Official Protocol Title:	A Phase 2a Single-Arm, Open-Label, Multicenter Exploratory Study to Assess the Effects of Sotatercept (ACE-011) for the Treatment of Pulmonary Arterial Hypertension
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Protocol A011-10

Protocol Title:

A Phase 2a Single-Arm, Open-Label, Multicenter Exploratory Study to Assess the Effects of Sotatercept (ACE-011) for the Treatment of Pulmonary Arterial Hypertension

Short Title:

A Phase 2a Open-Label Exploratory Study of Sotatercept for the Treatment of PAH

SPONSOR: Acceleron Pharma Inc.
128 Sidney Street
Cambridge, MA 02139 USA
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Regulatory Agency Identifying Number(s): IND 136150

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PROTOCOL AMENDMENT 03A:	31 October 2019
PROTOCOL AMENDMENT 04:	18 June 2020
PROTOCOL AMENDMENT 05:	12 August 2021

Signature Page

Acceleron Pharma Approval

Signature: PPD _____ **Date:** _____

Name (print): _____

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined in the protocol. The study will be conducted in accordance with current United States Food and Drug Administration (FDA) regulations, International Council for Harmonisation (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

Signature: _____ **Date:** _____

Name (print): _____

Institution Name and Address:

_____

_____

_____

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	PPD [redacted]	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 USA PPD [redacted]
Pharmacovigilance	Various	PPD Safety Hotline 3900 Paramount Parkway Morrisville, NC 27560-7200 USA Phone: 888-483-7729

Protocol Amendment Summary of Changes Table

Substantive changes from the Protocol Amendment 04 (18 June 2020) to Protocol Amendment 05 (12 August 2021) are detailed below. Minor edits are not included. See Appendix 10 for the rest of the Protocol Amendment History.

Protocol Location	Description of Change	Brief Rationale
Cover Page	Added: PROTOCOL AMENDMENT 05 Dated 12 August 2021	This is the protocol amendment identifier and release date.
Section 1, Synopsis	Participants will have the opportunity to transition into the sotatercept long-term follow-up study following completion of the third invasive cardiopulmonary exercise test (iCPET).	To clarify that participants are eligible, upon completion of the third iCPET, to transition to the sotatercept long-term follow-up study.
Section 2, Schedule of Events	Added footnote to the Schedule of Events for the Extension Period (Table 4).	To clarify that participants who complete the third iCPET and consent to the sotatercept long-term follow-up study will be asked to complete the End of Treatment Visit only.
Section 4.7, Follow-Up Period	Combined subsections 4.7.1. (End of Treatment or Discontinuation of Study Drug; End of Study) and 4.7.2. (Extension Period)	To simplify definition of Follow-Up Period.
Section 4.9, End of Study Definition	End of Study (EOS) visits are only required for participants who discontinue the study early or decline transition to the sotatercept long-term follow-up study.	To clarify EOS requirement for early discontinuation or declining transition to the sotatercept long-term follow-up study.
Section 8.2.1, Efficacy Assessments, iCPET	Updated iCPET being performed at Cycle 14 to Cycle 17	Revised to correct Cycle timepoint

EOS = End of Study; iCPET = Invasive Cardiopulmonary Exercise Test

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1. SYNOPSIS

Protocol Title

A Phase 2a Single-Arm, Open-Label, Multicenter Exploratory Study to Assess the Effects of Sotatercept (ACE-011) for the Treatment of Pulmonary Arterial Hypertension

Short Title

A Phase 2a Open-Label Exploratory Study of Sotatercept for the Treatment of PAH

Clinical Sites

Approximately five clinical sites in the United States.

Rationale

Study A011-10 is a Phase 2a, single-arm, open-label, multicenter exploratory study to determine the effects of sotatercept (ACE-011) in adults with World Health Organization (WHO) Group 1 functional class III pulmonary hypertension or pulmonary arterial hypertension (PAH). These patients experience marked limitations in physical activity and are at significant risk for disease progression and death.[1] Data from rodent models of PAH suggest that treatment with sotatercept may reduce muscularization and thickness of pulmonary vessel walls, right-sided heart pressures, and right-to-left ventricle weight ratios.[2] These improvements may be accompanied by reductions in pulmonary vascular resistance as well as increases in functional capacity, and right ventricular mechanics and function, all of which will be measured during the study.

The main objectives and endpoints for this study are found in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of sotatercept on an invasive cardiopulmonary exercise test (iCPET) measure in PAH patients treated with sotatercept plus standard of care (SOC)	Change from baseline in VO_2 max at 24 weeks
Secondary	
• To evaluate the effect of sotatercept on additional measures in PAH patients treated with sotatercept plus SOC • To evaluate effects of sotatercept on right ventricular stroke volume (RV SV), RV end-systolic volume (RV ESV), RV end-diastolic volume (RV EDV), RV ejection fraction (RV EF), RV stroke volume index (RV SVI), and RV mass in PAH patients treated with sotatercept plus SOC	• Exercise measures, including change in VE/VCO_2 slope (ventilatory efficiency), cardiac index, mean pulmonary arterial pressure, and $Ca\text{-}vO_2$ (arteriovenous O_2 content difference) at 24 weeks • Change from baseline in RV SV, RV ESV, RV EDV, RV EF, RV SVI, and RV mass by cardiac magnetic resonance (MR) imaging at 24 weeks

iCPET = invasive cardiopulmonary exercise test; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RV EDV = right ventricular end-diastolic volume; RV EF = right ventricular ejection fraction; RV ESV = right ventricular end-systolic volume; RV SV = right ventricular stroke volume; RV SVI = right ventricular stroke volume index; SOC = standard of care; VO_2=peak oxygen uptake.

Overall Design

This is a Phase 2a, single-arm, open-label, multicenter, exploratory study assessing the efficacy and safety of sotatercept for the treatment of WHO Group 1 functional class III PAH.

Number of Participants

Approximately 25 participants will be enrolled.

Treatment Groups and Duration

Each eligible participant will receive standard of care (SOC) plus sotatercept at a dose of 0.3 mg/kg SC for Cycle 1 and escalating to 0.7 mg/kg at Cycle 2 and for the remainder of the treatment period. Dosing will be every 3 weeks for 24 weeks. During the Extension Period, sotatercept dosing will be every 3 weeks for 18 months.

Standard of care (SOC) therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5 (PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist. Patients receiving monotherapy are not to be enrolled.

During the Extension Period, participants under investigator's supervision can substitute, remove, or adjust the dose of SOC for PAH-worsening and chronic concomitant medications,

including supplemental oxygen. Investigator discretion will be used to determine if sotatercept study drug discontinuation is necessary. Additional SOC details can be found in Section 4.3 and Appendix 3.

The study is divided into the Screening Period of up to 28 days, a Treatment Period of 24 weeks, followed by an 18-month Extension Period and an 8-week Follow-Up Period.

Participants will have the opportunity to transition into the sotatercept long-term follow-up study following the completion of the third invasive cardiopulmonary exercise test (iCPET).

2. SCHEDULE OF EVENTS

Table 3: Schedule of Events

	Screening Period (up to 28 days before Cycle 1 Day 1)	Treatment Period (24 Weeks)[1]									
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6-7	Cycle 8	Cycle 9
		Day 1 ±3 days	Day 8 ±3 days	Day 22 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 64 ±3 days	Day 85 ±3 days	Day 106; Day 127 ±3 days	Day 148 ±3 days	Day 169 ±3 days
Informed consent	X										
Inclusion/ exclusion criteria	X										
Medical history	X										
Physical examination[2]	X	X		X		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[3]	X	X		X		X	X	X	X	X	X
Hematology[4]	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X		X		X	X	X	X	X	X
Urinalysis		X						X			X
12-lead ECG	X	X		X							
Pulmonary tests[5]	X										
Anti-drug antibody (ADA)		X		X		X	X	X	X	X	X
Genetic sample		X									
Cardiac MR[6]	X										X
6MWT[7]	X							X			X
RHC + CPET (iCPET)[8]	X										X

	Screening Period (up to 28 days before Cycle 1 Day 1)	Treatment Period (24 Weeks)[1]									
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6-7	Cycle 8	Cycle 9
		Day 1 ±3 days	Day 8 ±3 days	Day 22 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 64 ±3 days	Day 85 ±3 days	Day 106; Day 127 ±3 days	Day 148 ±3 days	Day 169 ±3 days
Transpulmonary flux biomarkers[9]	X										X
WHO Functional Class Assessment	X	X		X		X	X	X	X	X	X
Clinical worsening		X		X		X	X	X	X	X	X
PK collection		X		X		X		X		X	X
PD blood biomarkers		X		X				X		X	X
Study drug administration[10]		X		X		X	X	X	X	X	X
AE/SAE review[11]	X[11]	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; CTPA = computed tomography pulmonary angiogram; ECG = electrocardiogram; eCRF = electronic case report form; Hgb = hemoglobin; iCPET = invasive cardiopulmonary exercise test; MR = magnetic resonance; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RHC = right heart catheterization; SAE = serious adverse event; VQ = ventilation-perfusion; WHO = World Health Organization.

[1] All visit day windows should be considered relative to the date of the previous dose of study drug. Cycles are every 3 weeks (±3 days) and there must be at least 7 days between each dose.

[2] A full physical examination should be completed at the Screening visit. A targeted cardiopulmonary examination should be completed at all other indicated visits.

[3] Pregnancy test (urine or serum) is required for female participants of childbearing potential at Screening and prior to each dose of study drug (see Appendix 8 for information regarding pregnancy follow-up).

[4] Results from the hematology panel should be evaluated prior to study drug administration. For C1D1 and C2D22 visits, blood samples should be taken and assessed for Hgb levels on the same day as study drug administration. For all other dosing cycles, blood samples may be taken and assessed for Hgb levels on the same day as study drug administration or 1 day prior to dosing. If Hgb is ≥ 17.0 g/dL during Cycles 1 and 2, participant should return weekly for Hgb monitoring (and continue to follow Dose Modification Guidance for dosing days [Section 6.3]).

[5] Additional screening procedures to include pulmonary function tests and VQ/CT pulmonary angiogram (CTPA) or pulmonary angiography as per inclusion criteria 5 and 6 (Section 5.1), if historical readings are unavailable.

[6] Cardiac MR and iCPET may be done on separate days. If performed on the same day, iCPET should be performed before cardiac MR, with ≥ 1-hour interval between procedures.
[7] 6MWT: to be performed twice during the Screening Period at least 4 hours (but no longer than 1 week) apart and distances must be within 15% of each other, calculated from the higher number.
[8] RHC with CPET (iCPET) to be completed within 10 days prior to Cycle 1, Day 1. A participant will not receive more than 3 iCPET assessments during the study. If other assessments are occurring on the same day, iCPET should be performed after all other procedures (Exception: cardiac MR).
[9] Transpulmonary flux biomarkers will be collected during iCPET as described in Section 8.7.
[10] Study procedures and sample collection must be done prior to administration of study drug. Dosing: The dose must be calculated based on the participant's weight on the day of dosing. Dose-modification guidelines must be reviewed and implemented prior to dosing as required per protocol (see Section 6.3).
[11] AEs and SAEs occurring after the signing of the informed consent form and before Cycle 1, Day 1 will be reported and documented on the AE eCRF. If related to protocol procedures (S)AEs should be indicated as such in the eCRF.

Table 4: Schedule of Events: Extension and Follow-Up Periods

	Extension Period (18 Months)[1]						Follow-Up Period (8 Weeks)	
	Cycle 10	Cycles 11-13	Cycle 14	Cycles 15-16, 18-20, 22-24, 26-28, 30-33	Cycle 17	Cycles 21, 25, 29, 34[2]	End of Treatment[11] At time of early discontinuation or 4 weeks (±7 days) post last dose of study drug	End of Study 8 weeks (±7 days) post last dose of study drug
	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	(±7 days)	(±7 days)
Physical examination[2]	X	X	X	X	X	X	X	X
Vital signs (including weight)	X	X	X	X	X	X	X	X
Pregnancy test[3]	X	X	X	X	X	X		
Hematology[4]	X	X	X	X	X	X	X	X
Serum chemistry	X		X		X	X	X	X
Urinalysis	X		X		X	X	X	X
12-lead ECG	X		X		X	X	X	X
Anti-drug antibody (ADA)[5]	X		X			X		X
Cardiac MR[6]					X			
6MWT	X		X		X	X	X	X
RHC + CPET (iCPET)[6,7]					X			
Transpulmonary flux biomarkers[8]					X			
WHO Functional Class Assessment	X	X	X	X	X	X	X	X
Clinical worsening	X	X	X	X	X	X	X	X
PD blood biomarkers	X		X			X		X
Study drug administration[9]	X	X	X	X	X	X		
AE/SAE review[10]	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; CPET = cardiopulmonary exercise test; ECG = electrocardiogram; eCRF = electronic case report form; EOT = end of treatment; Hgb = hemoglobin; iCPET = invasive cardiopulmonary exercise test; MR = magnetic resonance; PD = pharmacodynamics; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

[1] All visit day windows should be considered relative to the date of the previous dose of study drug. Cycles are every 21 days (±3 days).

[2] Targeted cardiopulmonary examination only.

[3] Pregnancy test (urine or serum) is required for female participants of childbearing potential prior to each dose of study drug (see Appendix 8 for pregnancy follow-up).

[4] Results from the hematology panel should be evaluated prior to study drug administration. For all dosing cycles, blood samples may be taken and assessed for Hgb levels on the same day as study drug administration or 1 day prior to dosing. If Hgb is ≥ 17.0 g/dL, participants should return weekly for Hgb monitoring (and continue to follow Dose Modification guidance for dosing days [Section 6.3]).

[5] If a participant has a positive ADA result at the EOT assessment, the participant may be asked to return approximately every 3 months for additional testing, until a negative result is obtained or the result is considered stabilized.

[6] Cardiac MR and iCPET may be done on separate days. If performed on the same day, iCPET should be performed before cardiac MR, with ≥ 1-hour interval between procedures.

[7] A participant will not receive more than 3 iCPET assessments during the study. The iCPETs, 2 in the Treatment Period and 1 in the Extension Period, must occur within 10 days prior to Cycle 1 (during the Screening Period), and within 10 days prior to Cycle 9 (during treatment period), and Cycle 14 during the Extension Period. For patients discontinuing the study prior to Cycle 9, an iCPET should be performed ± 10 days of the EOT visit. The third iCPET is to be performed at the time of early discontinuation if prior to Cycle 14. If other assessments are occurring on the same day, the iCPET should be performed after all other procedures (Exception: cardiac MR imaging).

[8] Transpulmonary flux biomarkers will be collected during iCPET as described in Section 8.7.

[9] Study procedures should be done prior to administration of study drug. Dose must be calculated based on the participant's weight on the day of dosing. Dose modification Guidance must be reviewed and implemented prior to dosing (Section 6.3).

[10] AEs and SAEs occurring after the signing of the informed consent form will be reported and documented on the AE eCRF. If related to protocol procedures, (S)AEs should be indicated as such in the eCRF.

[11] Participants who complete the third iCPET and consent to the sotatercept long-term follow-up study will be asked to complete the EOT Visit only.

3. INTRODUCTION

Pulmonary arterial hypertension (PAH) represents a group of diseases causing a progressive increase in pulmonary vascular resistance (PVR), resulting in right ventricular dysfunction and ultimately failure as well as premature death.[3,4] PAH pathophysiology involves pulmonary endothelial dysfunction, resulting in impaired production of vasodilators, such as nitric oxide and prostacyclin, and overexpression of vasoconstrictors, such as endothelin-1. The pathophysiology of PAH also entails the abnormal proliferation of pulmonary vascular smooth muscle cells (VSMCs) in pulmonary arterioles, which results in progressive pulmonary vascular remodeling, increased pulmonary vascular resistance and, eventually, right-sided heart failure.[5] In the absence of treatment, the majority of patients succumb to heart failure within a few years of diagnosis.[6] There is currently no pharmacological cure for PAH; treatment involves relieving symptoms by increasing blood flow through the pulmonary vasculature through pharmacologic manipulation of various pathways and slowing clinical worsening of the disease. Current disease-specific treatments for PAH include vasodilator-type agents such as endothelin-receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors, and prostanoids and are used to supplement general supportive care agents (e.g., anticoagulants, diuretics, digoxin).

Genetic mutations in the bone morphogenetic protein type II receptor (BMPR2) are associated with the majority of the familial forms of PAH[7,8] and approximately 25% of idiopathic PAH. Specifically, impairment of the BMPR2-associated signal pathway appears to lead to uncontrolled proliferation of pulmonary VSMCs. These data strongly suggest a key role of transforming growth factor-beta (TGF-β) superfamily members in the pathogenesis of PAH.

Sotatercept (ACE-011) is a first-in-class human fusion protein consisting of the extracellular domain of the activin receptor type IIA (ActRIIA) linked to the Fc domain of human immunoglobulin G1 (IgG1). Sotatercept works by targeting molecules in the TGF-β superfamily, which includes activins, growth and differentiation factors (GDFs), and BMPs. Sotatercept may improve pulmonary vascular remodeling by restoring balance to SMAD signaling.[8]

3.1. Study Rationale

Study A011-10 is a Phase 2a, single-arm, open-label, multicenter exploratory study to determine the effects of sotatercept (ACE-011) in adults with World Health Organization (WHO) Group 1 PAH.

This study is designed to evaluate whether sotatercept has the potential to modify the clinical course of PAH, as assessed by changes in various measures obtained in invasive cardiopulmonary exercise testing (iCPET), various imaging parameters collected via cardiac magnetic resonance (MR) imaging, and correlation with other functional measures and assessments of clinical worsening.

3.2. Rationale for Patient Population

Patients with WHO Group 1 pulmonary hypertension (i.e., PAH associated with idiopathic, heritable, drug-induced, connective tissue diseases, or post-shunt correction) and meet the WHO functional assessment definition for Class III PAH will be the population studied.

The WHO Functional Classification[9] (FC) is based on an assessment of the degree of physical activity limitation due primarily to associated dyspnea:

- FC I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
- FC II: Patients with pulmonary hypertension resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
- FC III: Patients with pulmonary hypertension 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.
- FC IV: Patients with pulmonary hypertension 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.

Previously diagnosed patients in FC I, II, III, and IV had an estimated 5-year survival rate of 88.0%, 75.6%, 57.0%, and 27.2%, respectively, compared with 72.2%, 71.7%, 60.0%, and 43.8% for newly diagnosed patients in FC I, II, III, and IV, respectively.[1]

Patients with functional class III PAH comprise approximately half of all previously diagnosed PAH patients in the REVEAL registry.[1] It is expected that the treatment effect of sotatercept can be more easily ascertained in this population. Patients with functional class I PAH are typically excluded from interventional studies due to their relative low identification rate, low prevalence, and mild symptomatology. Patients with functional class II PAH are typically enrolled in PAH studies, but are not as impaired physiologically, thus a treatment effect may be more challenging to ascertain compared with functional class III PAH patients. There is a relatively low prevalence of patients with class IV PAH due to higher mortality and transplant rates compared with other functional classes; given their severe disease burden, these class IV patients have limited ability to participate in longer interventional studies. Eligibility criteria for this study are consistent with those of other interventional studies in this population.

3.3. Rationale for Study Endpoints

The primary endpoint of the study is the change from baseline in peak oxygen uptake (VO_2 max), as measured by cardiopulmonary exercise test (CPET). This endpoint was chosen because of the importance of VO_2 max in describing overall cardiopulmonary health, and its correlation with cardiopulmonary hemodynamics. The final common pathophysiologic pathway to account for most organic causes of exertional dyspnea involves insufficient O_2 supply to skeletal muscle or impaired uptake of O_2 by skeletal muscle cells, which, collectively, may be

attributable to abnormal cardiac, pulmonary vascular, or neuromuscular function. The integrated function of these systems is broadly assessed by measuring the peak oxygen uptake ($\dot{V}O_2$), which is calculated as the product of minute ventilation (VE) and the difference in inspired and expired fractions of O_2. Thus, a fundamental objective of noninvasive (or invasive) CPET is quantification of maximum VO_2, which is considered abnormal when < 80% of predicted for the patient's age, gender, and height.[10]

In a study of patients with WHO Group 2 pulmonary hypertension and systolic heart failure (mean [standard deviation (SD)] age 58 [13] years; depressed left ventricular [LV] ejection fraction [EF] 0.27 [±0.05]; and VO_2 max 11.2 [±3.2] mL/kg/min), the patients underwent incremental CPET with simultaneous hemodynamic monitoring and first-pass radionuclide ventriculography before and after 12 weeks of treatment with sildenafil, a selective pulmonary vasodilator, or placebo. Sildenafil was associated with an approximate 28% decrease in pulmonary vascular resistance (PVR), an approximate 10% increase in VO_2 and an approximate 10% decrease in VE/VCO_2.[11]

An important CPET secondary endpoint is change from baseline in ventilatory efficiency (VE/VCO_2) slope. If, as predicted by the preclinical model data, treatment with sotatercept results in modification of pulmonary vascular wall architecture, improvement in right-sided lung perfusion pressures, and reduction in right heart mechanics, then gas exchange efficiency should be improved. This should result in an improved oxygen uptake rate VO_2, as well as a reduction in pulmonary dead space and an improved ventilatory efficiency (as measured by VE/VCO_2).

Another important secondary endpoint is change in right ventricular (RV) stroke volume (SV) at 24 weeks from baseline, which is designed to assess the effect of sotatercept on RV function. Given the pivotal role RV function has in determining much of the morbidity and mortality of PAH, a significant improvement in RV function on cardiac MR imaging could demonstrate that the clinical course of the subject's PAH has been meaningfully improved. Cardiac MR imaging is particularly suitable for accurately assessing the anatomical structure as well as function of the RV, and it is regarded as the gold standard test for quantifying ventricular volume, mass, structure, and function. It is non-invasive, and does not involve the use of ionizing radiation. Cardiac MR imaging provides high-resolution, 3-dimensional images that avoid the need for the geometrical assumptions required for some calculations when using echocardiography. However, cardiac MR imaging is also associated with the following range of limitations: higher cost, more limited availability relative to other methods, the need for more intensive and time-consuming analysis, and the requirement for significant technical support and expertise. In addition, cardiac MR imaging is incompatible with pacemakers and infusion pumps, and the need for breath holding may be difficult for PAH patients. However, given the relevance of the right heart in PAH, the advantages of the method outweigh these disadvantages in the monitoring of patients with established PAH and in assessment of treatment response in clinical trials. The clinical relevance of cardiac MR imaging in PAH was demonstrated in a study of 111 PAH patients evaluating the effect of implementing standard-of-care (SOC) therapy on cardiac MR imaging assessments of changes in stroke volume and correlating them with concurrent changes in 6-minute walk distance (6MWD), a frequently used measure of activity/function in PAH patients. The study found that an improvement in RV SV of as little as 10 mL was prognostically significant and correlated with a meaningful improvement in 6MWD in PAH patients.[12]

In addition, assessment of RV SV may correlate with other functional and physiologic measures commonly assessed in treated PAH patients (e.g., cardiac index, mean pulmonary arterial pressure [PAP], VO_2 max, Ca-vO_2, VE/VCO_2 slope, PVR, and N-terminal prohormone of brain natriuretic peptide [NT-proBNP]).

Other secondary endpoints in this study include change in RV end-systolic volume (ESV), RV end-diastolic volume (EDV), change in RV EF, change in RV stroke volume index (SVI), change in RV mass by cardiac MR imaging at 24 weeks from baseline, iCPET results for exercise hemodynamic measures (including change in cardiac index, mean PAP, Ca-vO_2 [arteriovenous O_2 content difference], VE/VCO_2 slope [ventilatory efficiency], evaluation of changes in PVR, changes in 6MWD, clinical worsening (including changes in WHO functional class assessment and hospitalizations), pharmacokinetic (PK) results, pharmacodynamic (PD) results, and safety. With the modification of pulmonary vessel wall architecture and pulmonary vessel pressure and patency, it is hypothesized that improvements in RV performance and structural measures, arteriovenous oxygen differences, ventilatory efficiency, and pulmonary vascular resistance will result. The relevant downstream clinical benefits of these improvements should also include improvement in 6MWD and quality of life and reduction in clinical worsening events. Of note, 6MWD and change in WHO functional class are predictors of mortality in PAH.[1,13,14] Safety will be assessed by evaluating adverse events (AEs) and laboratory results, which will be graded for severity using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).

3.4. Rationale for Dose Level and Frequency Selection

3.4.1. Treatment Period

A dose regimen of 0.3 mg/kg sotatercept SC for Cycle 1 and escalating to 0.7 mg/kg at Cycle 2 SC every 3 weeks (Q3W) was selected after reviewing all relevant PK, safety, and efficacy data for sotatercept. Based on population PK/PD modeling of data from a Phase 1 healthy volunteer study, exposure modeling of sotatercept from preclinical models of PAH, and $t_{½}$ of sotatercept (~23 days), Q3W dosing is expected to result in the maintenance of target drug levels in patients with PAH. See Section 4.10.

3.4.2. Extension Period

In the 18-month Extension Period, a dose regimen of every 3 weeks (Q3W) will be evaluated. Comparable dose levels based on exposure-matching will be selected to maintain steady-state exposures through the Extension Period.

3.5. Background

PAH applies to a group of diseases causing a progressive increase in PVR, resulting in RV dysfunction and ultimately failure as well as premature death.[3,4] PAH pathophysiology involves pulmonary endothelial dysfunction, resulting in impaired production of vasodilators, such as nitric oxide and prostacyclin, and overexpression of vasoconstrictors, such as endothelin-1. The pathophysiology of PAH also entails the abnormal proliferation of pulmonary VSMCs in pulmonary arterioles, which results in progressive pulmonary vascular remodeling, increased PVR and, progressive, right-sided heart failure.[5] In the absence of treatment, the majority of

patients succumb to heart failure within a few years of diagnosis.[6] There is currently no pharmacological cure for PAH; treatment involves relieving symptoms, principally by increasing blood flow through the pulmonary vasculature with 1 or more vasodilators and slowing clinical worsening of the disease. Current disease-specific treatments for PAH include vasodilator-type agents such as endothelin-receptor antagonists (ERAs), phosphodiesterase 5 (PDE5) inhibitors, and prostanoids, which are used to supplement general supportive care agents (e.g., anticoagulants, diuretics, digoxin). Recent preclinical data suggest that sotatercept (murine analogue, RAP-011) may positively affect vascular remodelling in animal models of PAH.[2] Affected animals treated with RAP-011 showed substantial improvements in pulmonary vascular and cardiac hemodynamic measurements that are comparable or superior to approved agents for treatment of PAH. Importantly, the animal models provide evidence of a disease-modifying effect, that is, a substantial reduction in the proliferation of pulmonary VSMCs in RAP-011-treated animals and a resultant reduction in pulmonary vascular wall thickness as assessed by histologic evaluation, in both preventative and therapeutic disease models. Taken together, these data indicate that RAP-011 can attenuate the development and progression of PAH, even when administered to rats with established disease. These preclinical data suggest that sotatercept is a mechanism-targeted, non-vasodilator PAH therapy that may positively affect vascular remodelling.[2]

A detailed description of the chemistry, pharmacology, efficacy, and safety of sotatercept is provided in the Investigator's Brochure (IB).

3.6. Benefit/Risk Assessment

The study will be conducted in participants who require treatment for the management of PAH. The study design, inclusion/exclusion criteria, and procedures have been developed in a manner to protect participant safety.

The evidence for potential benefits comes from data observed in rodent models of PAH. These potential clinical benefits include reduced muscularization and thickness of pulmonary vessel walls, reduced right-sided heart pressures, and reduced right-to-left ventricle weight ratios.[2] These clinical improvements might be accompanied by benefit in hemodynamic measures such as reductions in PVR as well as increases in functional capacity, which will also be measured during the study.

Possible risks to participants observed in prior clinical studies with sotatercept include increases in hemoglobin (Hgb), hematocrit, red blood cell (RBC) count, and blood pressure (BP). These will be diligently monitored and managed during the study, and interruption or adjustments of dosing as necessary (in addition to medical treatment) to ameliorate these risks. Potential risks of development of anti-drug antibodies (ADAs), reproductive effects, and renal injury, though not seen in clinical studies of sotatercept but observed in some preclinical studies, will also be monitored. Thorough monitoring of all AEs experienced by any participant will also be employed in this study.

In prior sotatercept clinical oncology studies in chemotherapy-induced anemia and osteolytic bone disease in multiple myeloma, the following have been described as treatment-emergent adverse events (TEAEs): leukopenia, neutropenia (including febrile neutropenia), granulocytopenia, and thrombocytopenia. As a result of the decrease in white blood cells and

infection and as a consequence of thrombocytopenia, bleeding may be a potential risk. Per health authority request, leukopenia, neutropenia, and thrombocytopenia have been identified as adverse events of special interest in this study (see Section 6.3 Dose Modification and Section 8.3 Adverse Events).

More detailed information about the known and expected benefits and risks and possible AEs of sotatercept can be found in the IB.

Table 5 indicates the objectives and endpoints of the study.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of sotatercept on an invasive cardiopulmonary exercise test (iCPET) measure in PAH patients treated with sotatercept plus standard of care (SOC)	• Change from baseline in VO_2 max at 24 weeks
Secondary	
• To evaluate the effect of sotatercept on additional iCPET measures in PAH patients treated with sotatercept plus SOC	• Exercise measures, including change in VE/VCO_2 slope (ventilatory efficiency), cardiac index, mean pulmonary arterial pressure, $Ca\text{-}vO_2$ (arteriovenous O_2 content difference) at 24 weeks
• To evaluate effects of sotatercept on right ventricular stroke volume (RV SV), RV end-systolic volume (RV ESV), RV end-diastolic volume (RV EDV), RV ejection fraction (RV EF), RV stroke volume index (RV SVI), and RV mass by cardiac MR imaging in PAH patients treated with sotatercept plus SOC	• Change from baseline in RV SV, RV ESV, RV EDV, RV EF, RV SVI, and RV mass by cardiac magnetic resonance (MR) imaging at 24 weeks
• To evaluate the effect of sotatercept on pulmonary vascular resistance (PVR) in PAH patients treated with sotatercept plus SOC	• Change from baseline in PVR at 24 weeks
• To assess the PK of sotatercept in PAH patients treated with sotatercept plus SOC	• Population PK parameters of sotatercept
• To evaluate the effect of sotatercept on 6-minute walk distance (6MWD) in PAH patients treated with sotatercept plus SOC	• Change from baseline in 6MWD at 24 weeks

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
• To evaluate the effect of sotatercept on PD biomarker(s) in PAH patients treated with sotatercept plus SOC	• Change from baseline in NT-proBNP at 24 weeks • Change from baseline in WHO functional class at 24 weeks
• To assess the safety and tolerability of sotatercept in PAH patients treated with sotatercept plus SOC	• Clinical worsening (e.g., hospitalizations, change in WHO functional class) • Occurrence of adverse events
Exploratory	
• To assess additional biomarkers in PAH patients treated with sotatercept plus SOC	• Change from baseline in PAH-related biomarkers
• To evaluate the primary and secondary endpoints during the Extension Period in PAH patients treated with sotatercept plus SOC	• Change in selected primary and secondary endpoints during the Extension Period
• Exercise hemodynamic measures in PAH patients treated with sotatercept plus SOC	• RV-pulmonary arterial (PA) coupling ratio (based on single beat assessment), VO_2 at anaerobic threshold (O_2 consumption at anaerobic threshold), heart rate recovery (> 12 beats at 1 minute recovery), exercise oscillatory ventilation (present or absent as defined by AHA consensus statement), distensibility, resting and peak exercise end tidal CO_2

6MWD = 6-minute walk distance; AHA = American Heart Association; Ca-vO_2 = arteriovenous O_2 content difference; iCPET = invasive cardiopulmonary exercise test; MR = magnetic resonance; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PA = pulmonary arterial; PAH = pulmonary arterial hypertension; PD = pharmacodynamic; PK = pharmacokinetics; PVR = pulmonary vascular resistance; RV = right ventricular; RV EDV = right ventricular end-diastolic volume; RV EF = right ventricular ejection fraction; RV ESV = right ventricular end-systolic volume; RV SV = right ventricular stroke volume; RV SVI = right ventricular stroke volume index; SOC = standard of care; VE/VCO_2 = ventilator efficiency; VO_2 max = peak oxygen uptake; WHO = World Health Organization.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, single-arm, open-label, multicenter, exploratory study assessing the efficacy and safety of sotatercept for the treatment of WHO functional class III PAH.

Study duration for each participant includes a Screening Period of up to 28 days, a 24-week Treatment Period, an 18-month Extension Period, and an 8-week Follow-Up Period.

4.2. Clinical Sites

This study will be conducted at approximately 5 clinical sites in the United States.

4.3. Standard of Care

In the Treatment Period, SOC therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an ERA, a PDE5 inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist. Small adjustments or titrations are routine SOC for PAH therapies and are considered stable dosing. Patients receiving monotherapy are not to be enrolled. The SOC details can be found in Appendix 3.

During the Extension Period, participants under investigator's supervision can substitute, remove, or adjust the dose of SOC for PAH-worsening and chronic concomitant medications, including supplemental oxygen. Investigator discretion will be used to determine if sotatercept study drug discontinuation is necessary.

4.4. Screening Period

Upon giving written informed consent, participants will enter the Screening Period to determine eligibility. Participant screening procedures are to take place within 28 days prior to the first dose of study drug. During the Screening Period, participants will undergo assessments to determine eligibility for the study and to obtain baseline measurements, including cardiac MR imaging parameters. Right heart catheterization (RHC) for assessment of baseline CPET, PVR, pulmonary capillary wedge pressure (PCWP), and right-sided heart pressures is to be completed within 10 days prior to first dose of study drug.

4.5. Treatment Period

Approximately 25 participants will receive standard of care plus a starting dose of sotatercept 0.3 mg/kg subcutaneously (SC) for Cycle 1 and escalate to 0.7 mg/kg SC at Cycle 2 Q3W for a total treatment duration of 24 weeks.

4.6. Extension Period

Participants who have not discontinued early from the 24-week Treatment Period may continue to an 18-month Extension Period. Participants will continue to receive sotatercept at comparable dose levels, based on exposure-matching, to maintain steady-state exposures through the Extension Period, plus SOC.

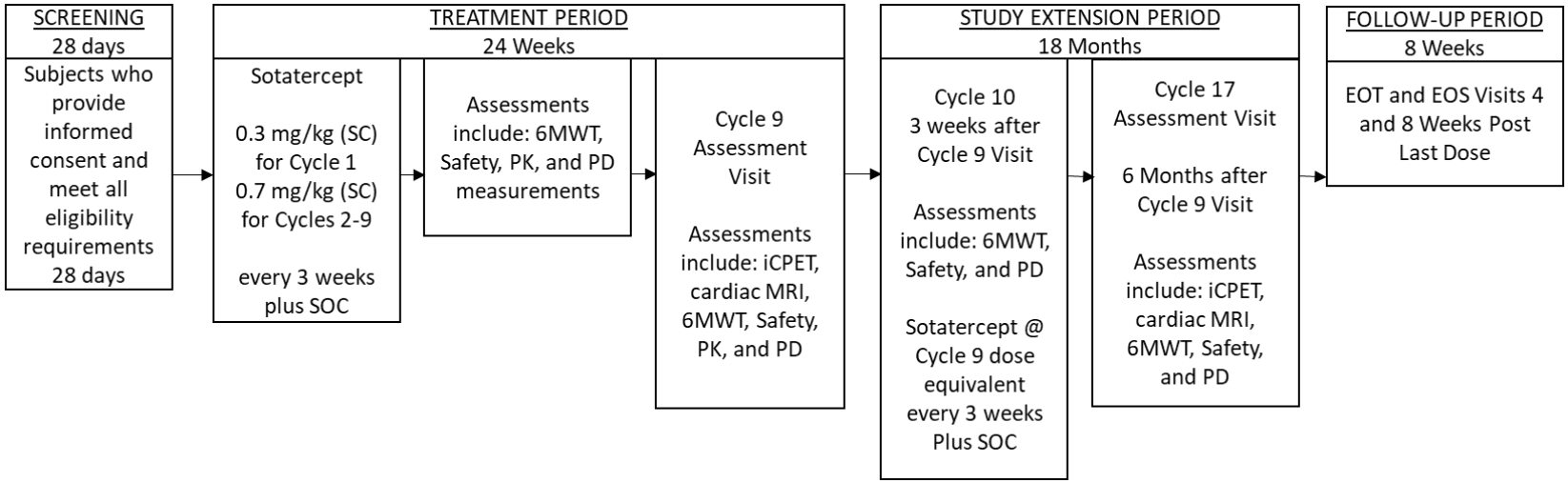
Study drug will be administered subcutaneously Q3W for 18 months.

4.7. Follow-Up Period

Participants will enter into a Follow-Up Period for 8 weeks after the last dose of study treatment during the Extension Period.

Participants who discontinue early, including during the 24-week Treatment Period or the 18-month Extension Period, will be asked to return for End-of-Treatment (EOT) and End-of-Study (EOS) visits.

Figure 1: Study Design



6MWT = 6-minute walk test; EOS = end of study; EOT = end of treatment; iCPET = invasive cardiopulmonary exercise test; MR = magnetic resonance; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneously; SOC = standard of care.

Refer to Section 8 for a full list of study procedures/assessments.

4.8. Participant and Study Completion

Approximately 25 participants will receive SOC plus sotatercept at a starting dose level of 0.3 mg/kg for Cycle 1 and then 0.7 mg/kg at Cycle 2 and Q3W for the remainder of the 24-week Treatment Period.

4.8.1. Extension Period

All participants will continue into the 18-month Extension Period. In the Extension Period, a dose regimen of Q3W will be continued.

Upon completion of the study, participants will be provided the opportunity to transition into the long-term follow-up study.

4.9. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study, including the EOT and EOS visits.

End of Study visits are only required for participants who discontinue the study early or decline transition to a future sotatercept long-term follow-up study. The End of Study is defined as when the last participant completes the last visit.

4.10. Justification for Dose

Selection of the dose and dosing frequency are based on data from studies in healthy volunteers and patients with other chronic diseases. In 2 completed Phase 1 studies (Studies A011-01 and A011-02), single doses of sotatercept up to 3.0 mg/kg intravenous (IV) and multiple doses of sotatercept up to 1.0 mg/kg SC were generally well tolerated in healthy postmenopausal women. Consistent with observations from nonclinical safety studies, many of the observed PD effects in the Phase 1 clinical studies were attributable to the expected biologic activity of activin inhibition (e.g., dose-dependent decreases in circulating follicle-stimulating hormone [FSH], and transient, reversible effects on red blood cell [RBC] parameters such as Hgb). Using data from the Phase 1 studies, a PK/PD model for Hgb as a surrogate marker for target engagement was developed. Simulations from this model also showed that the probability of having Hgb $\geq$ 18 g/dL and an increase in Hgb $\geq$ 2 g/dL is higher during the first 3 weeks after a dose of 0.7 mg/kg than after a dose of 0.3 mg/kg. Therefore, a starting dose level of 0.3 mg/kg was selected for Cycle 1 and a dose level of 0.7 mg/kg was selected at Cycle 2 and for the remainder of treatment, all administered SC Q3W. Simulations suggest that this dosing regimen may reduce the number of participants with increase in Hgb $\geq$ 2 g/dL.

Based on the PK model developed from the Phase 1 data, the projected mean C_{trough} level at steady state is 8.1 µg/mL at this dose and frequency. This projected exposure is similar to the C_{max} after the first dose of 1.0 mg/kg (7.4 µg/mL) in Study A011-02. At the planned dose and frequency in this study, the projected C_{max} and AUC_{21d} are 12.4 µg/mL and 217 day*µg/mL, respectively.

The risk of AEs due to Hgb increase will be ameliorated by implementation of dose reduction, delay, and stopping guidance in the subsequent treatment cycles (Section 6.3).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted, unless within the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards; March 2020 (FDA 2020)[18].

5.1. Inclusion Criteria

Participants must satisfy all of the following criteria to be enrolled in the study:

1. Age ≥ 18 years
2. Documented findings on right heart catheterization (RHC) at any time prior to Screening consistent with a diagnosis of WHO pulmonary hypertension Group 1: PAH of any of the following subtypes:
   - Idiopathic PAH
   - Heritable PAH
   - Drug- or toxin-induced PAH
   - PAH associated with connective tissue disease
   - PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair
3. Symptomatic pulmonary hypertension classified as WHO functional class III
4. Screening Period RHC (within 10 days prior to C1D1 visit) documenting a minimum PVR of ≥ 4 Wood units
5. Pulmonary function tests within 6 months prior to Screening as follows:
   a. Total lung capacity > 70% predicted; or if between 60% to 70% predicted, or not possible to be determined, confirmatory high-resolution computed tomography (CT) indicating no more than mild interstitial lung disease per investigator interpretation; or,
   b. Forced expiratory volume (first second) (FEV_1)/forced vital capacity (FVC) > 70% predicted
   c. For subjects with a history of lobectomy or pneumonectomy, and for whom there are no population-based normalization methods, assessment based on residual lung volume will be permitted to assess eligibility.
6. Ventilation-perfusion (VQ) scan (or, if unavailable, a negative CT pulmonary angiogram [CTPA] or pulmonary angiography result), any time prior to Screening or conducted during the Screening Period, with normal or low probability result
7. 6MWD ≥ 100 and ≤ 550 meters repeated twice during Screening Period and both values within 15% of each other, calculated from the highest value (see Appendix 4)
8. Combination PAH therapy at stable (per SOC) dose levels as defined in Section 4.3 for at least 90 days prior to Cycle 1 Day 1 (C1D1)

9. Females of childbearing potential (defined in Appendix 8) must:
    a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study and must agree to ongoing pregnancy testing during the course of the study and at end of study treatment.
    b. If sexually active, have used, and agree to continue to use, highly effective contraception** without interruption, for at least 28 days prior to starting investigational product (IP), during the study (including dose interruptions), and for 16 weeks (112 days) after discontinuation of study treatment.
    c. Refrain from breastfeeding a child or donating blood, eggs, or ovum for the duration of the study and for at least 112 days after the last dose of study treatment.

    ** (see Appendix 8 for additional contraceptive information)
10. Male participants must:
    a. Agree to use a condom, defined as a male latex condom or nonlatex condom NOT made out of natural (animal) membrane (for example, polyurethane), during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for at least 112 days following IP discontinuation, even if he has undergone a successful vasectomy. (see Appendix 8 for additional contraceptive information)
    b. Refrain from donating sperm for the duration of the study and for 112 days after the last dose of study treatment.
11. Ability to adhere to the study visit schedule and understand and comply with all protocol requirements
12. Ability to understand and provide written informed consent

5.2. Exclusion Criteria

Participants will be excluded from the study if they meet any of the following criteria:

1. Started or stopped receiving any general supportive therapy for pulmonary hypertension (e.g., diuretics, oxygen, anticoagulants, digoxin) within 60 days prior to C1D1
2. Received IV inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to C1D1
3. History of atrial septostomy within 180 days prior to Screening Visit
4. History of more than mild obstructive sleep apnea that is untreated
5. History of portal hypertension or chronic liver disease, defined as mild to severe hepatic impairment (Child-Pugh Classes A to C)
6. History of human immunodeficiency virus infection-associated PAH
7. Prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536)
8. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to C1D1 or planned initiation during the study (participants who are stable in the maintenance phase of a program and who will continue for the duration of the study are eligible)

9. Uncontrolled systemic hypertension as evidenced by sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg during Screening Visit after a period of rest
10. Systolic BP < 90 mm Hg during Screening Visit or at baseline (C1D1)
11. History of known pericardial constriction
12. RHC contraindicated during the study per investigator
13. Electrocardiogram (ECG) with QTcF > 480 msec during Screening or C1D1
14. Personal or family history of long QTc syndrome or sudden cardiac death
15. Cerebrovascular accident within 3 months of C1D1
16. History of restrictive or constrictive cardiomyopathy
17. Left ventricular ejection fraction < 45% on historical echocardiogram performed within 6 months prior to Screening Period (or done as a part of the Screening Period) or PCWP > 15 mmHg as determined in the Screening Period RHC
18. Any current symptomatic coronary disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain in the past 6 months prior to Screening Visit)
19. Acutely decompensated heart failure within 30 days prior to C1D1, as per investigator assessment
20. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease
21. Any of the following clinical laboratory values during the Screening Period prior to C1D1:
    a. Baseline Hgb > 16.0 g/dL within 28 days of C1D1
    b. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 3 × upper limit of normal (ULN) or total bilirubin > 1.5 × ULN within 28 days of C1D1
    c. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (4-variable Modification of Diet in Renal Disease equation) within 28 days of C1D1 or required renal replacement therapy within 90 days
22. History of opportunistic infection (e.g., invasive candidiasis or *Pneumocystis* pneumonia) within 6 months prior to Screening; serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) within 3 months prior to Screening
23. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in IP
24. Major surgery within 8 weeks prior to C1D1. Participants must have completely recovered from any previous surgery prior to C1D1
25. Prior heart or heart-lung transplants or life expectancy of < 12 months
26. Pregnant or breastfeeding females

27. At any time in the 30 days prior to the Screening Period received > 20 mg/day of prednisone (or equivalent) or started or changed the dose of a systemic corticosteroid. Participants receiving stable doses of ≤ 20 mg prednisone (or equivalent) in 30 days prior to the Screening Period are permitted in the study.
28. History of active malignancy, with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin
29. History of clinically significant (as determined by the investigator) non-PAH related cardiac, endocrine, hematologic, hepatic, immune, metabolic, urologic, pulmonary, neurologic, neuromuscular, dermatologic, psychiatric, renal, and/or other disease that may limit participation in the study
30. Participation in another clinical trial involving intervention with another investigational drug, approved therapy for investigational use, or investigational device within 4 weeks prior to C1D1, or if the half-life of the previous product is known, within 5× the half-life prior to C1D1, whichever is longer
31. Unwillingness or inability to comply with the protocol-required procedures

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not eligible to receive study treatment. Electronic case report forms need to be completed for all patients who sign the informed consent. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure adverse events, eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with the approval of the study medical monitor. Rescreened participants will be assigned a new participant number.

6. TREATMENTS

Study treatment is defined as any investigational treatment intended to be administered to a study participant according to the study protocol.

6.1. Treatments Administered

Sotatercept clinical drug product will be provided by the sponsor as a lyophilized powder.

The clinical drug product consists of sotatercept in 10 mM citrate buffer, pH 5.8, 8% sucrose, and 0.02% polysorbate 80. It is supplied as a lyophilized powder in labeled, rubber stoppered, 3-mL glass vials. The recommended storage temperature for sotatercept lyophilized drug product is 2°C to 8°C. Prior to administration, the lyophilized drug product is reconstituted with 1 mL water for injection. The reconstituted drug product consists of a 50 mg/mL solution of sotatercept. The reconstituted sotatercept, in its original container closure system, may be held for up to 6 hours at 2°C to 8°C. For details, refer to the Pharmacy Manual provided under a separate cover.

SOC treatments will be provided by the treating physician based on local treatment guidelines and participants must remain on the same SOC treatments during the course of the study (see Appendix 3 for more details on SOC).

6.2. Treatment Administration and Schedule

Subcutaneous (SC) sotatercept will be administered after reconstitution as an SC injection to participants by the study staff at the clinical site and administration will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh. Where rounding the weight and total volume is necessary, please refer to the Pharmacy Manual for further details.

Sotatercept dosing is weight based therefore an overdose would only be considered if the dose exceeds the no-observed-adverse-effect level (NOAEL) of 1 mg/kg. For information on overdose, refer to Section 8.3.8.

Standard of care treatments will be provided by the treating physician based on local treatment guidelines and participants must remain on the same SOC treatments during the study (see Section 4.3 and Appendix 3 for more details on SOC).

6.3. Dose Modification

Dose delay and/or reduction or discontinuation may be required for sotatercept. Guidance for dose modifications and dose delay are summarized in Figure 2 and Figure 3. The details of Dose Modification Guidance are based on the results of platelet and Hgb values during the Treatment and Extension Periods. Dose delays and reductions can be implemented for safety reasons at any time per Investigator's assessment, not being restricted to the Dose Modification Guidance provided.

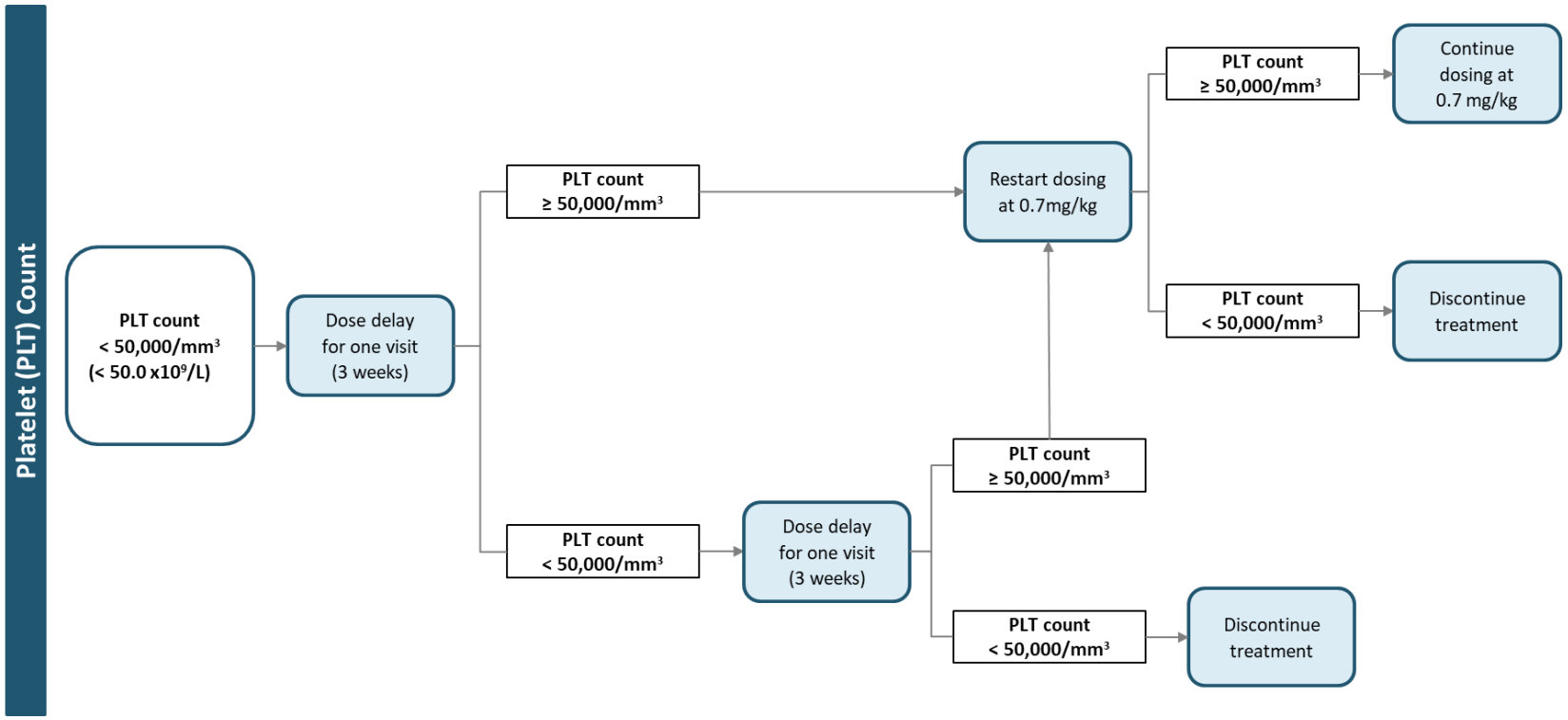
A maximum of 3 dose delays are allowed based on safety monitoring during the study.

If a fourth dose delay is required, the study treatment should be discontinued.

Questions regarding the applicability of the dose adjustment guidelines to specific situations must be directed to the medical monitor.

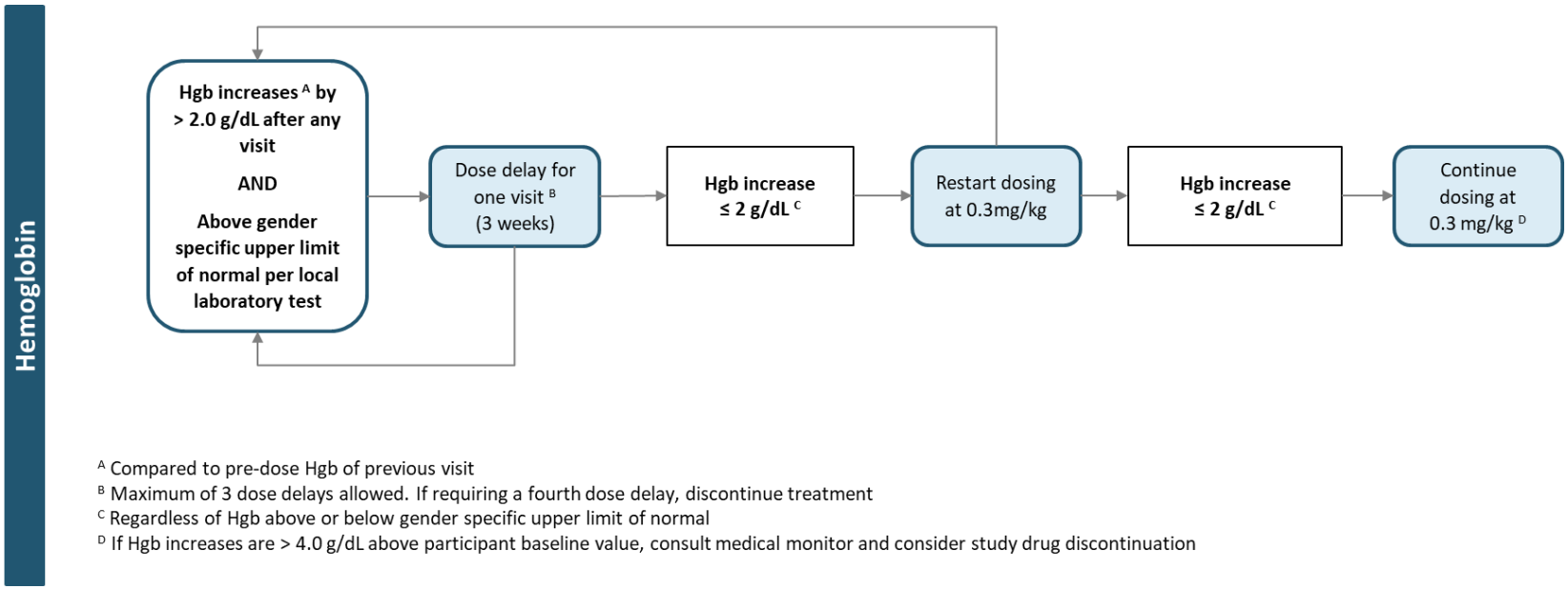
Results from the hematology panel should be evaluated prior to study drug administration. For C1D1 and C2D22 visits, blood samples should be taken and assessed for Hgb levels on the same day as study drug administration or 1 day prior. If Hgb increases are > 4.0 g/dL above the participant baseline value, the medical monitor should be consulted, and study drug discontinuation should be considered.

Figure 2: Platelet Count Dose Modification: Dose Delay, Dose Reduction and Discontinuation Guidelines



PLT = platelet.

Figure 3: Hemoglobin Dose Modification: Dose Delay, Dose Reduction and Discontinuation Guidelines



[A] Compared to pre-dose Hgb of previous visit
[B] Maximum of 3 dose delays allowed. If requiring a fourth dose delay, discontinue treatment
[C] Regardless of Hgb above or below gender specific upper limit of normal
[D] If Hgb increases are > 4.0 g/dL above participant baseline value, consult medical monitor and consider study drug discontinuation

Hgb = hemoglobin
Once Hgb returns to the required value for dose administration, the re-starting dose will be administered at the next planned cycle or if it is the first cycle, after a 3-week dose delay.

Leukopenia and neutropenia are defined as AESI in Section 8.4.

A dose reduction of study drug will be maintained unless subsequent dose reductions are indicated. No more than 2 dose reductions are allowed. If dose reductions were done due to an AE not related to study drug, the dose can be escalated when the AE is resolved. In cases of dose reduction due to increases in Hgb, the dose can be re-escalated after 2 consecutive cycles in which Hgb values are stable and equal or lower than the upper limit of normal.

Table 6: Dose Reductions for Sotatercept

Starting Dose Level	**First Dose Level Reduction**	**Second Dose Level Reduction**	
0.3 mg/kg	0.1 mg/kg	0.05 mg/kg	**No additional dose reductions permitted; discontinue treatment**
0.7 mg/kg	0.3 mg/kg	0.1 mg/kg	

6.4. Method of Treatment Assignment

This is a non-randomized, open-label, single treatment study. Participants who meet all inclusion and none of the exclusion criteria will receive all study treatments according to the Schedule of Events (Table 3).

6.5. Randomization and Blinding

This is an open-label, non-randomized study.

6.6. Packaging and Labeling

The study drug will be labeled per local requirements.

6.7. Preparation/Handling/Storage/Accountability

Accountability for study drug that is administered during the course of the study is the responsibility of the investigator or designee. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of study drug received, to whom it was administered (participant-by-participant accounting), and accounts of any sotatercept accidentally or deliberately destroyed or returned. Accurate recording of all study drug administration is to be made in the appropriate section of the participant's electronic case report form (eCRF) and source documents. Unless otherwise notified, all vials of study drug, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The investigator must return all unused vials of study drug to the sponsor at the end of the study, or the study drug may be destroyed at the clinical site with permission of the sponsor. For either scenario, the outcome must be documented on the drug accountability log. The sponsor or designee will provide direction for the outcome of all unused vials.

Acceleron (or designee) will review with the investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Acceleron (or designee).

Refer to the Pharmacy Manual for further instructions for preparation of study treatments and information regarding disposition of unused study treatments.

6.8. Treatment Compliance

Each dose of study treatment will be administered by SC injection(s) at the clinical site by the study staff and is to be documented in the study source record. Accurate recording of all study drug administration will be made in the appropriate section of the participant's eCRF and source documents. The investigator or designee is responsible for accounting for all study drug that is administered during the course of the study.

Standard of care treatment compliance will be the responsibility of each participant and his/her treating physician. The investigator should promote compliance by instructing the participant to take their SOC exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant should be instructed to contact the investigator if he/she is unable for any reason to take their SOC medication as prescribed (see Appendix 3 for more details regarding SOC).

SOC in the Extension Period is per the Investigator's discretion (see Section 6.9).

6.9. Concomitant Therapy

During screening and throughout the Treatment Period of the study, participants may take stable doses of medications for chronic conditions that are not specifically excluded by the protocol. If there is an immediate clinical need during the study to prescribe a new medication or a new dosage of an existing medication for either a new or chronic condition, concurrent therapy may be administered at the discretion of the investigator. If the new medication is a PAH-specific medication that is being added for clinical worsening (i.e., rescue therapy, refer to Section 8.5.5 for suggested criteria), or is disallowed by entry criteria (e.g., systemic corticosteroid), the investigator will need to discontinue study drug treatment and perform EOT visit assessments as directed by the protocol. The investigator may consult the medical monitor regarding what constitutes a stable dose or a chronic condition. Information regarding concomitant medications will be collected after signing of the ICF and will include all medications taken during the Screening Period to C1D1.

During the Extension Period, participants under investigator's supervision can substitute, remove, or adjust the dose of SOC for PAH-worsening and chronic concomitant medications, including supplemental oxygen. Investigator discretion will be used to determine if sotatercept study drug discontinuation is necessary.

If patients need additional concomitant medications, it should be recorded in the appropriate eCRF. Study drug can be adjusted or discontinued due to concomitant therapy based on the Investigator's discretion. The investigator may consult the medical monitor regarding discontinuation or modification of study treatment on a case-by-case basis.

7. DISCONTINUATION/WITHDRAWAL CRITERIA

The reason for treatment discontinuation/study withdrawal must be recorded in the corresponding participant's eCRF. The investigator must notify the sponsor and medical monitor when a participant has discontinued treatment or been withdrawn from the study. All participants who are discontinued/withdrawn from the study prior to the EOT visit should complete the tests and evaluations scheduled for the EOT visit at the time of discontinuation/withdrawal and will be asked to return to the clinic to complete the remaining Follow-Up EOS visit.

7.1. Discontinuation of Study Treatment

Reasons that may lead to discontinuation of study treatment include the following:

- Completion of treatment
- AE or serious adverse event (SAE)
- Participant request (withdrawal of consent)
- Clinical worsening requiring rescue therapy with a PAH agent
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- QTcF > 500 ms during treatment period

Clinical worsening, pregnancy, and QTcF > 500 ms should be recorded as an AE, see Section 8.3.

The sponsor may terminate study treatment or a dose level after consultation with the investigator at any time for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the participants. Refer to Section 6.3, Dose Modification, for further information regarding AEs that can lead to discontinuation.

7.2. Withdrawal from the Study

Reasons that may lead to a participant's withdrawal from the study include:

- Participant's request (withdrawal of consent)
- Screen failure
- Participant's unwillingness or inability to comply with the protocol
- AE with an outcome of death
- Death
- Lost to follow-up
- Study termination by the sponsor

- AE or SAE
- Pregnancy

Serious Adverse Events and AEs, including those with an outcome of death or pregnancy, should be recorded as an (S)AE (see Section 8.3).

If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a participant discontinues due to an AE or other medical reason, the participant must continue to be followed at regular intervals until the AE normalizes or returns to the participant's baseline condition, as per Section 8.3.5.

Participants to whom rescue therapy is administered (see Section 8.5.5) after demonstrating clinical worsening criteria (Section 8.5.4) must discontinue study drug and must be withdrawn from the study.

7.3. Lost to Follow-Up

A participant 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study source record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up, which should be noted on the participant's eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Events (SoE) (Section 2).
- No protocol waivers or exemptions will be allowed for eligibility criteria. Assessments performed outside of their defined windows will be handled as protocol deviations.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoE (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoE (Section 2).
- All protocol assessments are to be recorded on the participant's source documentation.
- EOS Assessment visit is the point at which the post 24-week Treatment Period and post-18-month Extension Period outcome measures are assessed.

8.1. Screening Procedures

- Screening procedures are to be performed as per the SoE (Section 2) and are to be completed and reviewed by investigator prior to dosing to confirm the participant meets eligibility criteria.
- Procedures also include review of participant's medical, surgical, and family history; collection of demographics, race, and ethnicity; and requests for medical records for external procedures.

8.2. Efficacy Assessments

8.2.1. iCPET

Invasive CPET (iCPET) will be performed at the Screening, Cycle 9, and Cycle 17 visits. Appendix 5 provides further instructions on iCPET. During Screening, if performed on the same day, the iCPET should take place after other assessments.

At the end of the 24-week Treatment Period (Cycle 9, Day 169), Cycle 17 of the 18-month Extension Period, the cardiac MR imaging and iCPET may be done on separate days. If

performed on the same day, iCPET should be performed before cardiac MR, with ≥ 1 hr interval between procedures.

RHC will be performed as per the iCPET manual. Zero-pressure calibration will be performed at the mid-axillary line with the patient in a supine position. Superior vena cava (SVC), right atrial (RA), right ventricular (RV), PCW, and PA pressures will be measured, and mean vascular pressures will be calculated based on systolic and diastolic pressure measurements. Heart rate and vascular pressures are monitored continuously. Cardiac output is measured by the Fick method. Diastolic and transpulmonary pressure gradients are obtained, systemic and PVRs are calculated.

8.2.2. Cardiac Magnetic Resonance Imaging

Cardiac MR imaging will be performed at Screening and at multiple time points throughout the study as per the SoE (Section 2). Cardiac MR imaging must include the first bullet below. Assessment of cardiac structure and function (SSFP sequences). The subsequent analyses are to be collected, if possible:

- Assessment of cardiac structure and function (SSFP sequences);
- Hemodynamic assessment of valvular flow (phase-contrast imaging), including pulmonary-systemic flow ratio (Qp/Qs);
- Assessment of diffuse fibrosis (using T1 mapping);
- Pulmonary artery (PA) compliance and vessel wall remodeling (using high-temporal resolution sequences).

Specific cardiac MR imaging measurements relevant to the PAH pathophysiology include the following: structural anatomy and morphology of cardiac chambers; functional performance of the RV and the LV; anatomy and morphology of great vessels; anatomic and hemodynamic findings suggestive of an intra-cardiac shunt; presence of scar/fibrosis of the LV and/or RV.

In addition to the views collected according to established methods and protocols, the following views and series are of vital interest and must be collected, if possible, for evaluation:

a. 3-plane loc
b. Transaxial black blood from above arch to diaphragm
c. 2-chamber cine localizer
d. Short-axis cine localizer
e. 4-chamber cine stack and localizer
f. 2-chamber cine
g. Short-axis cine
h. Short-axis T1 map of base and mid ventricle
i. Rvot cine
j. Oblique cines of the RT, LT, and main pulmonary art
k. Velocity encoding (vencs) of the pulmonary artery, ascending aorta, and the mitral and tricuspid valves

Further details of the cardiac MR imaging can be found in the imaging protocol.

Cardiac MR images will be centrally read and details of central read can be found in the imaging review charter. Cardiac MR and iCPET should be done on separate days. If performed on the same day, iCPET should be performed before cardiac MR, with ≥ 1 hr interval between procedures.

8.2.3. Pulmonary Vascular Resistance by Right Heart Catheterization

Pulmonary vascular resistance will be measured by RHC at the Screening, Cycle 9, and Cycle 17 visits. For participants who discontinue from the Treatment Period early, PVR will be assessed at their EOT visit at the time of their discontinuation. If performed on the same day, the RHC should take place after other assessments (i.e., 6-meter walking test [6MWT]) have been completed.

The first RHC must be performed within 10 days prior to Cycle 1 (during the Screening Period), the second RHC should be performed within 10 days prior to the 24-week Treatment Period/Cycle 9 visit (during the Treatment Period), and the third RHC should be performed within 10 days of Cycle 17 (during the Extension Period). RHC should be performed ±10 days of the EOT visit or at the time of their discontinuation for participants who discontinue prior to 24 weeks/Cycle 9. RHC will assess the long-term benefits and durability of the effect of sotatercept treatment.

A participant will not receive more than 3 RHC assessments during the study.

Right heart catheterization will be performed according to the iCPET manual and is to assess several prognostic hemodynamic variables in addition to PVR, including right atrial pressure (RAP), mean PAP, mean PCWP, and cardiac output (CO). The following hemodynamic parameters will be assessed when the participant is in a stable hemodynamic rest state (as demonstrated by 3 consecutive mean PAP and CO measurements within 10% of each other) while the participant is breathing ambient air or oxygen:

- RAP, mean PAP, mean PCWP, systolic pulmonary artery pressure, diastolic pulmonary artery pressure, systolic BP, diastolic BP, heart rate (HR)
- CO measured in triplicate by the Fick method

Pulmonary vascular resistance will be calculated and populated in the eCRF. Right ventricle pressure data from the RHC with simultaneously recorded ECG recordings may be collected and digitally stored at selected sites.

8.2.4. Six-Minute Walk Distance

Six minute walk distance will be measured by the 6MWT at Screening and at multiple time points throughout the study as per Section 2 SoE. During the Screening visit, the 6MWT is to be performed twice at least 4 hours but no more than 1 week apart and the distances must be within 15% of each other, based on the longer distance. If the difference between the first and second tests is > 15%, the test may be repeated once more, provided the repeat test is within 1 week of the previous test. If the difference between the distances remains > 15%, the participant will be considered a screen failure. If occurring on the same day, 6MWT should be performed before RHC. Appendix 4 provides further instructions on 6MWT. For assessment of clinical

worsening, a decrease of ≥ 15% in 6MWD at any time point as compared to Screening must be confirmed by a second 6MWT performed at least 4 hours and no more than 1 week apart from the first.

8.3. Adverse Events

8.3.1. Adverse Event Definitions

8.3.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant administered a study drug, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to study drug.

Abnormal laboratory and other abnormal investigational findings (e.g., physical examination, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

8.3.1.2. Unexpected Adverse Events

An unexpected AE is an AE that, the nature, severity, specificity, or outcome of which is not consistent with the summary of product characteristics described in the IB under the Reference Safety Information.

8.3.1.3. Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present 30 days prior to the Screening Period that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

8.3.1.4. Serious Adverse Event

An SAE is any AE, occurring at any dose level/regimen and regardless of causality that:

- Death: An adverse event that results in death e.g., cardiac arrest.
- Life threatening: Is an AE 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization; however, a hospitalization for an elective procedure will not be considered an SAE.

- Results in persistent or significant disability/incapacity. An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- Is a congenital anomaly/birth defect: Congenital anomaly/birth defect in a child of a subject or its partner that was exposed to study drug prior to conception or during pregnancy.
- Other, is an important medical event: An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting per regulations, any suspected transmission of an infectious agent via a medical product is by default a suspected unexpected serious adverse reaction (SUSAR) and should be reported in an expedited manner as described in Section 8.3.7.

8.3.1.5. Events Not to Be Considered as Serious Adverse Events are Hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to IP, rationale of the causality, the action taken regarding IP, and outcome.

8.3.1.6. Severity

Investigators must evaluate the severity/intensity of AEs and SAEs according to the current active version of the NCI-CTCAE (NCI-CTCAE), preferentially using the graded scales. If there is a change in severity of an AE, it must be recorded as a separate event. If a particular AE's severity/intensity is not specifically graded, the investigator should apply the general guidelines for determination of Grade 1 through Grade 5 as listed in the NCI-CTCAE cover page (as shown below), using their best medical judgment:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate- instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious," which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.3.2. Relationship to Study Drug

The investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of study drug, known side effects of study drug, concomitant therapy, course of the underlying disease and pertinent study procedures.

Not Suspected: Means a causal relationship of the AE to study drug administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a reasonable possibility that the administration of study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE.

8.3.3. Documentation and Methods of Detecting Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. Participants will be evaluated and questioned generally for AEs during the course of the study, starting at the signing of the informed consent. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. All clearly related signs and symptoms which are either volunteered by participants or are observed during or following the course of investigational product administration must be reported on the appropriate eCRF. AEs and SAEs reported from the signing of the ICF to the EOS visit are to be reported and documented on the AE eCRF. Any AE related to a protocol procedure should be marked as such on the eCRF.

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE eCRF. Any clinically relevant changes in laboratory assessments or other clinical findings as described in Section 8.3.1.1 are considered AEs and must be recorded on the AE eCRF. AEs are to be followed for resolution as described in Section 8.3.5.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with sotatercept, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of sotatercept), and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented. AEs categorized as SAEs must also be documented within the appropriate SAE section in the eCRF or a paper SAE form if the system is down or otherwise unavailable, as described in Section 8.3.4. Note that both methods should not be used beside each other, the paper SAE Form is for back up reporting only.

Specific guidance can be found in the eCRF Completion Guidelines provided by the sponsor or designee.

8.3.4. Documentation of Serious Adverse Events

For all SAEs, an SAE form must be completed with as much information as possible and submitted within the time frame described in Section 8.3.6.

When new significant information is obtained as well as when the outcome of an event is known, the investigator should record the information on a new SAE form. If the participant was hospitalized, a summary from the investigator should be included as part of the participant medical file. In all instances, the investigator should follow up with participants until the outcome of the SAE is known.

8.3.5. Reporting Period and Monitoring of Participants with AEs

As described in Section 8.3.3, all AEs must be recorded in the eCRF from the signing of the informed consent up until the EOS visit. All participants who took at least 1 dose of study drug, whether they completed the Treatment Period or not, should complete the EOT and EOS visits.

All AEs will be followed until return to screening baseline, resolution, or clinical database lock. All SAEs will undergo active follow-up until resolved or the event becomes chronic or stable.

Follow-up data for SAEs obtained after clinical database lock will be incorporated into the sotatercept safety database.

8.3.6. Notification About Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately, within a maximum 24 hours after becoming aware of the event, inform the sponsor via the contract research organization (CRO) by telephone, fax, or email. Per Section 8.3.3, paper SAE forms should be used to report an SAE if the eCRF is unavailable.

All written reports should be transmitted using the study-specific SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, email addresses, and telephone and fax numbers for SAE reporting are located on the SAE Report Form and in the completion, instructions provided for the Investigator Site File. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or email. Reporting procedures and timelines for follow-up information are the same as for the initially reported SAE.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant therapy). In all cases, the information provided in the SAE Report Form must be consistent with the data that are recorded in the corresponding sections of the eCRF.

The investigator/reporter must respond to any request for follow-up information or to any question the sponsor or designee may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the sponsor and (as applicable) to allow the sponsor to meet regulatory timelines associated with expedited reporting obligations.

Requests for follow-up will usually be made by the responsible clinical research associate or medical monitor, or an Acceleron pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

8.3.7. Safety Reporting to Health Authorities, Independent Ethics Committees, Institutional Review Boards, and Investigators

The sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her participants to the IEC that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the sponsor will inform the investigator of "findings that could adversely affect the safety of participants, impact the conduct of the study, or alter the IEC's approval/favorable opinion to continue the study."

The sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to sotatercept (SUSARs). The investigator should place copies of these Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to investigators will be followed.

When specifically required by regulations and guidelines, the sponsor will provide appropriate Safety Reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific-regulations, the investigator will be responsible for promptly notifying the concerned IEC of any Safety Reports and for filing copies of all related correspondence in the Investigator Site File.

8.3.8. Overdose

An overdose is defined as the administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information.

Sotatercept dosing is weight-based therefore, for purpose of this trial, an overdose is defined as any dose that has exposures in excess of monkey NOAEL dose of 1 mg/kg (IB Edition 14, Section 3.3.2, Table 4), which was also the highest dose tested in human volunteers study (Study A011-02) with resolvable AEs. Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved sotatercept) as defined in the protocol, with or without an AE, must be communicated to Acceleron or a specified designee within 24 hours and be fully documented as an AE in the eCRF.

There is no antidote for sotatercept, and it is not dialyzable from blood, therefore in case of overdose patients should be monitored/treated as per clinical practice based on symptoms of identified and potential risks as described in the IB.

8.3.9. Transmission of an Infectious Agent

Definition: Transmission of an infectious agent via study drug administration. Any organism, virus, or infectious particle (e.g., protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

Transmission of an infectious agent may be suspected from clinical signs or symptoms or laboratory findings indicating an infection in a patient exposed to study drug. As in the case of suspected adverse reactions and adverse reactions, the terms suspected transmission and transmission are considered synonymous.

In the context of evaluating a suspected transmission of an infectious agent via study drug administration, care should be taken to discriminate, whenever possible, between the cause (e.g., injection/administration) and the source (e.g., contamination) of the infection and the clinical conditions of the patient at the time of the infection (immune-suppressed/vaccine).

Any instance of transmission of an infectious agent must be communicated to Acceleron or a specified designee within 24 hours to the sponsor using appropriate channels (e.g., telephone, email) and be fully documented as an AE in the eCRF, or as an SAE if associated SAE occurs (see Section 8.3 for further instruction).

8.3.10. Pregnancy

The investigator will attempt to collect pregnancy information if a female participant or a male participant's female partner becomes pregnant while the participant is participating in this study

and up until 112 days after last dose of study drug treatment. The pregnancy information will be recorded on the appropriate form and must be submitted to the sponsor within 24 hours of learning of the pregnancy. The participant or partner will be followed for the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor or designee. 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 as an AE. Abnormal pregnancy outcomes (e.g., spontaneous abortion [includes miscarriage and missed abortion], fetal death, stillbirth, congenital anomalies, ectopic pregnancy, neonatal death) are considered SAEs. Any neonatal death that occurs within 1 month of birth should be reported, without regard to causality, as an SAE. Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 112 days after the last dose.

- If a pregnancy is reported, the investigator must inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 8.
- Additional pregnancy, breastfeeding, and sperm/ovum donor information is provided in Appendix 8.

8.4. Monitoring of Identified, Potential and Adverse Events of Special Interest

The risks outlined below are consistent with the list in Sotatercept IB (IB Edition 14). The AESI are considered important parameters to be monitored in order to assess the overall safety of the PAH patient population, therefore, added for safety monitoring in the sotatercept clinical trial.

The laboratory data and vital signs are monitored on an ongoing basis by the investigator and medical monitor in the study. Laboratory data and AEs are measured as per the study schedule or upon an unscheduled visit if applicable. Section 6.3 provides details for dose modifications due to decreases in platelets and Hgb.

Additional reviews will be performed periodically as part of standard safety signal detection and medical monitoring.

8.4.1. Identified Risk

Table 7 describes the identified risks that could occur during the study drug treatment.

Table 7: Identified Risks

Description	Monitor Parameter	Planned Action
Blood pressure increase	Hypertension SMQ (Narrow and broad)	Monitor the vital signs for any hypertension trending in combination with the events reported. Additionally, review for risk factors of systemic hypertension (diabetes, metabolic syndrome, and obesity), concomitant medications, and previous medical history of hypertension.

SMQ = standardized MedDRA queries

8.4.2. Potential Risks

Laboratory data and AEs are measured as per protocol schedule or upon an unscheduled visit if applicable. Section 6.3 provides details for dose modifications due to decreases in hematocrit and/or platelets. Table 8 provides potential risks that could occur during study drug treatment.

Table 8: Potential Risks

Description	Monitor Parameter	Planned Action
Increase in RBC	RBC parameters (RBC, Hgb, and Hct)	• Careful monitoring of RBC parameters is performed and in case of Hct ≤ 55% • Dose hold and/or dose decrease guidance is to be followed Additionally • Monitor by safety and Acceleron clinical physician using laboratory data (Hgb/Hct) • The medical monitor will ensure dosage adjustment according to the protocol • Monthly review of Hct/Hgb listings by safety team member (hematology expert)
Immunogenicity for biologic Compound	Anaphylactic reaction (SMQ) (Narrow and broad) and Hypersensitivity (SMQ) (Narrow and broad)	• Immunogenicity will continue to be evaluated on reported events • The study sampling of anti-drug antibody is to be reviewed at the end of the study
Renal toxicity	Acute renal failure (SMQ) (Narrow and broad)	• Renal monitoring of AEs in a combination of laboratory data monitoring of UA of protein/blood and eGFR

AE = adverse event; eGFR = estimated glomerular filtration rate; Hct = hematocrit; Hgb = hemoglobin; RBC = red blood cell; SMQ = standardized MedDRA queries; UA = urinalysis

8.4.3. Adverse Events of Special Interest

Table 9 describes AESIs that may occur during study drug treatment.

Table 9: Adverse Events of Special Interest

Description	Monitor Parameter	Planned Action
Fertility disorders with a focus on suppression of FSH	SMQ fertility disorders	Fertility disorders with a focus on FSH monitoring of AEs and laboratory data review of FSH
Hepatic toxicity	Hepatic disorders (SMQ) (Narrow and broad)	Hepatic monitoring of AEs in combination of laboratory data Hy's law laboratory data monitoring AST, ALT, ALP
Cardiac events and Embolic and thrombotic events	Ischaemic heart disease (SMQ)	Monitor of AEs in combination of risk factors of systemic hypertension (diabetes, metabolic syndrome, obesity), concomitant medications,

Description	Monitor Parameter	Planned Action
	Embolic and thrombotic events (SMQ)	previous medical history of heart and embolic, thrombotic events
Thrombocytopenia, leukopenia, and neutropenia	Thrombocytopenia, leukopenia, and neutropenia	Careful monitoring of platelet counts is performed and in case platelet counts are < 50.000/mm^3 (< 50.0x10^9/L), the dose hold and/or dose decrease guidance is to be followed. Additionally: • Monitoring of leukopenia and neutropenia as part of medical and periodic review • Monitoring of AEs and the medical history and concomitant medications that may cause thrombocytopenia, leukopenia, and neutropenia

AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA queries.
Per the request of the European Health Authority, thrombocytopenia, leukopenia, and neutropenia were added as AESIs.

8.5. Safety Assessments

Planned time points for all safety assessments are provided in Section 2, the SoE.

8.5.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. A full physical examination will be completed at the Screening visit only.
- A targeted physical examination will include, at a minimum, assessments of the cardiovascular and pulmonary systems and will be completed at all other visits after screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.5.2. Vital Signs

- Temperature, weight, pulse rate, respiratory rate, and BP will be assessed at every visit. Height will be measured once, during the screening period.
- BP and pulse measurements will be assessed with a completely automated device while seated. Manual techniques will be used only if an automated device is not available.
- Vital signs should be taken before blood collection for laboratory tests. BP and pulse measurements should be preceded by approximately 10 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) for the initial reading. Blood pressure values should be confirmed by mean of 2 readings

obtained approximately 5 minutes apart. The average of the BP readings will be recorded on the eCRF.

- Clinically significant abnormal findings will be reported as AEs (see Section 6.3 and Section 8.4).

8.5.3. Electrocardiograms

- A 12-lead ECG will be obtained as outlined in the SoE. Parameters obtained will be HR, PR, QRS, and QT; QTcF intervals will be calculated. If the ECG machine does not automatically calculate QTcF, it should be manually calculated.
- Clinically significant abnormal findings will be reported as AEs.
- If scheduled on the same day, ECGs should be performed prior to 6MWT.

8.5.4. Clinical Worsening

- Clinical worsening will be assessed by the investigator at each visit outlined in the SoE (or at any other time at the Investigator's discretion) and recorded on the eCRF.
- Assessments are the following:
  - Death
  - Worsening-related listing for lung and/or heart transplant
  - Need to initiate rescue therapy (see below), with an approved PAH SOC therapy
  - Need for atrial septostomy
  - PAH-specific hospitalization (> 24 hours)
  - Functional deterioration as defined by both of the below events occurring together at any time, even if they began at different times, as compared to their Screening values:
  - Worsened WHO functional class (III to IV)

    and

  - Decrease in 6MWD by ≥ 15% as compared to Screening (confirmed by two 6MWTs; Section 8.2.4)
- Clinically significant abnormal findings will be reported as AEs.

8.5.5. Rescue Therapy Criteria

Suggested clinical worsening criteria for the investigator to initiate rescue therapy with an approved PAH SOC therapy (and therefore discontinue study drug) include the following:

- Participants who experience worsening of PAH requiring hospitalization for more than 24 hours.
- PAH functional deterioration (worsening of WHO functional class by 1 level and a decrease in 6MWD of 15% as compared to Screening measured on 2 occasions).

8.5.6. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoE for the timing and frequency.
- If Hgb is ≥ 17 g/dL during Cycle 1 (Day 8) or Cycle 2 (Day 29), participants should return weekly for Hgb monitoring. Clinically significant abnormal Hgb findings will be reported as AEs. Dose Modification Guidance should be followed (see Figure 3).
- Clinically significant abnormal Hgb findings will be reported as AEs.
- 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 participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 6 weeks after the last dose of study treatment 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, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and Section 2, SoE.
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant 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.

8.6. Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of sotatercept as specified in Section 2 SoE. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of sotatercept. Samples collected for analyses of sotatercept serum concentration may also be used to evaluate PK of other concomitant medications and safety or efficacy aspects related to concerns arising during or after the study.

Participants who have already entered the Extension Period under Protocol Amendment 3A (Q4W dosing regimen) should have a pre-dose PK sample taken at an unscheduled visit before transitioning to Q3W dosing under this amendment.

8.7. Pharmacodynamics

Venous blood samples will be collected for measurement of PD biomarkers including but not limited to NT-proBNP, transforming growth factor-βeta 1 (TGF-β1), vascular endothelial growth factor receptor (VEGFR1), and sex hormone metabolites N-terminal prohormone of brain natriuretic peptide (NT-proBNP), at time points listed in Section 2 SoE. Samples collected for NT-proBNP analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Transpulmonary Flux Biomarkers: Samples from the RHC and from the radial artery will be collected at rest, peak exercise, and post-exercise during the iCPET procedure at the time points listed in the SoE and as described in the iCPET manual. These samples will be stored and may be analyzed at a later date for exploratory biomarkers.

8.8. Genetic Testing

Participants will have a genetic sample taken to assess the mutation status and allele frequency (e.g., BMPR2) at C1D1. Since genetic mutations in *BMPR2* are associated with PAH, this testing may provide insight into the genetic basis of PAH and potential response to sotatercept. Other potential genetic analyses include, but are not limited to, activin receptor-like kinase 1, caveolin 1, eukaryotic translation initiation factor 2-alpha kinase 4, endoglin, potassium channel subfamily K member 3, and mothers against decapentaplegic homolog 9; otherwise known as SMAD9. See Appendix 9 for more information regarding genetic testing.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

Assuming the change from baseline of peak VO_2 is 1.5 mL/min/kg, with a standard deviation of 3 mL/min/kg, the sample size needed will be 19 participants with 1-sided alpha=0.10 level and 80% power. This approximate level of improvement in pulmonary hypertension patients has been associated with a 28% decrease in PVR.[11]

This sample size of 19 participants will also provide 80% power to detect an increase from baseline of at least 10 mL in RV SV at 1-sided alpha=0.10 level, assuming the standard deviation of RV SV is 20 mL. It is expected that a 10-mL improvement in SV correlates with an ability for the patient to walk and additional 41 m on 6MWT in patients with PAH.[12]

Assuming a 25% drop-out rate, approximately 25 participants will be enrolled.

9.2. Populations for Analyses

Evaluable Population: All participants who have completed the Treatment Period and had the iCPET assessment and cardiac MR imaging at the 24-week time point, with no major protocol deviations, which includes major inclusion and exclusion criteria deviations, concomitant therapy or procedures that impact the efficacy evaluation, and other deviations that also have major impacts on the efficacy of the study treatment.

Safety Population: All participants who receive at least 1 dose of study treatment.

Pharmacokinetic Population: All participants who receive at least 1 dose of study treatment and have at least 1 PK sample analyzed.

9.3. Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before topline (24 weeks) database lock and will describe the analysis details. Data will be reviewed as needed to support regulatory filings. This section is a summary of the planned statistical analyses of the primary and key secondary endpoints. A separate SAP for the extension period analysis will be developed and finalized before the final database lock.

9.3.1. Efficacy Analyses

Table 10: Statistical Analysis of Endpoints

Endpoint	Statistical Analysis Methods
Primary	The mean and standard deviation for change from baseline of peak VO_2 will be calculated together with the corresponding 95% CI. The evaluable population will be used for the primary endpoint analyses.
Secondary	Descriptive statistics will be presented for secondary cardiac MR endpoints (RV SV, RV ESV, RV EDV, RV EF, RV SVI, and RV mass by cardiac MR imaging), iCPET endpoints (VE/VCO_2, Ca-vO_2), PVR, 6MWD, and biomarker endpoint NT-proBNP. Frequency summaries will be provided for WHO functional class assessments and participants with clinical worsening. Nonlinear mixed effects modeling will be employed to determine population PK parameters of sotatercept.
Exploratory	Descriptive statistics will be presented for biomarker endpoint change from baseline in PAH-related biomarkers. Change from baseline in selected primary and secondary endpoints during the 8-week Follow-Up Period will be summarized through descriptive statistics. Exercise hemodynamic measures will be summarized through descriptive statistics.
Other Endpoints	In general, continuous data will be summarized descriptively for absolute values and change from baseline with n, mean, SD, median, minimum, maximum, and categorical data will be summarized with frequency and percentage.

6MWD = six-minute walk distance; Ca-vO_2 = content difference, arteriovenous O_2; CI = confidence interval; iCPET = invasive cardiopulmonary exercise test; MR = magnetic resonance; NT-proBNP = N-terminal prohormone of brain natriuretic peptide, PAH = pulmonary arterial hypertension; PK = Pharmacokinetic; PVR = pulmonary vascular resistance; RV = right ventricular; RV EDV = right ventricular end-diastolic volume; RV EF = right ventricular ejection fraction; RV ESV = right ventricular end-systolic volume; RV SV = right ventricular stroke volume; RV SVI = right ventricular stroke volume index; SD = standard deviation; VE/VCO_2 = ventilator efficiency; VO_2 = peak O2 uptake; WHO = World Health Organization

Details will be described in the statistical analysis plan and finalized before database lock.

9.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent AEs (TEAEs) will be summarized by worst severity grade, system organ class, and preferred term. TEAEs related to the IP will also be summarized. TEAEs leading to death or discontinuation from treatment and serious TEAEs will be listed separately.

Clinical laboratory results will be summarized descriptively for the Safety Population. Clinically significant laboratory abnormalities will be flagged in the listing. Shift tables will be presented for hematology, serum chemistry, and urinalysis tests. Renal function laboratory tests (creatinine and urine albumin creatinine ratio) will be collected regularly during the Treatment Period and may be limited to creatinine in the Extension Period. The descriptive statistics (mean, SD, median, min, max) will be provided for each time point of the collection.

Vital sign measurements, ECG results, and physical examination data will be listed for each participant at each visit. Descriptive statistics for vital signs and ECG parameters, both observed values and changes from baseline, will be summarized.

Immunogenicity (incidence/titer of ADA) will also be analyzed.

9.3.3. Other Analyses

Pharmacokinetic, PD, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock.

9.3.4. Primary Endpoint Analysis

An analysis of the primary endpoint of change in VO_2 at 24 weeks Treatment Period (Cycle 9) versus the screening assessment will be performed on the evaluable population when all participants during the Treatment Period have completed their 24-week (Cycle 9) iCPET assessment or EOT iCPET for those subjects who discontinue early during the Treatment Period, as described in Section 9.3.1.

9.3.5. Extension Period Analysis

All the endpoints will be analyzed in a similar way for the Extension Period as with the main analysis in the Treatment Period.

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11. APPENDICES

APPENDIX 1. ABBREVIATIONS AND SPECIALIST TERMS

Abbreviation or Specialist Term	Explanation
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
ACE-011	Sotatercept
ADA	Anti-drug antibody
AE	Adverse event
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{21d}	Area under the concentration-time curve from time zero to Day 21
BMP	Bone morphogenetic protein
BMPR2	Bone morphogenetic protein type II receptor
BP	Blood pressure
Ca-vO_2	Content difference, arteriovenous O_2
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum concentration
CMR	Cardiac Magnetic Resonance Imaging
CO	Cardiac output
CONSORT	Consolidated Standards of Reporting Trials
CPET	Cardiopulmonary exercise test
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTPA	Computed tomography pulmonary angiogram
C_{trough}	Minimum concentration before dosing
CxDy	Cycle x Day y
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EF	Ejection fraction
EOS	End of study
EOT	End of treatment

Abbreviation or Specialist Term	Explanation
ERA	Endothelin-receptor antagonist
FC	Functional classification
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
Hgb	Hemoglobin
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
iCPET	Invasive cardiopulmonary exercise test
IEC	Independent ethics committee
IgG1	Immunoglobulin G1
IP	Investigational product
IRB	Institutional review board
IUD	Intrauterine device
IV	Intravenous
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MR	Magnetic resonance
NOAEL	no-observed-adverse-effect level
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDE5	Phosphodiesterase type 5
PK	Pharmacokinetic

Abbreviation or Specialist Term	Explanation
PPD	PPD Safety Hotline, medical monitor for this study
PVR	Pulmonary vascular resistance
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Qp/Qs	Pulmonary-Systemic Flow Ratio
RA	Right atrial
RAP	Right atrial pressure
RBC	Red blood cell
RHC	Right heart catheterization
RV	Right ventricular
RV EDV	Right ventricular end-diastolic volume
RV EF	Right ventricular ejection fraction
RV ESV	Right ventricular end-systolic volume
RV PA	Right ventricular pulmonary artery
RV SV	Right ventricular stroke volume
RV SVI	Right ventricular stroke volume index
SBP	Systolic blood pressure
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SOC	Standard of care
SoE	Schedule of Events
SSFP	Structure and Function Sequences
SUSAR	Suspected unexpected serious adverse reaction
SV	Stroke volume
SVC	Superior vena cava
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
UA	Urinalysis
UACR	Urine albumin creatinine ratio
ULN	Upper limit of normal
VAF	Variant allele frequency
VE/VCO_2	Ventilator efficiency
Venc	Velocity encoding (cardiac motion view via MRI)

Abbreviation or Specialist Term	Explanation
VO_2 max	Peak O_2 uptake
VQ	Ventilation-perfusion
VSMC	Vascular smooth muscle cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

APPENDIX 2. CLINICAL LABORATORY TESTS

The tests detailed in Table 11 will be performed by local laboratories at the time points specified in the Schedule of Events (SoE, Section 2).

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Complete blood count (CBC) with differential: CBC includes RBCs, white blood cells (WBCs), platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte count, and platelet count
Serum chemistry	Albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide, creatinine, glucose, phosphorus, potassium, sodium, total bilirubin, direct bilirubin
Urinalysis	Urinalysis

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CR = creatinine; Hgb = hemoglobin; Hct = hematocrit; RBC = red blood cell; WBC = white blood cell

Investigators must document their review of each laboratory safety report.

APPENDIX 3. STANDARD OF CARE THERAPY

Standard of care therapy refers to combination therapy consisting of at least 2 agents (each from a different class) from a list including the following: an ERA, a PDE5 inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist.

Standard of Care should remain stable throughout the study. Small adjustments or titrations are routine SOC for PAH therapies and are considered stable dosing. If a participant has an event of clinical worsening requiring rescue therapy (see Section 8.5.5), SOC therapy may be altered as per the treating physician's decision, and the participant will be discontinued from study drug treatment. Any other changes (aside from rescue therapy for clinical worsening) to a participant's SOC should be discussed with the medical monitor on a case-by-case basis to determine if the participant may stay on study treatment.

During the Extension Period, participants under investigator's supervision can substitute, remove, or adjust the dose of SOC for PAH-worsening and chronic concomitant medications, including supplemental oxygen. Investigator discretion will be used to determine if sotatercept study drug discontinuation is necessary.

APPENDIX 4. SIX-MINUTE WALK TEST

A standardized 6MWT will be performed in accordance with the guidelines of the American Thoracic Society.[15-17] The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course should preferably be 30 m in length. The length of the corridor should be marked every 3 m. The turnaround points should be marked (e.g., with a cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor (e.g., using brightly colored tape).

The 6MWD will be calculated and recorded. If the participant discontinues the test prematurely, the time (mm:ss) and distance walked will be recorded. Requirement of acute supportive rescue medication (e.g., oxygen therapy) and any AEs occurring during the 6MWT will be recorded. If a participant is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by the investigator. During the study, the 6MWT should be done about the same time of day to avoid diurnal variation.

Required Equipment

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator
10. Portable pulse oximeter

Participant Preparation

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Participants should use their usual walking aids during the test (cane, walker, etc.).
4. The participant's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Participants should not have exercised vigorously within 2 hours of beginning the test.

Measurements

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The participant 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 BP, and make sure that clothing and shoes are appropriate. Complete portion of eCRF.
4. Measure and record baseline HR and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact.
5. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

Instruct the participant as follows:

"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."

Demonstrate by walking one lap yourself. Walk and pivot 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. Start now, or whenever you are ready."

1. Position the participant at the starting line. You should also stand near the starting line during the test. Do not walk with the participant. As soon as the participant starts to walk, start the timer.
2. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the participant. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the participant the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the participant the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the participant the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the participant the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the participant: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the participant stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer.

If the participant stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the participant 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 participant. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

Post-test:

1. Measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
2. Record the number of laps from the counter
3. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides.
4. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
5. Congratulate the participant on good effort and offer a drink of water.

APPENDIX 5. CARDIOPULMONARY EXERCISE TEST

Right Heart Catheterization

Resting supine RHC will be performed according to the iCPET manual. Zero-pressure calibration will be performed at the mid-axillary line with the patient in a supine position. SVC, RA, RV, PCW, and PA pressures will be measured, and mean vascular pressures will be calculated based on systolic and diastolic pressure measurements. Heart rate and vascular pressures are monitored continuously. Cardiac output is measured by the Fick method. Diastolic and transpulmonary pressure gradients are obtained, systemic and PVRs are calculated.

Physiologic Measurements: iCPET

Maximum symptom-limited incremental iCPET is performed using an upright cycle ergometer and a breath-by-breath metabolic cart with subjects breathing room air.

Minute ventilation, breath-by-breath pulmonary gas exchange, HR, radial arterial BP, RAP, RV pressure, and PAP are measured throughout the test. PAWP is obtained at rest and at the end of each minute of exercise.

By co-oximetry, oxygen saturation, Hgb concentration, and O_2 content (C_aO_2 and C_vO_2, respectively) are measured for each blood sample. CO is then calculated by the Fick principle using a simultaneously measured VO_2. Predicted CO_{MAX} was calculated from predicted VO_{2MAX} and an assumed maximal arterial-mixed venous O_2 content difference equivalent to a normal (Hgb) of 14 g/dL for healthy subjects.

The full iCPET guideline will be included in a separate charter.

APPENDIX 6. CARDIAC MAGNETIC RESONANCE IMAGING

Secondary endpoints of interest include change from baseline in RV SV, RV EF, RV ESV, RV EDV, RV SVI, and RV mass. The central imaging vendor will perform review of site images and will qualify sites prior to any subject enrollment. Site cardiac MR equipment, test images, and the capability to transmit cardiac MR images for central reader review are validated for qualification. Only sites who are prequalified by the central imaging vendor are permitted to participate in the study. The quality of site cardiac MR imaging is continually monitored to maintain consistency and minimize variability throughout the study. A study-specific cardiac MR imaging manual in agreement with the imaging charter will be provided for consistency in imaging performance, reporting format, and image transmission.

APPENDIX 7. STUDY GOVERNANCE 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 (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure (IB), 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 participants.
- 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 SAEs 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants 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 (HIPAA) 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 participant 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant.
- The participant 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.

Publication Policy

- All information concerning sotatercept is considered confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without the sponsor's written approval. The investigator agrees not to disclose the sponsor's confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.
- It is understood by the investigator that the information developed from this clinical study will be used by the sponsor in connection with the development of sotatercept, and therefore may be disclosed as required to regulatory agencies. To allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study.
- No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between the sponsor and the investigator.
- 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.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic 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 eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification as indicated to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product, 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 participant 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 eCRF 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.

Study and Site Closure

The sponsor 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 participants by the investigator
- Discontinuation of further study treatment development

APPENDIX 8. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom when having penile-vaginal intercourse with a WOCBP who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile/vaginal intercourse or use a male condom during each episode of penile penetration while participating in the study and for 112 days after the last dose of study treatment. Refrain from donating sperm for the duration of the study and for 112 days after the last dose of study treatment.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12. Females who are exclusively in same-sex relationships are exempt for contraception guidelines.

Female participants must agree to use highly effective forms of birth control for at least 28 days prior to starting the study, while participating in the study, and for at least 112 days after the last dose of study treatment.

Participants should refrain from breastfeeding a child, donating blood, eggs, or ovum for the duration of the study and for at least 112 days after the last dose of study treatment.

Table 12: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[1] Failure rate of < 1% per year when used consistently and correctly
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[2] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[1]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[2] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized Partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[1] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[2] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the study and for at least 112 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included in the study after two confirmed negative pregnancy tests.
- Additional pregnancy testing should be performed prior to study drug administration at each dosing visit during the study as required locally.

Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- 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 Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant 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 participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant 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 AE or 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 post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.3.10. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

APPENDIX 9. GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.
- DNA samples will be used for research related to PAH. They may also be used to develop tests/assays including diagnostic tests related to sotatercept and PAH. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for BMPR2 (and other potential genes of interest) mutational status and variant allele frequency (VAF) at baseline.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to sotatercept or study treatments of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary and may be shared with regulatory authorities such as the Food and Drug Administration and the European Medicines Agency.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

APPENDIX 10. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Substantive changes from Protocol Amendment 3A (31 October 2019) to Protocol Amendment 04 (18 June 2020) are detailed below. Minor edits are not included.

Table 13: Protocol Amendment 03A to Protocol Amendment 04 Amendment History

Protocol Location	Description of Change	Brief Rationale
Cover Page	Added: PROTOCOL AMENDMENT 04 Dated 18 June 2020	This is the protocol amendment identifier and release date.
Section 3.6, Benefit/Risk Assessment	In prior sotatercept clinical oncology studies in chemotherapy-induced anemia and osteolytic bone disease in multiple myeloma, leukopenia, neutropenia (including febrile neutropenia), granulocytopenia, and thrombocytopenia have been described as TEAEs. As a consequence of the decrease in WBCs, infection maybe a potential risk and, as a consequence of thrombocytopenia, bleeding may be a potential risk. Per health authority request, leukopenia, neutropenia, and thrombocytopenia have been identified as AESIs in this study (see Section 6.3, Dose Modification and Section 8.3, Adverse Events).	The language regarding risks added to better synchronize between information presented in the IB and information presented in the ICF.
Section 1, Synopsis Table 4, Schedule of Events: Extension and Follow-Up Periods Section 3.4.2, Extension Period Figure 1, Study Design	Dosing in the Extension Period was changed from every 4-week dosing to every 3-week dosing.	Q3W is selected to be consistent with PULSAR OLE and Phase 3 A011-11 study.

Table 13: Protocol Amendment 03A to Protocol Amendment 04 Amendment History

Protocol Location	Description of Change	Brief Rationale
Section 1, Synopsis Section 4.3, Standard of Care Section 6.9, Concomitant Therapy Appendix 3, Standard of Care Therapy	Added: "During the Extension Period, participants under investigator's supervision can substitute, remove, or adjust the dose of SOC for PAH-worsening and chronic concomitant medications, including supplemental oxygen. Investigator discretion will be used to determine if sotatercept study drug discontinuation is necessary."	This revision allows the investigator to use his clinical judgement during this extended period of study treatment in an open-label setting.
Section 1, Synopsis Section 4.7.12, Extension Period Section 4.8.1, Treatment Extension Period	Upon completion of the study participants will be provided the opportunity to transition into a future long-term follow-up study.	This open-label study permits participants in the extension period of this study to continue sotatercept therapy after the completion of this clinical study.
Section 5, Study Population	Added: "Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted, unless within the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards; March 2020 (FDA 2020)."	To align with sotatercept clinical programs and the new COVID-19 guidelines.
Section 6.2, Treatment Administration and Schedule	Added: "Where rounding the weight and total volume is necessary, please refer to the Pharmacy Manual for further details."	This has been a common question clinical sites have asked Pharmaceutical Product Development (PPD) to clarify.
Section 6.3, Dose Modification	Dose modification 'rules' were revised to guidance. Hgb and platelet guidance were revised after reviewing safety data	Safety monitoring due to ongoing patient review and an extended 1-year duration in study drug. AESIs, including leukocytopenia,

Table 13: Protocol Amendment 03A to Protocol Amendment 04 Amendment History

Protocol Location	Description of Change	Brief Rationale
Section 8.3, Adverse Events Section 8.4, Monitoring of Identified, Potential Risks, and AESI	of participants who have been administered sotatercept. AEs and blood pressure guidance were removed from this section and moved to Section 8.3 and Section 8.4. Regarding the monitoring of identified, potential, risks and AESI the management of leukocytopenia, neutropenia and thrombocytopenia AESI were added per safety review decisions.	neutropenia, and thrombocytopenia will continue to be monitored. Safety monitoring guidance on these items can be found in Section 8.4, which covers the monitoring of identified, potential, and AESIs.
Section 7.1, Discontinuation Section 7.2, Withdrawal from Study	Removed "loss of treatment effect''.	At this time, the effect is not known, and the effect cannot be defined. Therefore, the reference to the loss of treatment effect has been deleted.
Section 8.2.3, Pulmonary Vascular resistance by Right Heart Catheterization Section 2, Schedule of Events	Added hemodynamic variables • Systolic pulmonary artery pressure Diastolic pulmonary artery pressure	These were added following safety review.
Section 8.3, Adverse Event	Further defined the following: Unexpected AE: updates below are indicated in bold font) An unexpected AE is an AE that, the nature, severity, **specificity,** or outcome of which, is not consistent with the **summary of product characteristics** described in the IB under the Reference Safety Information. SAE: Hospitalization Added: A hospitalization for an elective procedure will not be considered an SAE Incapacity or Disability:	Updated according to the reporting requirements for safety monitoring, and ICH Topic E 2: A Clinical Safety Data Management. Added the word "**specificity**'' to align with GCP guidance .and the summary of product characteristics to be used only for the marketed product. Updated according to Definitions and Standards for Expedited Reporting, and AESI and SAE requirements.

Table 13: Protocol Amendment 03A to Protocol Amendment 04 Amendment History

Protocol Location	Description of Change	Brief Rationale
	Updated safety monitoring moved AESIs to Section 8.4. Deleted other irrelevant materials.	
Section 8.3.8, Overdose	Specified the definition of Overdose for sotatercept dosing based on weight.	Added to the definition of overdose and recently standardize language from Acceleron PAH clinical programs.
Section 8.3.9, Transmission of an Infectious Agent	Added language in the case that a virus or infectious particle, pathogenic or non-pathogenic, is considered an infectious agent, in addition to instructions for reporting within 24 hours.	Preparation for an infectious disease during the study.
Section 8.3.10, Pregnancy	Removed: Any infant death that is assessed as possibly related to the in utero exposure to sotatercept therapy should be reported as an SAE.	Removal is reflective of ICH safety reporting for pregnancy.
Section 8.4, Monitoring of Identified, Potential, and Adverse Events of Special Interest	Updated AESI safety monitoring parameters and guidelines after reviewing active and past AESIs experienced by sotatercept administered PAH patients.	Ongoing monitoring and evaluation of active and past sotatercept patient's AESIs are necessary to assess the overall safety of the PAH patient population; therefore, a detail section for safety monitoring AESIs was added to this sotatercept clinical study.
Section 9.3.5, Extension Period Analysis	Added the analysis for the Extension Period. All the endpoints will be analyzed in a similar way for the Extension Period as with the main analysis in the Treatment Period.	The Extension Period will be analyzed and will have a separate statistical analysis plan (SAP).
Section 9.3.4, Primary Endpoint Analysis	Added: An analysis of the primary endpoint of change in VO_2 at 24 weeks Treatment Period (Cycle 9) versus the screening	This addition gives further clarification of the Primary Endpoint Analysis.

Table 13: Protocol Amendment 03A to Protocol Amendment 04 Amendment History

Protocol Location	Description of Change	Brief Rationale
	assessment will be performed on the evaluable population when all participants during the Treatment Period have completed their 24-week (Cycle 9) iCPET assessment or EOT iCPET for those subjects who discontinue early during the Treatment Period, as described in Section 9.3.1.	
Appendix 10, Protocol Amendment History	Moved the Protocol Amendments 02 and 03A history from the Summary of Changes section to Appendix 10.	Amendment history was provided for Protocol Amendment 04 in the Summary of Changes section and was moved to Appendix 10.

Substantive changes from Protocol Amendment 02 (04 December 2018) to Protocol Amendment 03A (31 October 2019) are detailed below. Minor edits are not included.

Table 14: Protocol Amendment 02 to Protocol Amendment 03A Amendment History

Protocol Location	Description of Change	Brief Rationale
Table 1, page 3	Medical monitor has changed from PPD to PPD, who will also perform safety monitoring	Change in assignments and responsibilities
Section 1, Synopsis, page 12	Treatment Groups and Duration edited to include sotatercept dosing during the Extension Period	Participants will receive sotatercept every 3 weeks (Q3W) during the Extension Period
Table 3, Schedule of Events (SoE), pages 14-15	SoE revised to remove the 16-week Follow-Up Period; table and footnotes revised to reflect or clarify these changes	All participants will transition from the 24-week Treatment Period to the 18-month Extension Period
Table 4, SoE, pages 16-17	Extension SoE table, with footnotes, added to present the 18-month Extension Period and the 8-week Follow-Up Period for all participants enrolled	SoE table added to present the 18-month Extension Period and 8-week Follow-Up Period for all participants enrolled.
Section 3.4, page 21	Rationale for Dose Level and Frequency Selection revised to divide the 24-week Treatment Period (every 3 weeks [Q3W] dosing) from the 18-month Extension Period (Q4W dosing)	Dosing Level and Frequency are different during the 24-week Treatment Period and the 18-month Extension Period
Section 3.5, page 21	Rationale for Off Study Drug Assessments removed	All participants transition directly from the 24-week Treatment Period to the 18-month Extension Period without an Off Study Drug Period
Table 5, pages 23-24	Revised to replace Off Study/Off Study Drug with Extension Period	All participants transition directly from the 24-week Treatment Period to the 18-month Extension Period without an Off Study Drug Period
Section 4.1, page 25	Overall Design revised to include description of the 18-month Extension Period and 8-week Follow-Up Period	To present the 18-month Extension Period and 8-week Follow-Up Period for all participants enrolled

Table 14: Protocol Amendment 02 to Protocol Amendment 03A Amendment History (Continued)

Protocol Location	Description of Change	Brief Rationale
Section 4.3, Standard of Care, page 25; Section 5.1, Inclusion Criteria, page 30; Section 8.5.5, Rescue Therapy Criteria, page 50; Appendix 3, page 63	Definition of stable standard of care for PAH clarified	Small adjustments to routine standard of care (SOC) for PAH are considered stable. However, changes, removal, or addition of PAH therapies during 90 days prior to enrollment are considered unstable SOC, and these subjects do not meet inclusion criteria 8.
Section 4.6, Extension Period, page 25	18-month Extension Period inserted	To present the 18-month Extension Period for all participants enrolled
Section 4.7, Follow-up Period, page 26,	Follow-Up Period revised to describe follow-up for participants who terminate early from the study, participant in the 24-week Treatment Period but choose not to enter the 18-month Extension Period, and participants who complete the 24-week Treatment Period and the 18-month Extension Period	To clarify the Follow-Up Period for all participants enrolled
Figure 1, page 27	Figure 1 edited to remove "placebo-controlled treatment period" from the 24-week Treatment Period, remove the 16-week Off Study Drug Follow-Up Period, include the 18-month Extension Period, and the 8-week Follow-Up Period	This Phase 2a study is open-label, not placebo controlled, changed to "Treatment Period" To reflect study design modifications as described for all participants
Section 4.8.1, Extension Period, page 28	Extension Period section inserted to describe the Q4W dosing schedule during the 18-month Extension Period	In the 18-month Extension Period, a dose regimen of Q4W will be evaluated, with dose adjustment as needed to maintain equivalent exposure

Table 14: Protocol Amendment 02 to Protocol Amendment 03A Amendment History (Continued)

Protocol Location	Description of Change	Brief Rationale
Section 4.10, Justification for Dose, pages 28-29	Justification For Dose during the 24-week Treatment Period (Q3W dosing) and the 18-month Extension Period (Q4W dosing) edited to clarify exposures and exposure-matching during these treatment periods	To justify the 2 different dosing intervals, and the data modeling to explain exposure-matching during the 18-month Extension Period.
Justification for the Off Study Drug Period	Removed Justification for the Off Study Drug Period	All participants transition directly from the 24-week Treatment Period to the 18-month Extension Period without an Off-Study Drug Period
Section 5.1, Inclusion Criteria, page 30	Pulmonary function test clarified for Inclusion criterion 5	Normalization of FVC (% predicted FVC) and FEV_1/FVC (% predicted FEV_1/FVC) are based on measure pulmonary function in a healthy normal population with 2 lungs. There is no population-based normalization method for patients who have less than complete lungs. Therefore, further adjustment will be permitted, based on the remaining fraction of lung volume in subjects with a history of lobectomy or pneumonectomy.

Table 14: Protocol Amendment 02 to Protocol Amendment 03A Amendment History (Continued)

Protocol Location	Description of Change	Brief Rationale
Table 6, pages 35-36	Dose modifications clarified If target blood pressure (BP) is maintained at the subsequent cycle, dose can be escalated, if applicable. Consider phlebotomy until hemoglobin (Hgb) < 16.0 g/dL; delay dose for 1 cycle. At the next cycle, if Hgb is: a) < 18.0 g/dL, reduce study drug by 1 dose level and restart dosing. If dose reductions were done due to an adverse event not related to study medication, the dose can be escalated when the adverse event is resolved. In cases of dose reduction due to increases in Hgb, the dose can be re-escalated after 2 consecutive cycles in which Hgb values are stable and equal or lower than the upper limit of normal.	To clarify dose modifications due to adverse events
Section 7.2, Withdrawal from Study, page 39	Withdrawal from the Study section revised to clarify rescue therapy and study withdrawal	To ensure that patients who need rescue therapy due to clinical worsening are withdrawn from the study
Section 8, Study Assessments and Procedures, page 41	Study assessments revised to define End of Study (EOS) assessment and 8-week Follow-Up for all participants	Study assessments revised to define EOS and 8-week Follow-Up Period in the 18-month Extension Period
Section 8.2.1, (iCPET), page 41	Invasive Cardiopulmonary Exercise Test (iCPET) Assessment clarified for participants at Cycle 9, Day 169, in the 24-week Treatment Period, and Cycle 14 in the 18-month Extension Period	iCPET Assessment clarified for participants to reflect changes in the SoE (Tables 3 and 4)

Table 14: Protocol Amendment 02 to Protocol Amendment 03A Amendment History (Continued)

Protocol Location	Description of Change	Brief Rationale
Section 8.2.2, Cardiac Magnetic Resonance Imaging, page 42	Cardiac Magnetic Resonance Imaging expanded to include measures to support Secondary and Exploratory Objectives	Cardiac Magnetic Resonance Imaging expanded to include request for additional measures to support Secondary and Exploratory Objectives of the study
Throughout	Mention of secondary endpoint RV SWI removed from synopsis and body of the protocol.	Not calculated via cardiac magnetic resonance imaging as pressure values are not obtained via CMR, which are required in order to calculate RVSWI.
Throughout	Additional section headers inserted in order to include sections in Table of Contents	To assist investigative personnel with more rapid searching for sections of interest

Substantive changes from the Protocol Amendment 01 (13 September 2018) to Protocol Amendment 02 (05 December 2018) are detailed below. Minor edits are not included.

Table 15: Protocol Amendment 01 to Protocol Amendment 02 Amendment History

Protocol Location	Description of Change	Brief Rationale
Table 2, Schedule of Events Section 8.2, Efficacy Assessments	Assessments and timepoints rearranged and clarified. Some footnotes were removed	Assessments and timepoints have been edited to better capture meaningful changes and timepoints throughout the study. Other edits of Treatment Period, Follow-Up Period, and EOS have been made for clarity. Redundant and unnecessary footnotes were removed.
Section 5.1, Inclusion Criteria	Inclusion criterion 8: increase 6MWD upper limit Inclusion criterion 10: Contraceptive guidelines language clarified. Changed timing of the requirement for effective contraception use prior to starting investigational product from 5 weeks to 28 days.	6MWD distance upper threshold increased to accommodate for effect from stable SOC. To align inclusion criterion with the Appendix 8 guidelines and definitions. To align contraception guidelines with study timelines.
Section 5.2, Exclusion Criteria	Exclusion criterion 10: Changed the baseline hemoglobin level for exclusion for women from > 15 g/dL to > 16 g/dL Exclusion criterion 24: removed "active on the lung transplant list."	To align the hemoglobin exclusion criterion for both genders. To allow participants to enroll in the study if they are active on the lung transplant list and meet all other inclusion/exclusion criteria.
Section 5.3, Screen Failures	Added details regarding capturing AEs and frequency of rescreening for screen failures.	To clarify that AE details are to be captured for screen failures and rescreening is allowed only once.
Section 6.3, Dose Modification	Table 5: Changed the dose modification rules for AEs, hemoglobin, and blood pressure.	To align with updated inclusion/exclusion criteria and to clarify when doses of study drug should be delayed, reduced, or escalated.
Section 7.1, Discontinuation of Study Treatment	Added that discontinuation of study treatment would occur if a subject has a QTcF > 500ms during the treatment period.	To ensure that participants who meet this threshold are discontinued appropriately.

Table 15: Protocol Amendment 01 to Protocol Amendment 02 Amendment History (Continued)

Protocol Location	Description of Change	Brief Rationale
Section 8.4, Safety Assessments.	Weight was moved from the physical exam section (8.4.1) to the vital signs section (8.4.2).	Weight is collected and recorded in the eCRF as a part of the vital signs.
Section 8.4.6, Clinical Safety Laboratory Assessments	Added, "If hemoglobin is ≥ 17 g/dL during Cycle 1 (Day 8) or Cycle 2 (Day 30), participants should return weekly for hemoglobin monitoring."	To ensure that participants whose hemoglobin levels become high are appropriately monitored.
Appendix 8, Contraceptive Guidance and Collection of Pregnancy Information	Contraceptive guidelines language clarified.	To align with Inclusion Criteria and study timelines.

Substantive changes from the protocol (17 July 2018) to Amendment 1 (13 September 2018) are listed below. Minor edits are not included.

Table 16: The Original Protocol to Protocol Amendment 01 Amendment History

Protocol Location	Description of Change	Brief Rationale
Table 1, page 3	Medical monitor at Acceleron: PPD Removing PPD medical monitor	Medical monitor has changed from PPD to PPD who will also perform safety monitoring.
Synopsis Section 3.1, Study Rationale Section 4, Study Design Section 4.4, Justification for Dose Section 6.3, Dose Modification	Starting dose for Cycle 1 has been changed to 0.3 mg/kg; starting dose for Cycles 2-8 is 0.7 mg/kg.	To reduce the chances of participants having elevated hemoglobin.
Table 2, Schedule of Events Section 8.2, Efficacy Assessments	• Removed quality of life assessments, serology, and non-invasive CPET • Moved 6-minute walk test from Cycle 3 to Cycle 5 • Timing of primary endpoint assessment clarified as occurring after 24 weeks of treatment • Follow-Up Period defined as 4 visits • Windowing around End of Study visit edited to 16 weeks post last dose plus 7 days (not plus/minus)	Assessments and timepoints have been edited to better capture meaningful changes and timepoints throughout the study. Other edits of Treatment Period, Follow-Up Period, and EOS have been made for clarity.
Section 8.3, Adverse Events	All AEs (serious and non-serious, related and non-related) are to be recorded on the eCRF from the time of signing of consent to the EOS visit.	Clarification on the intent of capturing all AEs.