to evaluate suicide risk (CLP, 2016). The rater-/clinician-administered versions of the C-SSRS for research assess severity and intensity of suicidal ideation, types of suicidal behaviors, and lethality of suicide attempts at time points and over time periods that are typical for randomized control studies. The C-SSRS has been identified by the FDA (FDA, 2012) as acceptable for use in clinical research and has been used extensively in clinical studies throughout the U.S. and around the world.

Training should be completed by any study staff delegated to perform this assessment. Online training is available, and a certificate of completion is issued once the training is completed and must be filed at the site. Training must be current within the previous 2 years. The sign-up and training portal can be found at the following link:

https://cssrs.columbia.edu/training/training-research-setting/

An example of the C-SSRS can be found in Appendix 10.

9.2.8.2. Hospital Anxiety and Depression Scale

The HADS is a 14-item, self-rated measure designed to be used as a brief screen for depression (7 items) and anxiety (7 items) disorders among nonpsychiatric, medically ill, outpatient populations (Zigmond & Snaith, 1983). As a screening instrument, the HADS does not provide a definitive diagnosis, but is the first step in a multistage process of selecting individuals at elevated risk for disorder to be evaluated through clinical interview.

An example of the HADS can be found in Appendix 11.

9.2.8.3. Quick Inventory of Depressive Symptomatology

The 16-item QIDS (Rush et al., 2003) is designed to assess the severity of depressive symptoms. The QIDS is available in the clinician-rated (QIDS-C) and self-reported versions (QIDS-SR). Both versions assess all the criterion symptom domains designated by the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders - 4th edition (DSM-IV) (APA, 1994) and the 5th edition adds reference to diagnose a major depressive episode. The QIDS-C version will be used in this study. The QIDS-C is sensitive to change with medications, psychotherapy, or somatic treatments, making it useful for both research and clinical purposes. The psychometric properties of the QIDS-C have been established in various study samples.

An example of the QIDS-C can be found in Appendix 12.

9.3. Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 14.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for follow up of AEs that are serious, considered related to the IP or study procedures, or that caused the patient to discontinue the study (see Appendix 14).

9.3.1. Adverse Events of Special Interest

AESIs include:

- Severe constipation (and/or severe, persistent, or worsening abdominal pain)
- Depression/other significant mood-related disturbance (active suicidal ideation or behavior, severe depressive and/or anxious symptoms, other severe psychiatric TEAE)
- Elevations in hepatic enzymes (see Appendix 3)
- Diarrhea (see Appendix 2)

9.3.2. Time Period and Frequency for Collecting Adverse Event, Adverse Events of Special Interest, Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until the Follow-Up Visit at the time points specified in the SoA (Section 1.3). All AEs will be collected from the first dose of IP.

Medical occurrences that begin before the start of IP but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 14. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Adverse events of special interest must be reported to the Sponsor should they meet the definition of an SAE, and all timelines for reporting of SAEs should be adhered to.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the Investigator must promptly notify the Sponsor.

9.3.3. Method of Detecting Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 14.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

9.3.4. Follow-up of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 9.3.1), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 14.

9.3.5. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of an IP under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

9.3.6. Pregnancy

Patients will be instructed that if they/their partner become pregnant during the study, this should be reported to the Investigator. The Investigator should also be notified of any pregnancy that occurs during the study but not confirmed until after completion of the study for at least 5 terminal half-lives (4 weeks) after the last dose. In the event that a patient/patient's partner is subsequently found to be pregnant after being included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed, and the status of the mother and/or child will be reported to the Sponsor after delivery.

Any patient reporting a pregnancy during the study will be discontinued from the IP. The patient will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

9.4. Treatment of Overdose

Prior to this study, there has been no experience with rodatristat ethyl in patients with PAH. In healthy subjects, no safety concerns were identified following single doses ranging from 100 mg to 2000 mg or following repeat dosing over 14 days of up to 800 mg administered BID or up to 800 mg administered once daily (QD).

An overdose in this study is defined as a dose > 1200 mg on any single dosing occasion, or > 2400 mg in any 24-hour period.

Altavant Sciences GmbH does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities as applicable
3. Obtain an unscheduled plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

9.5. Pharmacokinetics

Blood samples for PK analysis of plasma rodatristat ethyl, rodatristat, M15 metabolite, selexipag, and ACT-333679 will be collected by indwelling cannula or venipuncture at the time points indicated in the SoA (Section 1.3). Note, selexipag/ACT-333679 PK samples will only be collected in subjects using selexipag at baseline. The actual date and time of each blood sample collection will be recorded.

The date and time of the dose of IP taken prior to the collection of each PK sample will be recorded and if the meal the dose was taken with was high in fat, should also be recorded.

Sample analysis will be performed under the control of the Sponsor. Plasma concentrations of rodatristat ethyl, rodatristat, M15, selexipag, and ACT-333679 will be determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Raw data will be archived at the bioanalytical site(s). Once the sample(s) has been analyzed for rodatristat ethyl, rodatristat, M15, selexipag, and ACT-333679, any remaining sample may be analyzed for other rodatristat-related metabolites and the results may be reported separately.

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of blood collection, processing, storage, and shipment will be provided in the laboratory manual.

Rodatristat ethyl and rodatristat concentration information that would unblind the study will not be reported to investigative sites or blinded personnel (including the Sponsor) until the study has been unblinded.

9.6. Pharmacodynamics

Blood samples for determination of plasma 5-HIAA will be collected by indwelling cannula or venipuncture at the time points indicated in the SoA in Section 1.3. The actual date and time of each blood sample collection will be recorded.

Urine samples will be collected for determination of 5-HIAA (bioanalytical lab) and urine creatinine (central laboratory; for determination of creatine corrected 5-HIAA concentration) at the time points indicated in the SoA in Section 1.3 and Section 1.4.

Sample analysis will be performed under the control of the Sponsor. Plasma and urine concentrations of 5-HIAA will be determined using a validated LC-MS/MS method. Raw data will be archived at the bioanalytical site.

Details of sample containers and processing will be contained in the laboratory manual.

10. STATISTICAL CONSIDERATIONS

A detailed description of statistical methods will be provided in a separate Statistical Analysis Plan (SAP) and the SAP will be finalized prior to database lock.

10.1. Statistical Hypotheses

No formal hypotheses are planned for the study.

10.2. Sample Size Determination

The sample size for this study was not based on a formal hypothesis testing. It is expected that 30 patients per arm will provide sufficient data to assess the 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 patients with 30 patients to be randomized into 1 of the 3 treatment arms in a 1:1:1 randomization is planned. A sample size of 30 patients 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.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All patients who sign the ICF
Intent-to-Treat (ITT)	All patients randomized into the study. For all summaries based on the ITT population, patients will be assigned to the treatment arm to which they were randomized.
Modified Intent-to-Treat (m-ITT):	All safety population patients that had an evaluable baseline and completed at least 1 post-baseline efficacy assessment. Patients will be analyzed according to the treatment they actually received.
Per Protocol (PP)	All m-ITT population patients who had no major protocol deviations and completed the Week 24 visit.
Safety	All patients randomly assigned to IP and who take at least 1 dose of IP. Patients will be analyzed according to the treatment they actually received.

10.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the patient populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Primary efficacy analyses will be performed using the m-ITT and PP populations. Percent change from baseline in PVR will be analyzed using an analysis of covariance (ANCOVA) with Baseline PVR as the covariate. Additional baseline characteristics may also be evaluated as covariates in the model. The estimated between-treatment differences, 95% confidence intervals (CIs), and p-values will be presented. For patients who discontinue from the study early, the last-observation-carried-forward method will be used to impute the PVR at Week 24.
Secondary	Secondary efficacy analyses will be performed using the m-ITT and PP populations: Change in cardiac index, mPAP, mRAP, SvO2 at rest, and PAC from baseline to Week 24 • TTCW • Change in WHO FC • Change in 6MWD from baseline • Change in NT-proBNP • Change in right atrial size & RV function: TAPSE, tricuspid annular systolic velocity, and RV fractional area change from baseline • REVEAL Lite 2 score • Change in PAH-SYMPACT from Baseline to Week 24 • Change in 5-HIAA (plasma and spot urine concentration) The change from baseline to Week 24 endpoints will be analyzed using an ANCOVA model with treatment as a fixed effect, randomization stratum and baseline assessment as covariates. The estimated between-treatment differences, 95% CIs, and p-values will be presented. The change in 6MWD from baseline to Week 24 will also be compared between groups using non-parametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test. For endpoints measured over time, a mixed effect of repeated measure model may be used as sensitivity analyses. Details of statistical methods will be provided in the SAP. The time from the first dose of IP until to the first clinical worsening event will be summarized using Kaplan-Meier estimates and compared between treatment groups using the log-rank test.

Endpoint	Statistical Analysis Methods
Exploratory	Will be described in the SAP finalized before database lock

10.4.2. Safety Analyses

Safety and tolerability will be evaluated by assessment of AE incidence and changes in clinical laboratory tests, physical examinations, vital signs measurements, ECG readings, and suicidal ideation and behavior ratings at various time points during the study.

The following AE summaries will be generated:

- Adverse events
- Serious adverse events
- Adverse events leading to discontinuation
- Adverse events by severity
- Adverse events by relationship to the IP

AE verbatim text will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs, both serious and nonserious, will be listed. AE summaries by treatment group and consisting of the number and percent of patients reporting each event at least once will be generated.

Clinical values will be listed for each patient and flagged high or low relative to the normal range where appropriate. Descriptive summary statistics will be created by treatment and visit.

Other safety data (e.g., physical examination) will be summarized descriptively by treatment and visit.

10.4.3. Other Analyses

Patient reported outcomes (HADS and QIDS-C), PK, PD, and exploratory descriptive analyses will be described in the SAP finalized before database lock. Population PK and any PK/PD analyses will be documented in a separate analysis plan and may be reported separately.

The planned analyses for the OLE portion of the study will be provided in the SAP.

10.5. Interim Analyses

An external, multidisciplinary, IDMC will review the progress of the study and perform interim reviews of unblinded safety 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 patients, 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.

A separate SAP will describe the planned interim analyses in greater detail.

10.5.1. Independent Data Monitoring Committee

The primary role of the IDMC, which consists of independent physicians with experience in the care of patients with PAH and the conduct of randomized, controlled studies and one non-voting biostatistician, is to ensure the safety of the patients enrolled in the study, including the OLE. Details of the IDMC's specific activities will be defined by a mutually agreed charter, which will define the IDMC's membership, conduct and meeting schedule. This charter will be maintained by the Sponsor or designee.

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APPENDIX 1. CONCOMITANT AND PROHIBITED MEDICATIONS

NARROW THERAPEUTIC RANGE SUBSTRATES OF CYTOCHROME P450 (CYP)2C8, CYP3A, AND P-GLYCOPROTEIN (P-GP) Patients using the following systemic narrow therapeutic range substrates of CYP2C8, CYP3A and P-gp are allowed but should be monitored during coadministration with IP.

CYP2C8	Trepostinil Selexipag Torasemide Trimethoprim Gemfibrozil Rosiglitazone Pioglitazone
CYP3A	Alfentanil Cyclosporine (dihydro)ergotamine Everolimus Fentanyl Sirolimus Tacrolimus
P-gp	Digoxin Dabigatran Fexofenadine

PROHIBITED MEDICATIONS

The following medications should not be used during the study:

Class	**Drug Name** **Generic Name**
Monoamine Oxidase Inhibitors (MAOIs)	Isocarboxazid Phenelzine Selegiline Tranylcypromine
Tryptophan Hydroxylase Inhibitor	Telotristat Ethyl
Marketed drugs known to prolong QT/QTc AND which are also clearly associated with a known risk of Torsades de Pointe source: www.CredibleMeds.org (Woosley, 2021)	Amiodarone (Cordarone and others) Anagrelide (Agrylin and others) Arsenic trioxide (Trisenox) Astemizole (Hismanal Azithromycin (Zithromax and others Bepridil (Vascor) Chloroquine (Aralen)

Class	Drug Name Generic Name
	Chlorpromazine (Thorazine and others)
	Chlorprothixene (Truxal)
	Cilostazol (Pletal)
	Ciprofloxacin (Cipro and others)
	Cisapride (Propulsid)
	Citalopram (Celexa and others)
	Clarithromycin (Biaxin and others)
	Cocaine (Cocaine)
	Disopyramide (Norpace)
	Dofetilide (Tikosyn)
	Domperidone (Motilium and others)
	Donepezil (Aricept)
	Dronedarone (Multaq)
	Droperidol (Inapsine and others)
	Erythromycin (E.E.S. and others)
	Escitalopram (Cipralex and others)
	Flecainide (Tambocor and others)
	Fluconazole (Diflucan and others)
	Gatifloxacin (Tequin)
	Grepafloxacin (Raxar)
	Halofantrine (Halfan)
	Haloperidol (Haldol and others)
	Hydroxychloroquine (Plaquenil and others)
	Ibogaine
	Ibutilide (Corvert)
	Levofloxacin (Levaquin and others)
	Levomepromazine/methotrimeprazine (Nosinan and others)
	Levomethadyl acetate (Orlaam)
	Levosulpiride (Lesuride and others)
	Mesoridazine (Serentil)
	Methadone (Dolophine and others)
	Moxifloxacin (Aveloxand others)
	Ondansetron (Zofran and others)
	Oxaliplatin (Eloxatin)
	Papaverine HCl Intracoronary

Class	Drug Name Generic Name
	Pentamidine (Pentam) Pimozide (Orap) Probucol (Lorelco) Procainamide (Pronestyl and others) Propofol (Diprivan and others) Quinidine (Quinaglute and others) Roxithromycin (Rulide and others) Sertindole (Serdolect and others) Sevoflurane (Ultane and others) Sotalol (Betapace and others) Sparfloxacin (Zagam) Sulpiride (Dogmatil and others) Sultopride (Barnetil and others) Terfenadine (Seldane) Terlipressin (Teripress and others) Terodiline (Micturin and others) Thioridazine (Mellaril and others) Vandetanib (Caprelsa)

APPENDIX 2. DIARRHEA MANAGEMENT

CTCAE Grade	Description	IP	Symptom/Treatment
Mild = 1 (uncomplicated)	Increase of < 4 stools per day over Baseline	Continue same dose	Consider anti-diarrheal medicines e.g., 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day until bowel movements cease for 12 hours
Moderate = 2 (uncomplicated)	Increase of 4–6 stools per day over Baseline; IV fluids indicated < 24 hours; Not interfering with ADL	**If Grade 2 diarrhea persists for ≥ 48 hours, IP should be interrupted** until recovered to Grade ≤ 1 followed by dose reduction. Dose re-escalation is possible within 4 weeks after start of reduced dose.	Continue anti-diarrheal medicines, if Grade 2 persists for ≥ 48 hours assess for dehydration and electrolyte imbalance, consider IV fluids and electrolyte replacement as clinically indicated.
Severe = 3 (complicated)	Increase of ≥ 7 stools per day over Baseline; Incontinence; IV fluids ≥ 24 hours; Hospitalization; Interfering with ADL	**IP interruption** until recovery to Grade ≤ 1 followed by dose reduction. In case of recurrence of Grade 3 diarrhea despite optimal symptomatic treatment and dose reduction, IP should be permanently discontinued.	See Grade 2. Consider stool cultures and clostridium botulinum toxins to exclude any infection; aggressive IV fluid replacement ≥ 24 hours, hospitalization as clinically indicated, consider referral to a GI specialist to rule out potential differential diagnoses.
Life-threatening = 4 (complicated)	Life-threatening consequences (e.g., haemodynamic collapse)	See Grade 3.	See Grade 3.

Abbreviations: ADL = activities of daily life; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; IP = investigational product; IV = intravenous

APPENDIX 3. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

CTCAE Grade	Description	IP	Symptom/treatment
Mild = 1	AST or ALT > 1.5X ULN < 3X ULN	Continue as planned	No action taken
Moderate = 2	AST or ALT ≥ 3X ULN and < 5X ULN and no signs of severe liver damage	Reduce to one pill BID or interrupt treatment (to be decided by Investigator, based on individual risk assessment.)	Re-test ALT and AST, as well as ALP, TBL, and eosinophils within 48-72 hours, then at ~7 days, then at ~2 weeks, and assess for signs of severe liver damage: • If AST and ALT < 3X ULN after 2 weeks, return to initial dose if reduced, restart at reduced dose if interrupted. Monitor labs (see above) every 2 weeks for at least 8 weeks. • If AST and ALT ≥ 3X ULN after 2 weeks or anytime thereafter, permanently discontinue study medication.
Severe = 3	AST or ALT increase to ≥ 5X ULN and < 8X ULN and no signs of severe liver damage	Interrupt treatment	Re-test ALT and AST, as well as ALP, TBL, and eosinophils within 48-72 hours, then at ~7 days, then at ~2 weeks, and assess for signs of severe liver damage: • If AST and ALT < 3X ULN after 2 weeks, restart at reduced dose. Monitor labs (see above) every week for 4 weeks, then

CTCAE Grade	Description	IP	Symptom/treatment
			every 2 weeks for at least 8 weeks. • If AST and ALT ≥ 3X ULN after 2 weeks or anytime thereafter, permanently discontinue study medication.
Life-threatening = 4	AST or ALT increase to ≥ 8X ULN **or** signs of severe liver damage: -Increase of liver transaminases (ALT or AST ≥ 3X ULN) **and** Appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%) **or** TBL > 1.5X ULN **or** INR > 1.5	Permanently Discontinue	Patients showing these laboratory abnormalities need to be followed up closely

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; IP = investigational product; ULN = upper limit of normal

APPENDIX 4. COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
3. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
4. **Note:** Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
5. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     – A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue their HRT to allow confirmation of postmenopausal status before study enrollment.

Collection of Pregnancy Information

Male patients with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive the investigational product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who become pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the investigational product by the Investigator will be reported to the Sponsor as described in Section 9.3.5. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue the investigational product and be withdrawn from the study.

APPENDIX 5. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the patient or the patient's legally authorized representative.

Patients who are rescreened are required to sign a new ICF.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after last marketing approval unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Manual.

Study and Site Closure

The Sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further investigational product development

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 6. SIX-MINUTE WALK TEST GUIDELINES

The six-minute walk test (6MWT) should be performed in accordance with the American Thoracic Society Guidelines. Please refer to the ATS guidelines and the following general procedures for conducting the 6MWT:

Testing Location:

- The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The location should be quiet and free of distractions and drafts.
- The walking course must be 30 meters in length (any deviations from this must be reviewed with and approved by the Medical Monitor/Sponsor prior to initiating the study). A 100-foot hallway is, therefore, required. The length of the corridor should be marked every 3 meters. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60 meter lap, should be marked on the floor using brightly colored tape.

Required Equipment:

- Countdown timer (or stopwatch)
- Mechanical lap counter
- Two small cones to mark the turnaround points
- A chair that can be easily moved along the walking course
- Worksheets (to be provided) on a clipboard
- A source of oxygen
- Sphygmomanometer
- Automated electronic defibrillator

Testing:

Patient Preparation:

- Comfortable clothing should be worn
- Appropriate shoes for walking should be worn
- Patients should use their usual walking aids during the test (cane, walker, etc.)
- The patient's usual medical regimen should be continued on testing days
- A light meal is acceptable before early morning or early afternoon tests, at least 2 hours before testing

Patients should not have smoked or exercised vigorously within 2 hours of beginning the test

Testing Conditions:

- The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure and make sure that clothing and shoes are appropriate.
- To reduce the variability of the 6MWTs, it is of utmost importance that the eligibility tests (Screening and Baseline) and all following 6MWTs are performed under the same conditions:
    - The same tester should administer the 6MWT for a given patient throughout the trial whenever possible
    - The same time of day for conducting the 6MWT for a given patient should be used whenever possible to minimize intra-day variability
    - Patients who used walking aids at the eligibility tests (Screening and Baseline, e.g., cane or walker) need to use the same walking aids at every subsequent 6MWT
        - Site staff will need to document if a walking aid (and what type) was used at each test, if applicable
- If the patient normally requires supplemental oxygen when walking, then the test should be performed on the patient's "usual" walking oxygen flow rate at Baseline and during all subsequent 6MWTs whenever possible. If the patient usually breathes room air while walking, they should perform the test on room air.
    - Patients who add supplemental oxygen after the Baseline Visit should walk without oxygen during subsequent walk tests whenever possible so that data will be comparable to baseline conditions. However, if this is not possible (from a patient safety perspective) then the 6MWT may be conducted with the supplemental oxygen and this should be noted in the electronic case report form (eCRF).
    - For patients on supplemental oxygen at Baseline, if the oxygen flow rate must be increased during the trial due to worsening gas exchange, 6MWTs should be conducted using the same oxygen flow rate that was used at the Baseline Visit whenever possible. However, if this is not possible (from a patient safety perspective) then the 6MWT may be conducted at the increased flow rate and this should be noted in the eCRF.
    - If the patient reduces or discontinues supplemental oxygen use during the study, the patient should still perform the 6MWT with the same oxygen flow rate that was used at the Baseline Visit.

Instructions for the Patient and Test Administrator:

- A "warm-up" period should <u>not</u> be performed before the test
- Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment and move to the starting point.
- The Tester/Investigator should stand near the starting line during the test but should <u>not</u> walk with the patient. Patients will be instructed to walk alone, not run, from one end of the

walking course to the other, at their own pace, while attempting to cover as much ground as possible in 6 minutes.

- The tester should not influence the walking pace of the patient.
- During the walk, the patients will be allowed to stop intermittently and stand or sit, or lean against the wall, to rest if the patient can no longer continue, but they should resume walking as soon as they feel able to do so (see below for instructive language that should be used in this instance). The clock must continue to run during the brief rests.
- The Tester can stop the test at any time for safety-related reasons (e.g., chest pain, intolerable dyspnea, leg cramps, pale or ashen-looking appearance).

Patient Instructions <u>Before</u> the Test - The person administering the test will use the following dialog with the patient immediately before the test (repeat the entire set of instructions if the patient does not seem to understand):

  - "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest, as necessary. You may lean against the wall while resting but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation." (*The tester then demonstrates by walking one lap and pivots around a cone briskly*).
  - "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog." (*The tester should position the patient at the starting line and ask the patient if he/she has any questions about the test and should confirm that the patient understands what he/she is expected to do. Repeat the entire set of instructions if the patient does not seem to understand).*
  - "Start now, or whenever you are ready."

- **Patient Instructions <u>During</u> the Test** – As soon as the patient starts to walk, start the timer. The person administering the test should not walk with the patient. The Tester should not talk to anyone during the testing. Only standardized phrases for encouragement can be used during the test. To best ensure reproducibility and consistency of the testing, standardized phrases should be used every minute according to the following pattern:
  - After the 1st minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."
  - When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."
  - When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."
  - When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

- When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."
- Do not use other words of encouragement or body language to get the patient to speed up.
- If the patient is slowing down, stops or expresses that he/she wants to stop, the tester should say: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer.
- If the patient stops before the 6 minutes are up and refuses to continue (or the Tester decides that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.
- When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are, and I will come to you." When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Mark the spot where they stopped.
- If the patient walked for less than 6 minutes (i.e., stops prior to 6 minutes and does not start again), record the time walked as well as the distance.

- **Post-Test Procedures:**
  - The Tester will record the number of laps from the counter and the additional distance covered (the number of meters in the final lap). Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
  - Following the 6MWT, the Tester will always obtain and record the post-walk Borg Dyspnea Score.

Reference: (ATS, 2012)

APPENDIX 7. BORG SCALE AND INSTRUCTIONS

Instructions: Use this rating scale to report how strong your perception is. It can be exertion, pain or something else. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or ”Extremely strong”, “Maximal” is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is “Very weak”, you should say “1”, if it is “Moderate”, say “3”. Note that “Moderate” is “3” and thus weaker than “Medium”, “Mean” or “Middle”. If the experience is “Strong” or “Heavy” (it feels “Difficult”) say “5”. Note that “Strong” is about half of “Maximal”. If your feeling is “Very strong”, choose a number from 6 to 8. If your perception or feeling is stronger than ”10”, - “Extremely strong”, “Maximal” – you can use a larger number, e.g. 12 or still higher (that’s why “Absolute maximum” is marked with a dot.

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 ”Nothing at all”, means that you don’t feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 “Very weak” means a very light exertion. As taking a shorter walk at your own pace.

3 “Moderate” is somewhat but not especially hard. It feels good and not difficult to go on.

5 “Strong”. The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as “Maximal”.

7 “Very strong” is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 “Extremely strong – Maximal” is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

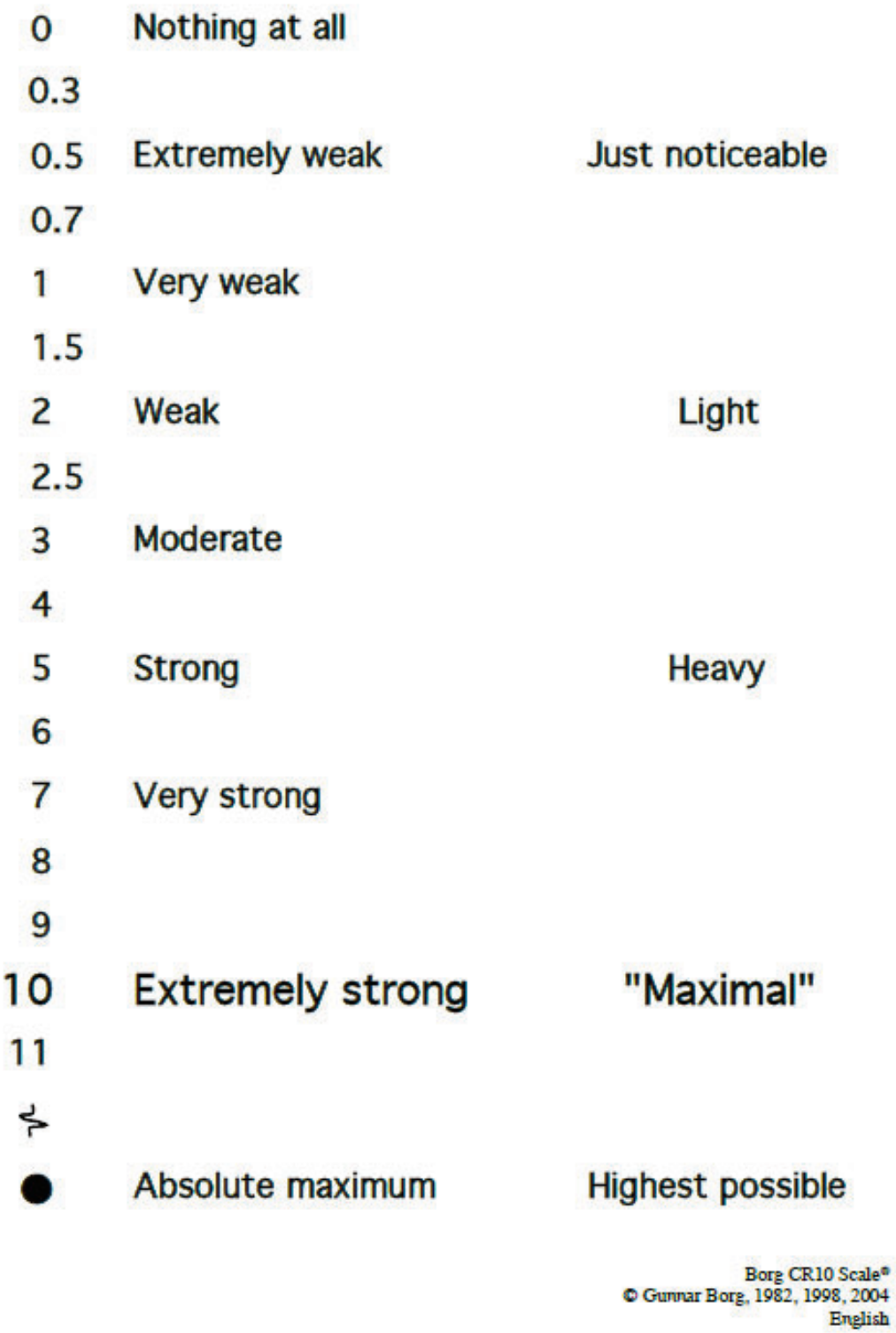
● Is ”Absolute maximum” for example ”12” or even more.

Any questions?

Borg CR10 scale®

English

Borg Scale



APPENDIX 8. WORLD HEALTH ORGANIZATION FUNCTIONAL CLASSIFICATION OF PULMONARY HYPERTENSION

CLASS	DESCRIPTION
Class I	Patients with pulmonary hypertension (PH) but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Reference: (Klinger et al., 2019)

APPENDIX 9. PULMONARY ARTERIAL HYPERTENSION-SYMPTOMS AND IMPACT™ QUESTIONNAIRE

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™)
Questionnaire

INSTRUCTIONS

Each day you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms**.

On the 7th day you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USori.docx

DAY 1 to DAY 6

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™)
Questionnaire

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USori.docx

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Questionnaire

SYMPTOMS

1. In the past 24 hours …

   Did you use oxygen?
   ☐0 No
   ☐1 Yes If yes: How many hours? _____

Answer the questions that follow based on your experiences **regardless of whether you were using oxygen or not.**

2. In the past 24 hours …

   How would you rate your **shortness of breath**?
   ☐0 No shortness of breath at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

3. In the past 24 hours …

   How would you rate your **fatigue**?
   ☐0 No fatigue at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

4. In the past 24 hours …

   How would you rate your **lack of energy**?
   ☐0 No lack of energy at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

5. In the past 24 hours …

   How would you rate the **swelling in your ankles or legs**?
   ☐0 No swelling in ankles or legs at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

6. In the past 24 hours …

   How would you rate the **swelling in your stomach area**?
   ☐0 No swelling in stomach area at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USori.docx

Pulmonary **A**rterial **H**ypertension-**Sym**ptoms and Im**pact** (**PAH-SYMPACT™**) Questionnaire

7. In the past 24 hours ...

   How would you rate your **cough**?
   ☐0 No cough at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

8. In the past 24 hours ...

   How would you rate your **heart palpitations (heart fluttering)**?
   ☐0 No heart palpitations (heart fluttering) at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

9. In the past 24 hours ...

   How would you rate your **rapid heartbeat**?
   ☐0 No rapid heartbeat at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

10. In the past 24 hours ...

    How would you rate your **chest pain**?
    ☐0 No chest pain at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

11. In the past 24 hours ...

    How would you rate your **chest tightness**?
    ☐0 No chest tightness at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

12. In the past 24 hours ...

    How would you rate your **lightheadedness**?
    ☐0 No lightheadedness at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USori.docx

DAY 7

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Questionnaire

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USori.docx

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Questionnaire

SYMPTOMS

13. In the past 24 hours …

Did you use oxygen?
☐0 No
☐1 Yes If yes: How many hours? _____

Answer the questions that follow based on your experiences **regardless of whether you were using oxygen or not.**

14. In the past 24 hours …

How would you rate your **shortness of breath**?
☐0 No shortness of breath at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

15. In the past 24 hours …

How would you rate your **fatigue**?
☐0 No fatigue at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

16. In the past 24 hours …

How would you rate your **lack of energy**?
☐0 No lack of energy at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

17. In the past 24 hours …

How would you rate the **swelling in your ankles or legs**?
☐0 No swelling in ankles or legs at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

18. In the past 24 hours …

How would you rate the **swelling in your stomach area**?
☐0 No swelling in stomach area at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USxx.docx

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Questionnaire

19. In the past 24 hours ...

How would you rate your **cough**?
- ☐0 No cough at all
- ☐1 Mild
- ☐2 Moderate
- ☐3 Severe
- ☐4 Very Severe

20. In the past 24 hours ...

How would you rate your **heart palpitations (heart fluttering)**?
- ☐0 No heart palpitations (heart fluttering) at all
- ☐1 Mild
- ☐2 Moderate
- ☐3 Severe
- ☐4 Very Severe

21. In the past 24 hours ...

How would you rate your **rapid heartbeat**?
- ☐0 No rapid heartbeat at all
- ☐1 Mild
- ☐2 Moderate
- ☐3 Severe
- ☐4 Very Severe

22. In the past 24 hours ...

How would you rate your **chest pain**?
- ☐0 No chest pain at all
- ☐1 Mild
- ☐2 Moderate
- ☐3 Severe
- ☐4 Very Severe

23. In the past 24 hours ...

How would you rate your **chest tightness**?
- ☐0 No chest tightness at all
- ☐1 Mild
- ☐2 Moderate
- ☐3 Severe
- ☐4 Very Severe

24. In the past 24 hours ...

How would you rate your **lightheadedness**?
- ☐0 No lightheadedness at all
- ☐1 Mild
- ☐2 Moderate
- ☐3 Severe
- ☐4 Very Severe

PAH-SYMPACT – United States/English – Original
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Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Questionnaire

IMPACTS

For the following questions, please select the answer that best describes how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**. Answer the questions based on your experiences regardless of whether you were using oxygen or not.

1. In the past 7 days …

   Were you able to **walk slowly on a flat surface**?
   - ☐0 Yes, with no difficulty at all
   - ☐1 Yes, with a little difficulty
   - ☐2 Yes, with some difficulty
   - ☐3 Yes, with much difficulty
   - ☐4 No, not able at all

2. In the past 7 days …

   Were you able to **walk quickly on a flat surface**?
   - ☐0 Yes, with no difficulty at all
   - ☐1 Yes, with a little difficulty
   - ☐2 Yes, with some difficulty
   - ☐3 Yes, with much difficulty
   - ☐4 No, not able at all

3. In the past 7 days …

   Were you able to **walk uphill**?
   - ☐0 Yes, with no difficulty at all
   - ☐1 Yes, with a little difficulty
   - ☐2 Yes, with some difficulty
   - ☐3 Yes, with much difficulty
   - ☐4 No, not able at all

4. In the past 7 days …

   Were you able to **carry things**, such as bags or baskets?
   - ☐0 Yes, with no difficulty at all
   - ☐1 Yes, with a little difficulty
   - ☐2 Yes, with some difficulty
   - ☐3 Yes, with much difficulty
   - ☐4 No, not able at all

5. In the past 7 days …

   Were you able to **do light indoor household chores**, such as preparing food, cleaning surfaces, or tidying up?
   - ☐0 Yes, with no difficulty at all
   - ☐1 Yes, with a little difficulty
   - ☐2 Yes, with some difficulty
   - ☐3 Yes, with much difficulty
   - ☐4 No, not able at all

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PAH-SYMPACT_AU2.1_eng-USen.docx

Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Questionnaire

6. In the past 7 days ...

Were you able to **wash or dress yourself**?
☐0 Yes, with no difficulty at all
☐1 Yes, with a little difficulty
☐2 Yes, with some difficulty
☐3 Yes, with much difficulty
☐4 No, not able at all

7. In the past 7 days ...

How much did you **need help from others**?
☐0 Not at all
☐1 A little bit
☐2 Some
☐3 Quite a bit
☐4 Very much

8. In the past 7 days ...

Were you able to **think clearly**?
☐0 Yes, with no difficulty at all
☐1 Yes, with a little difficulty
☐2 Yes, with some difficulty
☐3 Yes, with much difficulty
☐4 No, not able at all

9. In the past 7 days ...

How **sad** did you feel?
☐0 Not at all
☐1 A little bit
☐2 Somewhat
☐3 Very
☐4 Extremely

10. In the past 7 days ...

How **worried** did you feel?
☐0 Not at all
☐1 A little bit
☐2 Somewhat
☐3 Very
☐4 Extremely

11. In the past 7 days ...

How **frustrated** did you feel?
☐0 Not at all
☐1 A little bit
☐2 Somewhat
☐3 Very
☐4 Extremely

PAH-SYMPACT – United States/English – Original
PAH-SYMPACT_AU2.1_eng-USori.docx

APPENDIX 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE

BASELINE/SCREENING VISIT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation* Past X Months - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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Page 2 of 2

SINCE LAST VISIT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___

C-SSRS—Since Last Visit (Version 1/14/09)

Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 11. HOSPITAL ANXIETY AND DEPRESSION SCORE (HADS)

Hospital Anxiety and Depression Scale (HADS)

GL assessment

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL	☐	☐

APPENDIX 12. CLINICIAN-RATED QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY

NAME: _____ TODAY'S DATE: _____

Please circle one response to each item that best describes the patient for the last seven days.

1. Sleep Onset Insomnia:

0 Never takes longer than 30 minutes to fall asleep.
1 Takes at least 30 minutes to fall asleep, less than half the time.
2 Takes at least 30 minutes to fall asleep, more than half the time.
3 Takes more than 60 minutes to fall asleep, more than half the time.

2. Mid-Nocturnal Insomnia:

0 Does not wake up at night.
1 Restless, light sleep with few awakenings.
2 Wakes up at least once a night, but goes back to sleep easily.
3 Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.

3. Early Morning Insomnia:

0 Less than half the time, awakens no more than 30 minutes before necessary.
1 More than half the time, awakens more than 30 minutes before need be.
2 Awakens at least one hour before need be, more than half the time.
3 Awakens at least two hours before need be, more than half the time.

4. Hypersomnia:

0 Sleeps no longer than 7-8 hours/night, without naps.
1 Sleeps no longer than 10 hours in a 24 hour period (include naps).
2 Sleeps no longer than 12 hours in a 24 hour period (include naps).
3 Sleeps longer than 12 hours in a 24 hour period (include naps).

Enter the highest score on any 1 of the 4 sleep items (1–4 above) _____

5. Mood (Sad):

0 Does not feel sad.
1 Feels sad less than half the time.
2 Feels sad more than half the time.
3 Feels intensely sad virtually all the time.

6. Appetite (Decreased):

0 No change from usual appetite.
1 Eats somewhat less often and/or lesser amounts than usual.
2 Eats much less than usual and only with personal effort.
3 Eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others.

7. Appetite (Increased):

0 No change from usual appetite.
1 More frequently feels a need to eat than usual.
2 Regularly eats more often and/or greater amounts than usual.
3 Feels driven to overeat at and between meals.

8. Weight (Decrease) Within The Last Two Weeks:

0 Has experienced no weight change.
1 Feels as if some slight weight loss occurred.
2 Has lost 2 pounds or more.
3 Has lost 5 pounds or more.

9. Weight (Increase) Within the Last Two Weeks:

0 Has experienced no weight change.
1 Feels as if some slight weight gain has occurred.
2 Has gained 2 pounds or more.
3 Has gained 5 pounds or more.

Enter the highest score on any 1 of the 4 appetite/weight change items (6–9 above) _____

10. Concentration/Decision Making:
    - 0 No change in usual capacity to concentrate and decide.
    - 1 Occasionally feels indecisive or notes that attention often wanders.
    - 2 Most of the time struggles to focus attention or make decisions.
    - 3 Cannot concentrate well enough to read or cannot make even minor decisions.

11. Outlook (Self):
    - 0 Sees self as equally worthwhile and deserving as others.
    - 1 Is more self-blaming than usual.
    - 2 Largely believes that he/she causes problems for others.
    - 3 Ruminates over major and minor defects in self.

12. Suicidal Ideation:
    - 0 Does not think of suicide or death.
    - 1 Feels life is empty or is not worth living.
    - 2 Thinks of suicide/death several times a week for several minutes.
    - 3 Thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide.

13. Involvement:
    - 0 No change from usual level of interest in other people and activities.
    - 1 Notices a reduction in former interests/activities.
    - 2 Finds only one or two former interests remain.
    - 3 Has virtually no interest in formerly pursued activities.

14. Energy/Fatiguability:
    - 0 No change in usual level of energy.
    - 1 Tires more easily than usual.
    - 2 Makes significant personal effort to initiate or maintain usual daily activities.
    - 3 Unable to carry out most of usual daily activities due to lack of energy.

15. Psychomotor Slowing:
    - 0 Normal speed of thinking, gesturing, and speaking.
    - 1 Patient notes slowed thinking, and voice modulation is reduced.
    - 2 Takes several seconds to respond to most questions; reports slowed thinking.
    - 3 Is largely unresponsive to most questions without strong encouragement.

16. Psychomotor Agitation:
    - 0 No increased speed or disorganization in thinking or gesturing.
    - 1 Fidgets, wrings hands and shifts positions often.
    - 2 Describes impulse to move about and displays motor restlessness.
    - 3 Unable to stay seated. Paces about with or without permission.

Enter the highest score on either of the 2 psychomotor items (15 or 16 above) ____

Scoring		Interpretation	
Enter the highest score on any 1 of the 4 sleep items (1 – 4)	____	Normal	0 – 5
Item 5	____	Mild	6 – 10
Enter the highest score on any 1 appetite / weight item (6 – 9)	____	Moderate	11 – 15
Item 10	____	Severe	16 – 20
Item 11	____	Very Severe	21+
Item 12	____		
Item 13	____		
Item 14	____		
Enter the highest score on either of the 2 psychomotor items (15 and 16)	____		
Total Score (Range 0 – 27)	____		

APPENDIX 13. REVEAL LITE 2.0 (BENZA ET AL., 2020)

REVEAL Lite 2 is based on REVEAL 2.0, but includes only six noninvasive and modifiable parameters:

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

FC I = -1, FC II = 0, FC III = +1, FC IV = +2

2. Systolic BP;

SBP < 110 mm Hg = + 1, SBP ≥ 110 = 0

3. Heartrate

HR > 96 bpm= + 1, HR ≤ 96 = 0

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

≥ 440 min = -2,
320 - 440 min = -1
165 – 319 = 0
<165 min = +1

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

BNP < 50 pg/mL OR NT-proBNP < 300 pg/mL = -2
BNP 50 – 199 pg/mL = 0
BNP 200 - 799 pg/mL = +1
BNP ≥800 pg/mL OR NT-proBNP ≥1100 pg/mL:+2

6. Renal insufficiency: if estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m2 or reported as “renal insufficiency,” as assessed by the principal investigator when eGFR was unavailable +1); If ≥ 60 then score is 0

For the REVEAL Lite 2 assessment (with scores ranging from 1 to 14);

a score between 1 and 5 was considered low risk,
a score of 6 or 7 was considered intermediate risk,
a score of 8 or higher was considered high risk.

APPENDIX 14. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATION, FOLLOW UP, AND REPORTING

Definition of Adverse Event

Adverse Event Definition

- An adverse event (AE) is any untoward medical occurrence in a patient, temporally associated with the use of investigational product (IP), whether or not considered related to the IP.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IP administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the case report form.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Sponsor in lieu of completion of the AE/SAE case report form page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**

Assessment of Causality

- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow Up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed case report form.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found on the Contact Information page.

Serious Adverse Event Reporting to the Sponsor via Paper Case Report Form

- Email transmission of the SAE paper case report form is the preferred method to transmit this information to the Sponsor's Medical Monitor or the SAE Coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE case report form pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the Contact Information page.