Official Protocol Title:	A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study to Compare the Efficacy and Safety of Sotatercept (ACE-011) Versus Placebo When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH)
NCT number:	NCT03496207
Document Date:	31 July 2020

Protocol A011-09

Protocol Title:

A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study to Compare the Efficacy and Safety of Sotatercept (ACE-011) Versus Placebo When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH)

Short Title:

A Phase 2 Study of Sotatercept for the Treatment of PAH

SPONSOR: Acceleron Pharma Inc.
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Regulatory Agency Identifying Number(s):	IND 136150 EudraCT 2017-004738-27
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PROTOCOL AMENDMENT 01B:	15 February 2018
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PROTOCOL AMENDMENT 05D:	12 August 2018
PROTOCOL AMENDMENT 06D:	18 December 2018
PROTOCOL AMENDMENT 07D:	31 July 2020

Signature Page

Acceleron Pharma Approval

Signature: PPD **Date:** 31 Jul 2020

Name (print): PPD

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 to 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 (Appendix 4).

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	Janethe de Oliveira Pena, MD, PhD	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 USA Direct Line: + 617-649-9210 Mobile: 617-909-6241 jpena@acceleronpharma.com
Medical Monitor, PPD	Edward Matheis, MD, FCCP	PPD 3900 South Paramount Parkway 3rd floor Morrisville, NC 27560-8408 USA Phone +888 483 7729 edward.matheis@ppdi.com
Pharmacovigilance	Various	PPD Safety Hotline Granta Park Great Abington, Cambridge CB21 6GQ England, UK Phone: +44 122 337 4240

Protocol Amendment Summary of Changes Table

Substantive changes from Amendment 6D (18 December 2018) to Protocol Amendment 7D (31 July 2020) are detailed below. Minor edits are not included. See Appendix 8 for the rest of the Protocol Amendment History.

Protocol Location	Description of Change	Brief Rationale
Title Page	Added: PROTOCOL AMENDMENT 07D: Dated 31 July 2020	Protocol amendment identifier and release date.
Table 1, page3	Updated Contact for the Pharmacovigilance safety contact.	The Pharmacovigilance safety contact has changed. The contact information has been updated.
Section 1, Synopsis Section 4.1, Overall Design	Objectives, endpoints, and study design were updated.	Sections were updated to include study design modifications to assess long-term benefit and persistence of the effect of sotatercept.
Section 1, Synopsis Section 2, Schedule of Events Section 4.1, Overall Design Figure 1	Eighteen-month Extension Period was extended by an additional 12 months to a 30-month Extension Period.	It was revised to accommodate patients completing the 18-month Extension Period that would like to continue study treatment at the investigator's discretion.
	Change to Extension Period from blinded to unblinded.	Upon completion of primary endpoint analysis, the extension will be unblinded for patient transparency and to allow investigators to up titrate dose level up to 0.7 mg/kg dose level as needed.
	Upon completion of the study, participants will be provided the opportunity to transition into a separate Sotatercept Long-Term Follow-Up Study.	Permits participants in the extension period of this study to continue sotatercept therapy after the completion of this clinical study.

Protocol Location	Description of Change	Brief Rationale
Section 2, Schedule of Events	Additional 3rd RHC will be done at C25. For participants who passed C25, RHC should be done at the next possible visit up to C33.	The additional RHC has been added to C25 to assess long-term benefits and persistence of the effect of sotatercept.
	Add the evaluation of RHC Add Cycle 42 and Cycle 51 Add the assessment of 12-lead ECG.	RHC and 12-lead ECG during the extension visit will further evaluate the safety and efficacy of the study drug. RHC added to assess long-term benefits and durability of the effect of sotatercept treatment.
	Add Cycles 35, 36, 37, 38, 39, 40, 41, 43, 44, 45, 46, 47, 48, 49, and 50. Remove the evaluation of serum chemistry, and anti-drug antibody.	Serum chemistry and anti-drug antibody are not needed as frequently for safety monitoring in the extension period of the study.
	Corrected UA and UACR assessments in the Extension Period (Table 4).	To clarify that UACR will be performed in combination with UA up to C33 but will not be performed at C42 or C51 in the Extension Period.
	Added footnote to the Schedule of Events for the Extension Period (Table 4).	To clarify that participants are eligible, upon completion of the third RHC, to enroll in the Sotatercept Long-Term Follow-Up Study.
	Updated SOE to include ECHO, 6MWD, WHO FC, pre-dose PK, and NT-proBNP evaluations at the respective third RHC visit.	Additional echocardiography imaging, 6MWT, WHO FC, pre-dose PK, and NT-proBNP were added to support maintenance of clinical benefits including the beneficial effect of sotatercept on right ventricular function and structure.
Synopsis Section 4.1, Overall Design Section 6.3, Dose Modification Section 6.5, Randomization and Blinding Section 8.2, Efficacy Assessments	Added additional Cycles 35 to 51 and additional assessment, safety monitoring evaluations, dose modification adjustments, and updated blinding process and study schematic (Figure 1)	Provide additional treatment and follow-up evaluations/visits and updated the unblinding process for transparency and align language to reflect these sections.

Protocol Location	Description of Change	Brief Rationale
Section 6.2, Treatment Administration and Schedule	Added: "Where rounding is necessary to calculate the total volume to be administered based on weight, rounding should be at 1 decimal place. Please refer to the IRT manual for details."	This has been a common question Investigator Sites have asked Pharmaceutical Product Development (PPD) for additional clarification.
Section 6.3, Dose Modification	Corrected guidance for dose modifications and dose delay (Figure 2 and Figure 3).	To clarify that participants are to RESTART/CONTINUE on the same dose level administered prior to the dose delay.
	Amended text: "Upon approval of Protocol Amendment 07D and unblinding of study sites and participants, study treatment dose may be escalated up to 0.7 mg/kg. If dose reductions are conducted due to an AE not related to study treatment, the dose can be escalated when the AE resolves. In cases of dose reduction due to an increase in Hgb or decrease in platelets, the dose can be escalated after 2 consecutive cycles in which Hgb or platelet values are stable."	To clarify the dose modification guidelines.
Section 6.3, Dose Modification Section 8.3, Adverse Events Section 8.4., Monitoring of Identified, Potential, and Adverse Events of Special Interest	Dose modification "rules" were revised to guidance. Hgb and thrombocytopenia guidance was revised due to the 1-year extension of study treatment. AEs, leukocytopenia, neutropenia, and blood pressure guidances were removed from this section and moved to Section 8.3, Adverse Events and Section 8.4, Monitoring of Identified, Potential, and Adverse Event of Special Interest. Moved management of leukocytopenia, neutropenia, and AESI per DMC decisions.	Safety monitoring due to ongoing patient review and an extended 1-year duration in study treatment. AESIs, neutropenia, and leukocytopenia 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 6.5., Randomization and Blinding	Added unblinding process: Following the conduct and results of the C9D1 primary endpoint and the approval of Protocol A011-09 amendment 07D, the study treatment	This assists the investigator in using discretion on SOC treatment during the Extension Period.

Protocol Location	Description of Change	Brief Rationale
	will be unblinded to study teams, investigators, and study participants.	
Section 6.9., Concomitant Therapy	During the Extension Period, following Protocol Amendment 07D, the decision criteria for permitting concomitant medications additions, removal, or adjustments for PAH or other chronic conditions will be based on the investigator's discretion. This includes the decision to adjust or discontinue sotatercept study treatment. If changes occur for concomitant medications, it should be recorded in the appropriate eCRF.	This revision allows the investigator the decision to adjust or discontinue sotatercept study treatment while adding, removing, or adjusting the dose of SOC concomitant medications (for any chronic conditions or PAH worsening). The criteria are more permissible since during the Extension Period, the study will be unblinded, and C9D1 primary endpoint results will have been collected at this time.
Section 7.1., Discontinuation of Study Treatment Section 7.2., Withdrawal from the Study	Remove loss of treatment effect.	At this time, the effect is not known, and we cannot define the effect. Therefore, the reference to the loss of treatment effect has been deleted.
Section 8.2.1., Pulmonary Vascular Resistance by Right Heart Catheterization	**Revised with an additional RHC performed at C25**. For participants who passed C25, RHC should be done at the next possible visit up to C33.	Revised to reflect the additional RHC added to assess long-term durability and efficacy of sotatercept.
Section 8.2.3., Echocardiogram Parameters	Added LVEF.	LVEF to be measured in the placebo-controlled period.
Section 8.3., Adverse Event	Further defined the following: Unexpected AE: (added bold) An unexpected AE, the nature, severity, **specificity**, or outcome of which is not consistent with the current IB under the Reference Safety Information (added specificity) 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 E2: 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

Protocol Location	Description of Change	Brief Rationale
	Updated safety monitoring moved AESIs to Section 8.4. Deleted other irrelevant materials.	Reporting, and AESI and SAE requirements.
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 Phase 3 Acceleron PAH clinical programs.
Section 8.3.9, Transmission of an Infectious Agent	Added language in the case of a virus or infectious particles pathogenic or nonpathogenic, is considered an infectious agent and reporting instructions 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 or blinded therapy should be reported as an SAE.	Safety monitoring and reporting 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 trial.
Section 9.3, Statistical Analyses	Updated to refer include the statistical analysis plan (SAP) for the Extension Period.	The Extension Period SAP is added in this section to address the study updated design.
Appendix 2, Standard of Care Therapy	Added: "During the Extension Period, PAH-specific medications can be modified (substituted, removed, or adjust the dose), including supplemental oxygen discontinuation of sotatercept study drug discontinuation is based on investigator's discretion."	In the Extension Period, participants under investigator's supervision are allowed to substitute, remove, or adjust the dose of SOC concomitant medications (for any chronic conditions or PAH worsening). The criteria are more permissible since, during the Extension Period, the study will be unblinded and C9D1 primary endpoint results will have been collected at this time.

Protocol Location	Description of Change	Brief Rationale
Appendix 8, Protocol Amendment History	Moved amendments 03A, 04A, and 05A Protocol Amendment history from Summary of Changes to Appendix 8.	Weight is collected and recorded in the eCRF as a part of the vital signs. Amendment history was provided for amendment 05A in the Summary of Changes section of the protocol and was moved to Appendix 8.
Appendix 1, Clinical Laboratory Tests, Table 12, Protocol-Required Safety Laboratory Assessments	In Table 12, Chemistry section, Added bicarbonate, reads "carbon dioxide/bicarbonate."	Added bicarbonate to accommodate regional differences in chemistry testing for carbon dioxide.

AE = adverse event; AESI = adverse event of special interest; Cx = Cycle x; DMC = Data Monitoring Committee; ECG = electrocardiogram; ECHO = echocardiogram; eCRF = electronic case report form; EOT = End of Treatment; FC = functional class; GCP = Good Clinical Practice; Hgb = hemoglobin; ICH = International Council for Harmonisation; IRB/EC = institutional review board/ethics committee; IRT = interactive response technology; LVEF = left ventricular ejection fraction; PAH = pulmonary arterial hypertension; PK = pharmacokinetic; PPD = Pharmaceutical Product Development; RHC = right heart catheterization; SAP = statistical analysis plan; SAE = adverse event; SAP = statistical analysis plan; SOC = standard of care; SOE = Schedule of Events UA = urinalysis; UACR = urine albumin creatinine ratio.

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1. SYNOPSIS

Protocol Title

A Phase 2, Double-Blind, Placebo-Controlled Randomized Study to Compare the Efficacy and Safety of Sotatercept (ACE-011) Versus Placebo When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH)

Short Title

A Phase 2 Study of Sotatercept for the Treatment of PAH

Rationale

Study A011-09 is a Phase 2, double-blind, randomized, placebo-controlled, multicenter, parallel-group study to determine the efficacy and safety of Sotatercept (ACE-011) plus standard of care (SOC) versus placebo plus SOC in adults with pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1). The study is divided into the Screening Period, Placebo-Controlled Treatment Period, Extension Period, and Follow-Up Period.

Table 2: Objectives and Endpoints

Primary –– Placebo-Controlled Treatment and Extension Periods	
Primary Objective	Primary Endpoints
Placebo-Controlled Treatment Period • To evaluate the effect on PVR in WHO functional class II-III PAH patients treated with sotatercept plus SOC compared with placebo plus SOC	Placebo-Controlled Treatment Period • Change in PVR at 24 weeks (C9D1A) vs. screening PVR
Extension Period • To evaluate the disease-modifying effect of sotatercept and additional efficacy analysis • To evaluate the long-term safety of sotatercept in WHO FC II-III PAH participants	Extension Period • Change from baseline in PVR at Cycle 25 (or next cycles up to Cycle 33) for the Delayed Start efficacy analysis • Change from baseline in PVR at Cycle 25 (or next cycles up to Cycle 33) for the Placebo-Crossed treatment group • Safety and tolerability assessments based on AEs, clinical laboratory values, and vital signs

Secondary – Placebo-Controlled Treatment and Extension Periods	
Secondary Objectives	Secondary Endpoints
• To assess the effects of sotatercept plus SOC on functional and PD endpoints in patients with PAH compared with placebo plus SOC • To assess the safety and tolerability of sotatercept in participants with PAH • To assess the PK of sotatercept in participants with PAH	Placebo-Controlled Treatment Period Key Secondary Endpoint: • Change from baseline (screening or C1D1) in 6MWD at 24 weeks (C9D1A) Other Secondary Endpoints: • Change from baseline (C1D1) in NT-proBNP at 24 weeks (C9D1A) • Change from baseline (C1D1) in TAPSE at 24 weeks (C9D1A) • Clinical worsening (e.g., hospitalizations, change in WHO functional class, and as defined in Section 8.5.4) from C1D1 to C9D1A • Change in WHO functional class at 24 weeks (C9D1A) vs. screening • Change from baseline (C1D1) in QoL (CAMPHOR, SF-36) at 24 weeks (C9D1A) • Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, vital signs, electrocardiograms (ECGs) • Population PK parameters of sotatercept
Extension Period • To evaluate the disease modifying effect of sotatercept and additional efficacy analysis	Extension Period Key Secondary Endpoints: • Change from baseline in 6MWD at Cycle 25 (or next cycles up to Cycle 33) for the Delayed-Start efficacy analysis • Change from baseline in 6MWD at Cycle 25 (or next cycles up to Cycle 33) for the Placebo-Crossed efficacy analysis Other Secondary Endpoints: • Change from baseline in WHO FC at Cycle 25 (or next cycles up to Cycle 33) for the Delayed-Start efficacy analysis

	• Change from baseline in WHO FC at Cycle 25 (or next cycles up to Cycle 33) for the Placebo-Crossed efficacy analysis
Exploratory – Placebo-Controlled Treatment and Extension Periods	
Exploratory Objectives	Exploratory Endpoints
• To assess relevant biomarkers for PAH • To assess efficacy parameters in participants with PAH	• Change from baseline (C1D1) in TGF-β ligands (e.g., activin A) and other PAH-related biomarkers at 24 weeks (C9D1A) • Change from baseline (historical or C1D1) in ECHO parameters (e.g., RVEF, PAP) at 24 weeks (C9D1A) • Correlation of clinical efficacy vs. BMPR2 expression in PBMCs • Correlation of clinical efficacy vs. sex hormone levels in males and females (e.g., estradiol metabolites)

6MWD = 6-minute-walk distance; AE = adverse event; BMPR2 = bone morphogenetic protein receptor type II; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CxDy = Cycle x Day y; ECG = electrocardiogram; ECHO = echocardiogram; FC = functional class; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; QoL = quality of life; RVEF = right ventricular ejection fraction; SF-36 = 36-Item Short Form Health Survey; SOC = standard of care; TAPSE = tricuspid annular plane systolic excursion; TGF-β = transforming growth factor-beta; WHO = World Health Organization

Overall Design

This is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group study of sotatercept plus SOC versus placebo plus SOC in participants with PAH of WHO functional class (FC) II-III. Participants will remain on SOC therapies during all periods of the study.

In the Placebo-Controlled Treatment Period, participants will be randomly assigned in a 3:3:4 ratio to receive subcutaneous (SC) injections of placebo, sotatercept 0.3 mg/kg, or sotatercept 0.7 mg/kg, respectively, every 21 days for a period of 24 weeks. During all periods of the study, all participants will also remain on SOC therapies. Participants who have not discontinued early from the Placebo-Controlled Treatment Period and have had a Cycle 9 Day 1A (C9D1A) pulmonary vascular resistance (PVR) assessment will continue into the 30-month Extension Period. After the primary endpoint analysis is completed, the trial will be unblinded and extended for an additional 12 months. Investigators will be provided with the treatment assignments of their respective patients. In the Extension Period, participants who received sotatercept in the Placebo-Controlled Treatment Period will continue to receive their current dose of sotatercept SC every 21 days plus SOC. Participants who received placebo will be re-randomized 1:1 to receive either sotatercept 0.3 mg/kg SC or sotatercept 0.7 mg/kg SC every 21 days plus SOC (see Section 6.5 for details).

Participants will have the opportunity to transition into a future sotatercept long-term follow-up study following completion of the third right heart catheterization (RHC).

An independent Data Monitoring Committee (DMC) will be used to provide unblinded safety monitoring, see Section 9.3.4 for the DMC review details, after at least 15 participants have been enrolled and completed Cycle 2, and at 6-month intervals thereafter. Section 9.3.3 and a detailed charter will outline all activities of the DMC (including, but not limited to, type of data to be reviewed, DMC responsibilities, and frequency of meetings).

The primary endpoint analysis will be performed when all participants have completed the Cycle 9 Day 1 (C9D1A) PVR assessment or End of Treatment (EOT) PVR (for those subjects to discontinue early in the Placebo-Controlled Treatment Period). Further information is available in Section 9.3.5. After primary endpoint analysis is completed, the trial will be unblinded, and the DMC will continue to provide safety monitoring at approximately 6-month intervals, or ad hoc as necessary thereafter throughout the Extension Period.

Number of Participants

Approximately 100 participants will be randomly assigned in a 3:3:4 ratio to the 3 treatment groups.

Randomization Stratification Factor

Randomization will be stratified based on baseline (C1D1) WHO FC classification (II or III) as described in the Study Manual.

Treatment Groups and Duration

Study participation for each participant includes a Screening Period of 28 days, a 24-week, double-blind, Placebo-Controlled Treatment Period, and, if applicable, a 30-month Extension Period. The Follow-Up Period will last 8 weeks following the last dose of study treatment.

Each eligible participant will be randomly assigned in a 3:3:4 ratio to 1 of the 3 treatment groups during the Placebo-Controlled Treatment Period:

- Arm 1: Placebo SC every 21 days plus SOC for 24 weeks
- Arm 2: Sotatercept (0.3 mg/kg, SC) every 21 days plus SOC for 24 weeks
- Arm 3: Sotatercept (0.7 mg/kg, SC) every 21 days plus SOC for 24 weeks

Standard of care therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with endothelin-receptor antagonists (ERAs), phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. Additional SOC details can be found in Appendix 2. Participants who have not discontinued early from the Placebo-Controlled Treatment Period and have had the 24-week (C9D1A) PVR assessment will continue into the 30-month Extension Period and will be treated as follows:

- Placebo participants will be randomized 1:1 to receive either 0.3 or 0.7 mg/kg, sotatercept every 21 days plus SOC
- Sotatercept-treated participants will continue on their current dose every 21 days plus SOC

2. SCHEDULE OF EVENTS

Table 3: Schedule of Events: Placebo-Controlled Treatment Period

	Screening Period (up to 28 days before Cycle 1 Day 1)	Placebo-Controlled Treatment Period (24 Weeks)[1]										
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9 Day 1A[2]
		Day 1 ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 8 ±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent	X											
Inclusion/ exclusion criteria	X											
Medical history	X											
Physical examination[3]	X	X		X		X	X	X	X	X	X	X
Vital signs including weight	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[4]	X	X		X		X	X	X	X	X	X	X
Hematology[5]	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X		X		X	X	X	X	X	X	X
Urinalysis/urine albumin creatinine ratio		X						X				X
12-lead ECG	X	X		X								X
Pulmonary tests (if necessary)[6]	X											
Anti-drug antibody		X		X		X		X			X	X
Randomization		X										
Genetic sample (optional)		X										
Right heart catheterization (RHC)[7]	X											X
ECHO[8]	X	X		X		X		X				X
6MWT[9, 10]	X[9]	X					X		X		X	X

Table 3: Schedule of Events: Placebo-Controlled Treatment Period (Continued)

	Screening Period (up to 28 days before Cycle 1 Day 1)	Placebo-Controlled Treatment Period (24 Weeks)[1]										
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9 Day 1A[2]
		Day 1 ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 8 ±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
QoL[10]		X		X			X		X		X	X
WHO Functional class assessment	X	X		X		X	X	X	X	X	X	X
Clinical worsening		X		X		X	X	X	X	X	X	X
Pre-dose (or no dose) PK collection		X	X	X	X	X		X			X	X
Post-dose PK collection[11]		X						X				
PD blood biomarkers		X		X				X			X	X
Seminal fluid collection (optional)[12]	X											
Study treatment administration[13]		X		X		X	X	X	X	X	X	
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X

6MWT = 6-meter walking test; AE = adverse event; CT = computed tomography; CxDy = cycle x day y; ECG = electrocardiogram; ECHO = echocardiogram; Hgb = hemoglobin; LVEF = left ventricular ejection fraction; PAP = pulmonary arterial pressure; PD = pharmacodynamics; PK = pharmacokinetic; QoL =quality of life; RHC = right heart catheterization; SAE = serious adverse event; TAPSE = tricuspid annular plan systolic excursion; VQ = ventilation-perfusion (scan).

[1] All visit day windows should be considered relative to the date of the previous dose of study treatment. Cycles are every 21 days (±3 days) except for RHC and ECHO as noted below.

[2] C9D1A procedures are to occur prior to C9D1B procedures on the same day except for RHC and ECHO, which may be performed earlier per protocol.

[3] A full physical examination should be completed at the Screening Visit; a targeted cardiopulmonary exam should be completed at all other visits.

[4] Pregnancy test (urine or serum) is required for female participants of childbearing potential at Screening and prior to each dose of study treatment. (See Appendix 5 for pregnancy follow-up).

[5] Results from the hematology panel should be evaluated prior to study treatment administration. For C1D1, C2D1, C9D1A/B, and C10D1 visits, blood samples should be taken and assessed for Hgb levels on the same day as study treatment administration. For all other dosing cycles, blood samples may be taken and assessed for Hgb levels on the same day as study treatment administration or 1 day prior. If Hgb is ≥ 17.0 g/dL at Day 8 visits for Cycles 1 or 2, participants should return weekly for Hgb monitoring (and continue to follow Dose Modification guidance for dosing days [Section 6.3]).

[6] Additional screening procedures to include pulmonary functional tests (PFTs) and VQ/CT pulmonary angiogram (CTPA) as per Inclusion criteria 5 and 6 (Section 5.1) if historical readings are unavailable.
[7] Three RHCs should be performed during the course of this study. The RHCs in the Placebo-Controlled Treatment Period must occur **within 10 days prior** to C1D1 (during the Screening Period) and C9D1A. For participants discontinuing the study before C9D1A, an RHC should be performed **± 10 days** of the EOT visit. If other assessments are occurring on the same day, RHC should be performed last.
[8] ECHO parameters include but are not limited to: TAPSE, PAP, right ventricular ejection fraction, and LVEF. Additional screening procedures to include ECHO as per exclusion criterion 16 (Section 5.2) if historical readings are unavailable. If an ECHO is performed during screening, these values may be used as the baseline for this study and an additional ECHO is not required for these participants at C1D1. If a historical ECHO is evaluated during the Screening Period, the participant should receive an ECHO at the C1D1 visit which will serve as the baseline for the study for these participants. All ECHOs from C1D1 onward may be performed **within 1 week** of study visit.
[9] 6MWT to be performed twice during the Screening Period at least 4 hours (but no longer than 1 week) apart. 6MWT may also be done twice based on criteria outlined for clinical worsening (Section 8.5.4). If screening 6MWT is done **within 10 days** of C1D1, this value can serve as the baseline value and an additional 6MWT does not need to be conducted at C1D1. If the screening 6MWT is conducted > 10 days prior to C1D1, then the 6MWT should be done as part of the C1D1 assessments.
[10] QoL: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), SF36, should be performed before 6MWT, blood draws, AE discussions, and RHC.
[11] The post-dose PK sample will be collected within 4 hours of dosing (minimum of 15 minutes from dose administration).
[12] Seminal fluid collection is optional for male participants (Section 8.9).
[13] Study procedures should be done prior to the administration of study treatment except for postdose PK collection. 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).

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

	Extension Period (30 months)[1,13]										Follow-Up Period (8 Weeks)	
	Cycle 9		Cycle 10		Cycles 11-12, 14-16, 18-20, 22-24	Cycles 13, 17, 21	Cycles 25-33	Cycle 34	Cycles 35, 37, 39, 41, 43, 45, 47, 49	Cycles 36, 38, 40, 44, 46, 48, 50	Cycles 42 and 51	End of Treatment[13]	End of Study[13]
	Day 1B[2] ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 8 ±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	4 weeks[2] or at the time of early discontinuation (±3 days)	8 weeks (±7 days) post last dose of study treatment)
Physical examination[3]			X		X	X	X	X			X		X
Vital signs (including weight)		X	X	X	X	X	X	X	X	X	X		X
Pregnancy test[4]			X		X	X	X	X	X	X	X		
Hematology[5]		X	X	X	X	X	X	X	X	X	X		X
Serum chemistry			X		X	X	X	X			X		X
Urinalysis						X					X		X
Urine albumin-creatinine ratio						X							X
12-lead ECG							X				X		X
Anti-drug antibody			X			X		X		X	X		X
Randomization	X												
Right heart catheterization							X[6]					X	
ECHO[7]			X			X	X[14]				X	X	X
6MWT[8]			X		X[14]	X	X				X	X	X
QoL[9]			X			X					X	X	X
WHO Functional Class Assessment			X		X	X	X	X			X	X	X
Clinical worsening			X		X	X	X	X	X	X	X	X	X
Pre-dose (or no dose) PK collection		X	X	X	X[14]	X	X[14]	X				X	X

	Extension Period (30 months)[1,13]											Follow-Up Period (8 Weeks)	
	Cycle 9		Cycle 10		Cycles 11-12, 14-16, 18-20, 22-24	Cycles 13, 17, 21	Cycles 25-33	Cycle 34	Cycles 35, 37, 39, 41, 43, 45, 47, 49	Cycles 36, 38, 40, 44, 46, 48, 50	Cycles 42 and 51	End of Treatment[13]	End of Study[13]
	Day 1B[2] ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 8 ±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	4 weeks[2] or at the time of early discontinuation (±3 days)	8 weeks (±7 days) post last dose of study treatment)
Post-dose PK collection[10]	X					X		X					
PD blood biomarkers			X		X[14]	X	X[14]	X					X
Seminal fluid collections (optional)[11]													
Study treatment administration[12]	X		X		X	X	X	X	X		X		
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X

6MWT = 6-meter walking test; AE = adverse event; CT = computed tomography; CxDy = cycle x day y; ECG = electrocardiogram; ECHO = echocardiogram; EOS = End of Study; EOT = End of Treatment; Hgb = hemoglobin; IRB/IEC = Institutional Review Board/Independent Ethics Committee; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PAP = pulmonary arterial pressure; PD = pharmacodynamics; PK = pharmacokinetic; QoL = quality of life; RHC = right heart catheterization; SAE = serious adverse event; TAPSE = tricuspid annular plan systolic excursion; VQ = ventilation-perfusion (scan); WHO = World Health Organization.

[1] All visit day windows should be considered relative to the date of the previous dose of study treatment. Cycles are every 21 days (±3 days) except for ECHO as noted below. Upon IRB/IEC approval of the updated protocol (amendment 07D), investigators will be unblinded for treatment assignments of their participants.

[2] Cycle 9 Day 1A (C9D1A) procedures are to occur prior to Cycle 9 Day 1B (C9D1B) procedures on the same day except for RHC and ECHO, which may be performed earlier per protocol.

[3] Targeted cardiopulmonary exam only.

[4] Pregnancy test (urine or serum) is required for female participants of childbearing potential at Screening, prior to each dose of study treatment (see Appendix 5 or pregnancy follow-up).

[5] Results from the hematology panel should be evaluated prior to study treatment administration. For C9D1A/B and C10D1 visits, blood samples should be taken and assessed for Hgb levels on the same day as study treatment administration. For all other dosing cycles, blood samples may be taken and assessed for Hgb levels on the same day as study treatment administration or 1 day prior to dosing. If Hgb is ≥ 17.0 g/dL at Day 8 visits for Cycles 9 or 10, participants should return weekly for Hgb monitoring (and continue to follow Dose Modification guidance for dosing days [Section 6.3]).

[6] If a participant has previously completed Cycle 25, the third RHC is to be completed at the next possible dosing visit up to Cycle 33 and should be performed **within 3 days** of that visit. Procedures to accompany the third RHC include pre-dose PK, NT-proBNP, ECHO, and 6MWT; RHC should be performed last. No more than 3 RHCs are to be performed in total during the study: baseline, C9D1A, and at Cycle 25 (or first available dosing after Cycle 25 [up to Cycle 33]) or EOT if discontinued early from extension.
[7] ECHO parameters include but are not limited to: TAPSE, PAP, right ventricular ejection fraction, and LVEF. ECHO may be performed **within 1 week** of study visit.
[8] 6MWT may be done twice based on criteria outlined for clinical worsening (Section 8.5.4).
[9] QoL: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), 36-item short form survey (SF36), should be performed before 6MWT, blood draws, AE discussions, and RHC.
[10] The post-dose PK sample will be collected within 4 hours of dosing (minimum of 15 minutes from dose administration).
[11] Seminal fluid collection is optional for male participants (Section 8.9).
[12] Study procedures should be done prior to the administration of study treatment except for post-dose PK collection. 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).
[13] Participants who complete the third RHC and consent to sotatercept long-term follow-up study will roll over directly without completing EOT/EOS.
[14] If third RHC will be performed at this visit, the procedure should be performed prior to the RHC. For participants whose third RHC assessment is performed at the next available dosing visit after C25D1 up to C33D1, ECHO may be performed within 1 week of the third RHC visit. The ECHO procedure should only be performed once during this period matching the third RHC visit. For PD biomarkers, only NT-proBNP is to be performed.

3. INTRODUCTION

Sotatercept (ACE-011) is a first-in-class human fusion protein consisting of the extracellular domain of the activin receptor IIA linked to the Fc domain of human immunoglobulin G1. Sotatercept works by targeting molecules in the transforming growth factor-beta (TGF-β) superfamily, which includes activins and bone morphogenetic proteins (BMPs). Aberrant TGF-β superfamily signaling is associated with a wide range of human pathologies, including autoimmune, fibrotic diseases, cancer, and cardiovascular disorders such as pulmonary arterial hypertension (PAH). Disruptions in TGF-β and BMP signaling are associated with the development of PAH.

3.1. Study Rationale

Study A011-09 is a Phase 2, double-blind, randomized, placebo-controlled, multicenter, parallel-group study to determine the efficacy and safety of sotatercept plus standard of care (SOC) versus placebo plus SOC in adults with PAH (World Health Organization [WHO] Group 1). The study is divided into the Screening Period, Treatment Period, Extension Period, and Follow-Up Period.

The design of this study will control bias in the assignment of study treatment as well as in data interpretation, particularly of the measures that may have clinical variability (e.g., PVR and 6-minute-walk distance [6MWD]).

Rationale for Participant Population

Patients with diagnostic WHO Group I PAH associated with idiopathic/heritable, drug-induced, connective tissue diseases, or post-shunt correction PAH within the WHO functional class II-III PAH will be selected for this study. PAH is considered a rare condition, with approximately 80% of patients presenting as class II-III PAH. It is expected that the treatment effect of sotatercept can be more easily detected in this patient population. Patients with class I PAH are typically excluded from interventional studies due to their relatively low identification rate, low prevalence, and mild symptomatology. Similarly, there is a low prevalence of patients with class IV PAH, and given their severe disease burden, those patients have limited ability to participate in longer interventional studies. Eligibility criteria for this study are consistent with those of other studies in this population.

Rationale for Study Endpoints

The primary endpoint is change in PVR at 24 weeks Cycle 9 Day 1A (C9D1A) as compared to the PVR value obtained during the Screening Period. This analysis will assess change in resistance to flow across the pulmonary vasculature; a reduction is anticipated based on the activity of sotatercept in animal models and the hypothesized mechanism of action and activity of sotatercept in patients with PAH. Secondary objectives include evaluation of changes in 6MWD, echocardiogram (ECHO) parameters, such as tricuspid annular plane systolic excursion (TAPSE), clinical worsening (including WHO Functional class assessment and hospitalizations), quality of life (QoL; 36-Item Short Form Health Survey [SF-36]), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and safety. TAPSE, 6MWD, and WHO functional class have been established as having significant mortality prognostic capacity.[1-3]

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; Appendix 7).

Rationale for Comparator

The choice of placebo as the comparator is to enable robust assessments of the effectiveness and safety of sotatercept in a controlled setting. Participants in the placebo group (and sotatercept groups) will be on stable doses of SOC therapies for PAH prior to study entry and will maintain SOC therapies during the study, thus ensuring that participants randomized to the placebo arm are treated and managed as per established treatment guidelines.

Rationale for Dose and Frequency Selection

Selection of the dose and frequency are based on estimates of biologically active sotatercept doses and frequencies studied in several patient populations with other chronic diseases. The doses proposed for the Phase 2 study in PAH are 0.3 and 0.7 mg/kg. Doses in this range have been associated with pharmacodynamic (PD) effects and an acceptable safety profile. The projected mean exposure levels at the steady state are 93 day*µg/mL for AUC_{21d} and 5.3 µg/mL for C_{max} at 0.3 mg/kg every 21 days, and 217 day*µg/mL for AUC_{28d} and 12.4 µg/mL for C_{max} at 0.7 mg/kg every 21 days. Pharmacokinetic (PK) modeling data showed every 21-day and every 28-day dosing to be similar in terms of predicted hemoglobin (Hgb) response but different in regards to exposure.

3.2. Background

Genetic mutations in the bone morphogenetic protein receptor type II (BMPR2) are associated with the majority of the familial form of PAH[4,5] and approximately 25% of idiopathic PAH. Specifically, the impairment of the BMPR2-associated signal pathway appears to lead to the uncontrolled proliferation of pulmonary vascular smooth muscle cells (VSMCs), the principal cause of PAH. These data strongly suggest a key role of TGF-β family members in the pathogenesis of PAH. Sotatercept acts to block activin ligands and growth and differentiation factors (GDFs), may attenuate BMPs, and improve pulmonary vascular remodeling by restoring balance to SMAD signaling.[6]

PAH applies to a group of diseases causing a progressive increase in PVR, resulting in right ventricular dysfunction and ultimately failure as well as premature death.[7,8] The 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, eventually, right-sided heart failure.[9] In the absence of treatment, the majority of patients succumb to heart failure within a few years of diagnosis.[10] 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 ERAs, phosphodiesterase 5 (PDE5)

inhibitors, and prostanoids and 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. 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 the treatment of PAH. Importantly, the animal models provide evidence of a disease-modifying effect - a substantial reduction in the proliferation of pulmonary VSMCs in RAP-011-treated animals, as assessed by histologic evaluation, in both preventative and therapeutic disease models.

RAP-011, was evaluated in both preventative and therapeutic disease models. 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 the treatment of PAH. Importantly, a substantial reduction in the proliferation of pulmonary VSMCs was observed in RAP-011 treated animals as assessed by histologic evaluation in both preventative and therapeutic disease models. 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 potentially may positively affect vascular remodelling.[6]

A detailed description of the chemistry, pharmacology, efficacy, and safety of sotatercept is provided in the Investigator Brochure.

3.3. 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 to protect participant safety.

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

Possible risks to participants observed in prior clinical studies with sotatercept include increases in Hgb, hematocrit (Hct), red blood cell count (RBC), and blood pressure. These will be diligently monitored during the study, and adjustment to dosing made as necessary (following medical treatment) to ameliorate these risks. Potential risks of development of anti-drug antibodies, reproductive effects, and renal injury, though not experienced as AEs in other sotatercept clinical studies (but observed in some preclinical studies), will also be monitored. 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 treatment-emergent adverse events (TEAEs). As a consequence of the decrease in white blood cells (WBCs), infection maybe a potential risk and as a consequence of the decrease in platelets, bleeding maybe a potential risk. Per health authority request, leukopenia, neutropenia, and thrombocytopenia have

been identified as adverse events of special interest (AESIs) in this study (see Section 8.4). Thorough monitoring of all AEs experienced by any participant will also be employed in this study.

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

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group study of sotatercept plus SOC versus placebo plus SOC in participants with PAH of WHO functional class II-III. Participants will remain on SOC therapies during all periods of the study.

Standard of care therapy refers to approved PAH-specific medications, and may consist of monotherapy or combination therapy with ERAs, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. Additional SOC details can be found in Appendix 2.

For the 24-week Placebo-Controlled Treatment Period, participants will be randomly assigned in a 3:3:4 ratio to receive placebo subcutaneously (SC) every 21 days plus SOC, sotatercept 0.3 mg/kg SC every 21 days plus SOC or sotatercept 0.7 mg/kg SC every 21 days plus SOC. Participants who have not discontinued early from the double-blind Placebo-Controlled Treatment Period and have had the 24-week (C9D1A) PVR assessment will continue into the 30-month Extension Period. After the primary C9D1 endpoint analysis is completed, the trial will be unblinded. In the Extension Period, participants who received sotatercept during the Placebo-Controlled Treatment Period will continue at their current dose, plus SOC, and participants who received placebo during the Placebo-Controlled Treatment Period will be randomized 1:1 to receive sotatercept, either 0.3 or 0.7 mg/kg, SC every 21 days plus SOC.

Study duration for each participant includes a Screening Period of 28 days, a 24-week, double-blind, Placebo-Controlled Treatment Period, a 30-month Extension Period, and an 8-week Follow-Up Period after the last dose of study treatment.

Upon approval of protocol amendment 07D, participants will be presented with an informed consent form (ICF) for the additional 12-months in Extension Period.

Approximately 100 eligible participants will be randomly assigned in a 3:3:4 ratio to 1 of the 3 treatment groups in the Placebo-Controlled Treatment Period:

- Arm 1: Placebo SC every 21 days plus SOC for 24 weeks
- Arm 2: Sotatercept (0.3 mg/kg, SC) every 21 days plus SOC for 24 weeks
- Arm 3: Sotatercept (0.7 mg/kg, SC) every 21 days plus SOC for 24 weeks

Participants who have not discontinued early from the Placebo-Controlled Treatment Period and have had the 24-week (C9D1A) PVR assessment will continue into the 30-month Extension Period and will be treated as follows:

- Placebo participants will be randomized 1:1 to receive either 0.3 or 0.7 mg/kg sotatercept every 21 days plus SOC.
- Sotatercept-treated participants will continue on their current dose every 21 days plus SOC.

- Upon approval of amendment 07D, investigators will be allowed to increase a participant's study treatment dose up to 0.7 mg/kg at the investigator's discretion based on clinical assessments and in compliance with the dose modification guideline outlined in Section 6.3.

Randomization will be stratified based on baseline (C1D1) WHO functional class classification (II or III) as described in the Study Manual.

Screening Period

Upon giving written informed consent, participants will enter the Screening Period to determine eligibility for the study. Participant screening procedures are to take place within 28 days prior to randomization (C1D1).

Placebo-Controlled Treatment Period

Participants will receive either placebo plus SOC, sotatercept 0.3 mg/kg SC plus SOC, or sotatercept 0.7 mg/kg plus SOC as per randomization assignment. Study treatment will be administered SC every 21 days for 24 weeks. Safety analyses will be performed for the Data Monitoring Committee (DMC) review (Section 9.3.4 for more details).

Extension Period

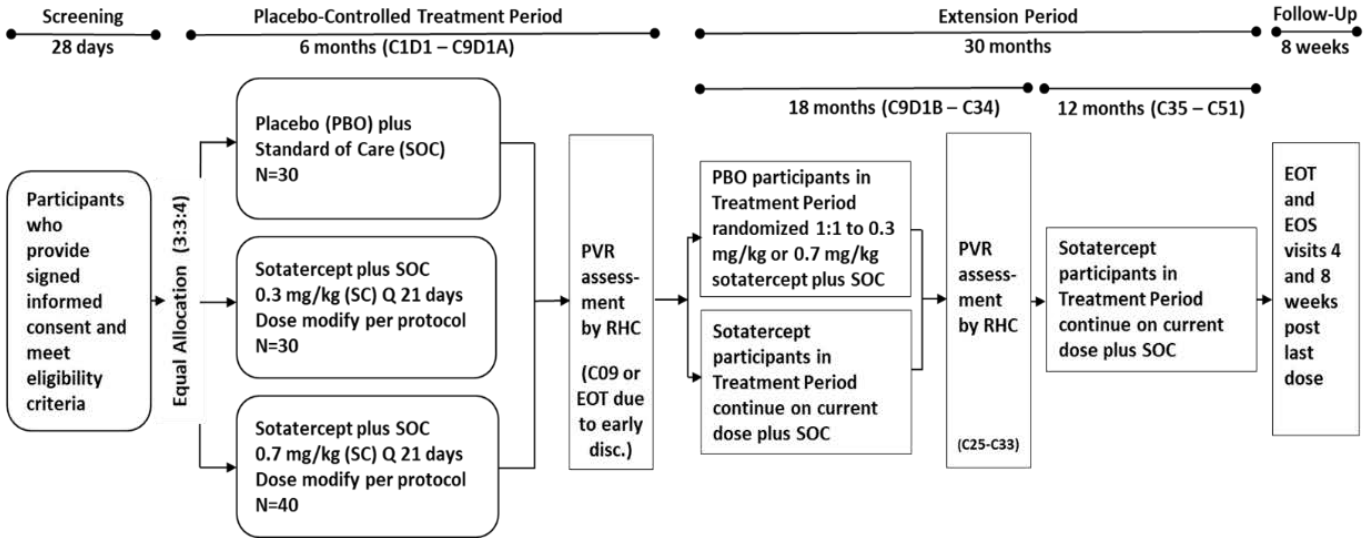
Participants who have not discontinued early from the Placebo-Controlled Treatment Period will continue directly into the Extension Period. Participants who have been on sotatercept will continue to receive sotatercept at their current dose SC plus SOC. Participants who were in the placebo arm will be re-randomized 1:1 to receive sotatercept 0.3 or 0.7 mg/kg SC plus SOC. Study treatment will be administered SC every 21 days for 30 months. Following the approval protocol amendment 07D, investigators and patients will be unblinded to the current dose (see Section 6.5 for additional details).

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 the study early, including during either the Placebo-Controlled Treatment Period or the Extension Period, will be asked to return for EOT and End of Study (EOS) visits. Additional safety assessments, including urinalysis (UA) and hematology, as determined by the investigator, may be done at this time.

Figure 1: Study Design



C09 = Cycle 9; EOS = End of Study; EOT = End of Treatment; N = number; PBO = placebo; PVR = pulmonary vascular resistance; Q = every; RHC = right heart catheterization; SC = subcutaneously; SOC = standard of care.
Refer to Section 8 for a full list of study assessments/procedures.

Table 5: Objectives and Endpoints

Primary – Placebo-Controlled Treatment and Extension Periods	
Primary Objectives	Primary Endpoints
Placebo-Controlled Treatment Period • To evaluate the effect on PVR in WHO functional class II-III PAH participants treated with sotatercept plus SOC compared with placebo plus SOC	Placebo-Controlled Treatment Period • Change in PVR at 24 weeks (C9D1A) vs. screening PVR
Extension Period • To evaluate the disease-modifying effect of sotatercept and additional efficacy analysis • To evaluate the long-term safety of sotatercept in WHO functional class II-III PAH participants	Extension Period • Change from baseline in PVR at Cycle 25 (or next cycles up to Cycle 33) for the Delayed-start efficacy analysis • Change from baseline in PVR at Cycle 25 (or next cycles up to Cycle 33) for the Placebo-Crossed efficacy analysis • Safety and tolerability assessments based on AEs, clinical laboratory values, and vital signs.

Table 5: Objectives and Endpoints (Continued)

Secondary – Placebo-Controlled Treatment and Extension Periods	
Secondary Objectives	Secondary Endpoints
Placebo-Controlled Treatment Period • To assess the effects of sotatercept plus SOC on functional and PD endpoints in participants with PAH compared with placebo plus SOC • To assess the safety and tolerability of sotatercept in participants with PAH • To assess the PK of sotatercept in participants with PAH	Placebo-Controlled Treatment Period Key Secondary Endpoint: • Change from baseline (screening or C1D1) in 6MWD at 24 weeks (C9D1A) Other Secondary Endpoints: • Change from baseline (C1D1) in NT-proBNP at 24 weeks (C9D1A) • Change from baseline (C1D1) in TAPSE at 24 weeks (C9D1A) • Clinical worsening (e.g., hospitalizations, change in WHO functional class, and as defined in Section 8.5.4) from C1D1 to C9D1A • Change in WHO functional class at 24 weeks (C9D1A) vs. screening • Change from baseline (C1D1) in QoL (CAMPHOR, SF-36) at 24 weeks (C9D1A) • Safety and tolerability assessments based on AEs, clinical laboratory values, vital signs, and electrocardiograms (ECGs) • Population PK parameters of sotatercept
Extension Period • To evaluate the disease-modifying effect of sotatercept and additional efficacy analysis	Extension Period Key Secondary Endpoint: • Change from baseline in 6MWD at Cycle 25 (or next cycles up to Cycle 33) for the Delayed-Start efficacy analysis • Change from baseline in 6MWD at Cycle 25 (or next cycles up to Cycle 33) for the Placebo-Crossed efficacy analysis Other Secondary Endpoints: • Change from baseline in WHO FC at Cycle 25 (or next cycles up to Cycle 33) for the Delayed-Start efficacy analysis • Change from baseline in WHO FC at Cycle 25 (or next cycles up to Cycle 33) for the Placebo-Crossed efficacy analysis

Table 5: Objectives and Endpoints (Continued)

Exploratory– Placebo-Controlled Treatment and Extension Periods	
Exploratory Objectives	Exploratory Endpoints
• To assess relevant biomarkers for PAH • To assess efficacy parameters in participants with PAH	• Change from baseline (C1D1) in TGF-β ligands (e.g., activin A) and other PAH-related biomarkers at 24 weeks (C9D1A) • Change from baseline (historical or C1D1) in ECHO parameters (e.g., RVEF, PAP) at 24 weeks (C9D1A) • Correlation of clinical efficacy vs. BMPR2 expression (in PBMCs) • Correlation of clinical efficacy vs. sex hormone levels in males and females (e.g., estradiol metabolites)

6MWD = 6-minute-walk distance; AE = adverse event; BMPR2 = bone morphogenetic protein receptor type II; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CxDy = Cycle x Day y; ECG = electrocardiogram; ECHO = echocardiogram; FC = functional class; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; QoL = quality of life; RVEF = right ventricular ejection fraction; SF-36 = 36-Item Short Form Health Survey; SOC = standard of care; TAPSE = tricuspid annular plane systolic excursion; TGF-β = transforming growth factor-beta; WHO = World Health Organization.

4.2. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases 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.

4.3. Justification for Dose

For the current study, doses of 0.3 and 0.7 mg/kg were selected and will be administered SC every 21 days (i.e., every 3 weeks [Q3W]). The projected mean exposure levels at the steady state are 3.5 and 8.1 µg/mL for 0.3 and 0.7 mg/kg Q3W, respectively. These projected exposures are comparable to those observed in healthy volunteers who received SC 0.3 mg/kg Q4W (C_{max} = 2.4 µg/mL) and 1.0 mg/kg doses Q4W (C_{max} = 7.4 µg/mL). In the current protocol, the starting exposure levels (i.e., after the first dose) are estimated to be approximately half of that at the steady state.

Simulations based on population PK model show that there will be an adequate separation in the systemic sotatercept exposure between the currently selected doses of 0.3 and 0.7 mg/kg Q3W [mean (5^{th}, 95^{th} percentile): 3.5 µg/mL (2.00, 4.90) versus 8.10 µg/mL (4.80, 11.4)]. This will facilitate the evaluation of the dose-response relationship for effectiveness and toxicity.

Based on the safety data from the 2 completed Phase 1 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 0.3 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 Phase 1 clinical studies were attributable to the expected biologic activity of activin inhibition, i.e., dose-dependent decreases in circulating follicle-stimulating hormone (FSH), and transient, reversible effects on RBC parameters. In Study A011-02, 1 participant experienced persistent, progressive hypertension, which was reported as a treatment-related serious adverse event (SAE), together with headaches approximately 1 week following her second dose of 1.0 mg/kg sotatercept SC that were attributable to a rapid and significant rise in Hgb.

Using data from these Phase 1 studies, an indirect response PK/PD model for Hgb following IV or SC administration of sotatercept was developed. The final PK/PD model was used to calculate the individual-predicted values of Hgb at each of the virtual sample times. Summary statistics of Hgb at steady state and the associated sotatercept concentrations were calculated stratified by population, dose level, and dosing interval. For simulations, PAH patients were assumed to be similar to healthy volunteers in terms of baseline Hgb level and likely Hgb responses to sotatercept dosing. Mean (90% confidence interval) predicted steady state Hgb was 15.4 g/dL (13.7, 17) and 16.0 g/dL (14.4, 17.4) for 0.3 and 0.7 mg/kg Q3W, respectively. These projected Hgb levels appeared to be similar to the Hgb levels observed in 2 Phase 1 studies. Though simulations show that doses in the range of 0.3 and 0.7 mg/kg are expected to be safe overall, AE rates due to sotatercept-mediated Hgb increases will be further ameliorated by the implementation of dose reduction, delay, and stopping rules in the subsequent treatment cycles (Section 6.3). In addition, a comprehensive safety monitoring plan will be incorporated into the study to mitigate risk. This will include comprehensive dose-modification guidance as well as the incorporation of study oversight by both a scientific steering committee as well as an independent DMC to assess safety events on an ongoing basis.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Participant and Study Completion

Approximately 100 participants will be randomly assigned in a 3:3:4 ratio to receive placebo plus SOC, sotatercept 0.3 mg/kg plus SOC, or sotatercept 0.7 mg/kg plus SOC.

Additional details are provided in Section 9.

5.2. Inclusion Criteria

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

1. Age ≥ 18 years
2. Documented diagnostic RHC at any time prior to Screening confirming the diagnosis of WHO diagnostic pulmonary hypertension Group I: PAH in 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 II or III
4. Baseline RHC performed within 10 days prior to C1D1 visit during the Screening Period documenting a minimum PVR of ≥ 400 dyn·sec/cm^5 (5 Wood units)
5. Pulmonary function tests (PFTs) within 6 months prior to the Screening Visit 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)/ forced vital capacity > 70% predicted
6. Ventilation-perfusion (VQ) scan (or, if unavailable a negative CT pulmonary angiogram result or pulmonary angiography result), any time prior to Screening Visit or conducted during the Screening Period, with normal or low probability result
7. No contraindication per investigator for RHC during the study

8. Six-Minute-Walk Distance ≥ 150 and ≤ 550 meters repeated twice during the Screening Period and both values within 15% of each other, calculated from the highest value (Appendix 3)

9. PAH therapy at stable (per investigator) dose levels of SOC therapies as defined in Section 6.2 or at least 90 days prior to C1D1.

10. Females of childbearing potential (defined in Appendix 5) must:

    a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study and until 8 weeks after the last dose of study treatment.
    b. If sexually active, have used, and agree to continue to use highly effective contraception (See Appendix 5 for definitions) without interruption, for at least 28 days prior to starting investigational product, 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 5 for additional contraceptive information.

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 investigational product discontinuation, even if he has undergone a successful vasectomy. (see Appendix 5 for additional contraceptive information).
    b. Refrain from donating blood or 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

5.3. Exclusion Criteria

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

1. Stopped receiving any pulmonary hypertension chronic general supportive therapy (e.g., diuretics, oxygen, anticoagulants, digoxin) within 60 days prior to C1D1
2. Received intravenous 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. Known history of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication), defined as mild to severe hepatic impairment (Child-Pugh Class A-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 blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg during Screening after a period of rest
10. Systolic blood pressure < 90 mmHg during Screening Visit or at baseline (C1D1)
11. History of known pericardial constriction
12. Electrocardiogram (ECG) with Fridericia's corrected QT interval (QTcF) > 480 msec during Screening Period or C1D1
13. Personal or family history of long corrected QT (QTc) syndrome or sudden cardiac death
14. Cerebrovascular accident within 3 months of C1D1
15. History of restrictive or congestive cardiomyopathy
16. Left ventricular ejection fraction (LVEF) < 45% on historical ECHO within 6 months prior to the Screening Period (or done as part of the Screening Period), or pulmonary capillary wedge pressure (PCWP) > 15 mmHg as determined in the Screening Period RHC
17. Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) in the past 6 months prior to Screening Visit.
18. Acutely decompensated heart failure within 30 days prior to C1D1, as per investigator assessment
19. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease
20. Any of the following clinical laboratory values during the Screening Period prior to C1D1:
    a. Baseline Hgb > 16.0 g/dL
    b. Serum alanine aminotransferase or aspartate aminotransferase levels > 3X upper limit of normal (ULN) or total bilirubin > 1.5X ULN within 28 days of C1D1
    c. WBC count < 4000/mm^3
    d. Platelets < 100,000/µL
    e. Absolute neutrophil count < 1500/mm^3

21. 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
22. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in the investigational product
23. Major surgery within 8 weeks prior to C1D1. Participants must have completely recovered from any previous surgery prior to C1D1.
24. Prior heart or heart-lung transplants or life expectancy of < 12 months
25. Pregnant or breastfeeding females
26. If on corticosteroids, and at any time in the last 30 days prior to the Screening Period: have been receiving doses of > 20 mg/day of prednisone (or equivalent) or on a new or changing dose of ≤ 20 mg/day; only participants receiving stable doses of ≤ 20 mg prednisone (or equivalent) in last 30 days prior to the Screening Period permitted in the study
27. 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
28. History of clinically significant (as determined by the investigator) non-PAH related cardiac, endocrine, hematologic, hepatic, (auto)immune, metabolic, urologic, pulmonary, neurologic, neuromuscular, dermatologic, psychiatric, renal, and/or another disease that may limit participation in the study. Autoimmune diseases are excluded with the exception of those related to PAH etiologies included in this study.
29. 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 times the half-life prior to C1D1, whichever is longer
30. Weight > 140 kg at Screening
31. History of renal disease, including:
    a. Chronic renal disease at any time prior to screening; or
    b. Any episode of acute renal failure, with or without a prior history of renal disease, occurring within the 3 months prior to screening in which acute dialysis (e.g., intermittent hemodialysis or continuous veno-venous hemofiltration) was required
32. History of rare hereditary fructose intolerance, glucose / galactose malabsorption, or sucrose / isomaltase deficiency

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. Electronic case report forms (eCRFs) must be completed for all participants 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, the reason for screen failure, AEs, and 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, or placebo 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 of 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 separate cover.

Placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection). Sterile, normal saline should be supplied by the site. The investigational site's designated individuals will prepare the placebo syringes to match the active syringes. The investigator and participants will be blinded during the Treatment Period, and unblinded during the Extension Period (see Section 6.5 for additional details). The manufacturer's directions for storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

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 Appendix 2 for more details on SOC).

6.2. Treatment Administration and Schedule

There will be unblinded site personnel at each site designated for preparing the investigational product during the Placebo-Controlled Treatment Period. Sotatercept or placebo will be administered after reconstitution as an SC (subcutaneous) 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. Each injection will not exceed 1.0 mL; a minimum of 2 injections will be required per dose. Where rounding weight and total volume is necessary, please refer to the pharmacy manual and interactive response technology (IRT) 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) = 1 mg/kg (for information on overdose refer to Section 8.3.8).

6.3. Dose Modification

Dose delay and/or reduction or discontinuation may be required in any treatment arm (sotatercept or placebo). Guidance for dose modifications and dose delay are summarized in Figure 2 and Figure 3.

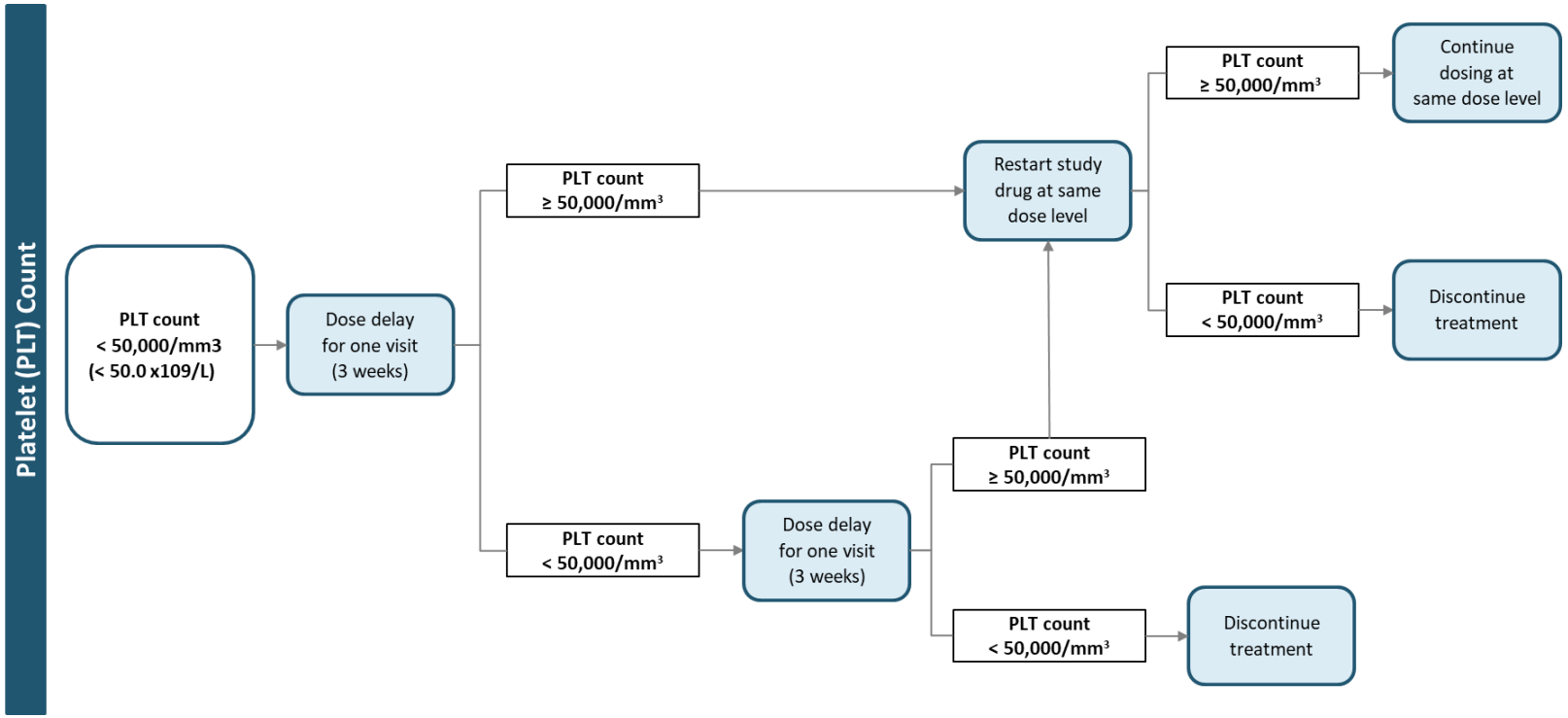
A maximum of 3 dose delays are allowed during the study. If a fourth dose delay is required, the study treatment should be discontinued. Questions regarding the applicability of the dose adjustment guidance to specific situations must be directed to the PPD medical monitor for assessment.

Results from the hematology panel should be evaluated prior to study treatment administration. For C1D1, C2D1, C9D1A/B, and C10D1 visits, blood samples should be taken and assessed for Hgb levels on the same day as study treatment administration. For all other dosing cycles, blood samples may be taken and assessed for Hgb levels on the same day as study treatment administration or 1 day prior.

After the primary endpoint analysis, dose modification guidelines were revised to address only changes in platelet and hemoglobin values (Figure 2 and Figure 3). If Hgb increases are > 4.0 g/dL above participant baseline value, consult the medical monitor and consider study treatment discontinuation.

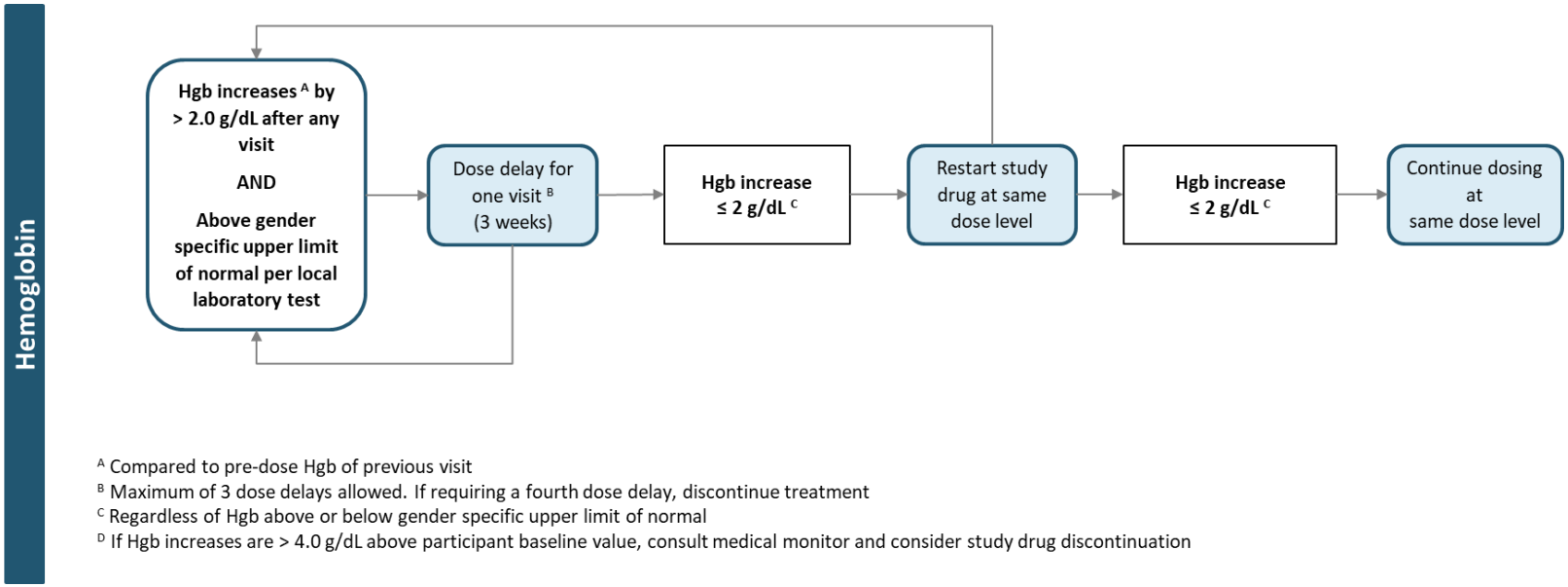
Dose delays and reductions can be implemented for safety reasons at any time per investigator's assessment, not being restricted to the dose modification guidance provided.

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

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.
Hgb = hemoglobin.

Upon approval of Protocol Amendment 07D and unblinding of study sites and participants, study treatment dose may be escalated up to 0.7 mg/kg. If dose reductions are conducted due to an AE not related to study treatment, the dose can be escalated when the AE resolves. In cases of dose reduction due to an increase in Hgb or decrease in platelets, the dose can be escalated after 2 consecutive cycles in which Hgb or platelet values are stable.

Table 6: Dose Reductions for Study Treatment

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

6.5. Randomization and Blinding

Participants who have signed the informed consent and met all eligibility criteria will be stratified by WHO functional class and then randomized to receive placebo plus SOC, sotatercept 0.3 mg/kg plus SOC, or sotatercept 0.7 mg/kg plus SOC in the Placebo-Controlled Treatment Period. Randomization assignments will be generated through a computerized system, provided by IRT. After the completion of the 24-week Placebo-Controlled Treatment Period, placebo participants will be re-randomized 1:1 to treatment with sotatercept 0.3 mg/kg plus SOC or sotatercept 0.7 mg/kg plus SOC and sotatercept-treated participants will continue on their current dose in the Extension Period.

Among study personnel, the pharmacist or his/her designee who prepares the study treatment (sotatercept or placebo), and the study team at each site, and a sponsor clinical trial manager and/or designee will be unblinded to the participant treatment assignments during the Placebo-Controlled Treatment Period. All other study personnel (including but not limited to the sponsor, the sponsor's representatives, investigators, study coordinators, nursing staff, and clinical monitors) and all participants will remain blinded to the study treatment assignments until all participants in the Treatment Period have completed their post-Placebo-Controlled Treatment Period (C9D1A/24 week) PVR assessment.

During the Extension Period, following the conduct and results of the C9 primary endpoint, and the approval of Protocol A011-09 Amendment 07D, study treatment will be unblinded to study teams, investigators, and study participants. Investigators will be provided with treatment assignments by the site designee of study treatment. All investigators will be allowed, at the investigator's discretion, to increase study treatment dose up to 0.7 mg/kg based on the investigator's clinical assessment.

In the event of a medical emergency for an individual participant in which knowledge of the study treatment is critical to the participant's medical management (Section 8.3.4), the investigator may break the blind for that participant by contacting IRT (see the IRT User Manual for further instructions). The investigator is free to break the blind if it is required to manage the

participant's medical emergency based on their judgment. In non-urgent situations, the investigator is encouraged where possible to discuss with the study medical monitor prior to breaking the blind. Where the investigator has broken the blind without prior discussion they are requested to inform the sponsor/medical monitor at the earliest opportunity. Further, it must be determined by the investigator that breaking the treatment blind is necessary information for the medical management of that participant. If the blind is broken, the investigator can consult with the medical monitor as needed. Investigator discretion should be used to determine if the participant should continue on treatment or be discontinued from the study.

6.6. Packaging and Labeling

The study treatment will be labeled per local requirements.

6.7. Preparation/Handling/Storage/Accountability

Accountability for the study treatment 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 treatment 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 treatment administration will be made in the appropriate section of the participant's eCRF and source documents. Unless otherwise notified, all vials of study treatment, 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 and expired vials of study treatment to the sponsor at the end of the study, or the study treatment may be destroyed at the clinical site with the 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 the investigational product return, disposal, and/or destruction including responsibilities for the site versus Acceleron (or designee).

Refer to the Pharmacy Manual for further instructions for the preparation of study treatments and information regarding the 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 will be documented in the study record. Accurate recording of all study treatment 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 treatment that is administered during the study.

Standard of care treatment compliance will be the responsibility of each participant and his or 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 as prescribed (see Appendix 2 for more details regarding SOC).

6.9. Concomitant Therapy

During the screening and throughout the Placebo-Controlled 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 worsening pre-existing 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 during the Placebo-Controlled Treatment Period (i.e., rescue therapy; please refer to Section 8.5.5 for suggested criteria), the investigator will need to discontinue study treatment and perform EOT visit assessments as directed by the protocol. The investigator may consult the PPD medical monitor regarding what constitutes a stable dose or a chronic condition. Information regarding concomitant medications will be collected beginning after signing ICF and will include all medications taken during Screening Period to C1D1.

During the Extension Period, any concomitant medications including PAH medication and supplemental oxygen can be modified (removed, substituted, or dose adjusted) and should be recorded in the concomitant medication eCRF.

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 evaluation 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. Additional safety assessments, including UA and hematology, as determined by the investigator, may be done at this time.

7.1. Discontinuation of Study Treatment

Reasons that may lead to discontinuation of study treatment include:

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

Clinical worsening, pregnancy, and QTcF > 500 ms will need to be recorded as an AE (see Section 8.3).

The sponsor may terminate study treatment or a dose level after consultation with the investigator and the DMC at any time for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests an 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
- An AE with an outcome of death
- Lost to follow-up

- Study terminated by the sponsor
- AE or SAE
- Pregnancy

Serious adverse events/adverse events, including the outcome of death or pregnancy, will need to 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, attempts to follow participants should be made, at regular intervals, until the AE normalizes or returns to the participant's baseline condition, as per Section 8.3.5.

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 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, 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 Treatment Period and the Extension Period.
- All protocol assessments are to be recorded on the participant's source documentation.

8.1. Screening Procedures

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

8.2. Efficacy Assessments

8.2.1. Pulmonary Vascular Resistance by Right Heart Catheterization

Pulmonary vascular resistance will be measured by the RHC procedure. There will be a total of 3 RHCs to assess pulmonary vascular resistance (PVR). The first RHC must be performed within 10 days prior to C1D1 (during the Screening Period), and the second RHC should be performed within 10 days prior to the 24 weeks/C9D1A visit (during the Treatment Period). The third RHC should be performed within 3 days of C25D1 or at the next available dosing visit upon consent to Protocol Amendment 07D, up to C33D1 (during the Extension Period). If a

participant discontinues early from the Extension Period, a third RHC should be performed at EOT. The third RHC has been added to assess the long-term benefits and durability of the effect of sotatercept treatment. If performed on the same day at any of these timepoints, the RHC should take place after other assessments (i.e., 6-minute-walk test [6MWT]) have been completed and prior to dosing.

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

Right heart catheterization will be performed according to the RHC manual and will assess several prognostic hemodynamic variables in addition to PVR, including right atrial pressure (RAP), mean pulmonary arterial pressure (PAP), mean pulmonary wedge pressure (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 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, heart rate
- CO measured in triplicate by the thermodilution technique or by the Fick method (the same method must be used for all RHC assessments for each participant).

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.

8.2.2. Six-Minute-Walk Distance

Six-minute-walk distance (6MWD) will be measured by the 6MWT during the Screening Period and at multiple timepoints throughout the study as per the SoE. During the Screening Period, 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, the 6MWT should be performed after QoL and before RHC. Appendix 3 provides further instructions on 6MWT. For evaluation of clinical worsening, as indicated by the 6MWT, a decrease of ≥ 15% in 6MWD at any timepoint 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. If the screening 6MWT is performed within 10 days prior to C1D1, the value may serve as the baseline and an additional 6MWT is not required at C1D1.

8.2.3. Echocardiogram Parameters

ECHO assessments to include tricuspid annular plane systolic excursion (TAPSE), right ventricular ejection fraction (RVEF), left ventricular ejection fraction (LVEF), pulmonary artery pressure (PAP), as well as other parameters will be conducted at baseline (C1D1) and at multiple timepoints throughout the study as per the SoE. If a historical ECHO reading is unavailable for evaluation during Screening, an ECHO may be performed during the Screening Period. If an

ECHO is performed as a part of the Screening Period, these values may be used as the baseline for this study and an additional ECHO is not required for these participants at C1D1. If a historical ECHO is evaluated during the Screening Period, the participant should receive an ECHO at the C1D1 visit, which will serve as the baseline for the study for these participants. Echocardiograms will be centrally read. For participants whose third RHC assessment is performed at the next available dosing visit after C25D1 up to C33D1, ECHO may be performed within 1 week of the third RHC visit.

8.2.4. Quality of Life Assessments

The CAMPHOR and SF-36 QoL assessments will be given at the timepoints noted in the SoE. If occurring on the same day, QoL assessments should be performed before 6MWT, blood draws, AEs discussions, and RHC.

8.3. Adverse Events

Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a clinical investigation participant administered a study treatment, 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 treatment whether or not it is considered related to the study treatment.

Abnormal laboratory and other abnormal investigational findings (e.g., physical exam, 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 the case of a fatality, the cause of death is considered as the AE, and death is considered as its outcome.

Unexpected Adverse Events

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

Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present 30 days prior 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 as AEs.

Serious Adverse Event

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

- Results in **death**.
- Is **life-threatening**: Life-threatening means that the participant was at immediate risk of death from the reaction as it occurred, it does not include a reaction, which hypothetically might have caused death had it occurred in a more severe form.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**.
- **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 participant's ability to carry out normal life functions.
- **Is a congenital anomaly/birth defect**: Congenital anomaly/birth defect in a child of a participant or its partner that was exposed to study treatment 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 on appropriate medical judgment, it may jeopardize the participant 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.

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 the absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on the 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.

8.3.1. Severity

Investigators must evaluate the severity/intensity of AEs and SAEs according to the active minor version of the NCI-CTCAE v4.0, preferentially using the graded scales. If there is a change in the 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 v4.0 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 the participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning.

8.3.2. Relationship to Study Treatment

The investigator must determine the relationship between the administration of study treatment 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, the temporal relationship between the AE and the administration of study treatment, known side effects of study treatment, medical history, concomitant therapy, course of the underlying disease and pertinent study procedures.

Not Suspected: Means a causal relationship of the AE to study treatment 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 treatment caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study treatment 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. The investigator must report in detail all adverse signs and symptoms which are either volunteered by participants or observed during or following the course of investigational product administration on the appropriate eCRF page. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded under 1 diagnosis. All 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 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 study treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of study treatment) 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 both methods should not be used beside each other; the paper is for backup reporting only.

Specific guidance can be found in the CRF 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 timeframe described in Section 8.3.6 (Notification about SAEs).

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 Adverse Events

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 treatment, 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 of 24 hours after becoming aware of the event, inform the sponsor via the contract research organization by the entry on the eCRF, or if not available, by telephone, fax, or email. Paper SAE forms should be used to report an SAE if the eCRF is down or otherwise 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, 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 independent ethics committee (IEC) that approved the study.

In accordance with International Council for Harmonisation (ICH) 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 study treatment (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.

For studies covered by the European Union Clinical Trials Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related Detailed Guidances.

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, and therefore, for the purpose of this trial, an overdose is defined as any dose that has exposures in excess of the monkey NOAEL dose of 1 mg/kg (IB, Section 3.3.2, Table 4), which was also the highest dose tested in a human volunteer 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, participants 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 treatment 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 participant exposed to study treatment. 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 treatment 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 participant 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., electronic protocol inquiry portal) and be fully documented as an AE in the eCRF, or as an SAE if an associated SAE occurs (see Section 8.3 for further instructions).

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 the last dose of study 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 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 5.
- Additional pregnancy, breastfeeding, and sperm/ovum donor information are provided in Appendix 5.

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

The risks outlined below are consistent with the list in Sotatercept IB (Edition 14.0). The AESIs 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 related to platelets and Hgb.

Additional reviews will be performed periodically as part of standard safety signal detection and medical monitoring; finally, an independent DMC will be convened to monitor the safety of the participants as described in Section 9.3.4 and a detailed charter.

8.4.1. Identified Risks

Table 7 describes the identified risks that could occur during study 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 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 (Hgb/Hct) • The medical monitor will ensure dosage adjustment according to the protocol • Monthly review of unblinded Hct/Hgb listings by Data Safety Monitoring Board 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 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	Ischemic heart disease (SMQ) Embolic and thrombotic events (SMQ)	Monitoring of AEs in combination of risk factors of systemic hypertension (diabetes, metabolic syndrome, obesity), concomitant medications, and previous medical history of heart, embolic, and thrombotic events
Thrombocytopenia, leukopenia, and neutropenia	Thrombocytopenia, leukopenia, and neutropenia	Careful monitoring of platelet counts is performed, and in case platelet count are < 50.000/mm^3 (< 50.0 × 10^9/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

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

8.5. Safety Assessments

Planned timepoints for all safety assessments are provided in 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 exam 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 blood pressure will be assessed at every visit. Height will be measured once, during the Screening Period.
- Blood pressure and pulse measurements will be assessed while seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs (to be taken before blood collection for laboratory tests): blood pressure 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 blood pressure readings will be recorded on the eCRF.
- Weight will be measured (in indoor clothing but without shoes) and recorded at each dosing visit. Dose will be calculated based on the participant's weight on the day of dosing.
- Clinically significant abnormal findings will be reported as AEs (Section 6.3 and Section 8.4).

8.5.3. Electrocardiograms

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

8.5.4. Clinical Worsening

Clinical worsening will be assessed by the investigator at each dosing visit and recorded on the eCRF.

Assessments are:

- 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 (II to III, III to IV, II to IV, etc.)
- Decrease in 6MWD by ≥ 15% (confirmed by two 6MWTs; Section 8.2.2)
- 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 (and therefore discontinue study treatment) include:

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

8.5.6. Clinical Safety Laboratory Assessments

- See Appendix 1 for the list of clinical laboratory tests to be performed and to the SoE for the timing and frequency.
- If hemoglobin is ≥ 17 g/dL during Cycles 1-2 Day 8, or Cycles 9-10 Day 8, participants should return weekly for hemoglobin monitoring. Clinically significant abnormal Hgb findings will be reported as AEs. Dose modification guidance should be followed (see Figure 3).
- Seminal fluid collection is optional; samples will be collected from male participants who consent to this assessment.
- 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 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 1, must be conducted in accordance with the laboratory manual and the 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 the 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 safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.7. Pharmacodynamics

Venous blood samples will be collected for measurement of PD biomarkers including but not limited to activin A, BMPR2, BMPR2 expression (via peripheral blood mononuclear cells), GDF15, matrix metalloproteinase-2 (MMP2), N-terminal prohormone of brain natriuretic peptide (NT--proBNP), TGF-β1, vascular endothelial growth factor receptor (VEGFR1), and sex hormone metabolites at timepoints listed in the 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.

8.8. Genetic Testing

Participants may opt to 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, potassium channel subfamily K member 5, and mothers against decapentaplegic homolog 9; otherwise known as SMAD9. See Appendix 6 for more information regarding genetic testing.

8.9. Seminal Fluid Analyses

Male participants who have not undergone a successful vasectomy may opt to have seminal fluid samples taken to assess sperm count, sperm motility, and sperm morphology. Since the effects of sotatercept on fertility are unknown, these analyses may provide insight into changes sotatercept may mediate in sperm concentration or function. The initial baseline sample will be taken during the screening period, and a sample will be collected for comparison at the EOS visit. If there is a clinically significant difference between the baseline and EOS samples with

regard to sperm count, motility, or morphology, as per the investigator's assessment, the subject will be asked to return up to 232 days after the last dose of study treatment to provide an additional seminal fluid sample for analysis.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The sample size calculation is based on the primary endpoint of change from baseline PVR measurement. The baseline PVR is expected to be approximately 800 dyn sec/cm^5 (standard deviation 400). Assuming a decrease from baseline PVR at 24 weeks of 240 dyn sec/cm^5 (30%) for sotatercept groups and 0% for placebo, with 1-sided alpha=0.10 and 80% power, the sample size is 26 per treatment group. The dropout rates may be different from 3 treatment groups. The placebo group and 0.3 mg/kg sotatercept group may have about a 15% dropout rate, but the 0.7 mg/kg sotatercept group may have an increased dropout rate due to potential Hgb increase based on PK modeling (about 20% more) and hence the total dropout rate in this group may be about 35%. Thus, the total sample after accounting for dropouts in the 3 arms: placebo, 0.3 mg/kg sotatercept, and 0.7 mg/kg sotatercept is 3:3:4, respectively, for a total of 100.

For the 6MWD at 24 weeks, assuming the change from baseline is 50 meters for the sotatercept group and 20 meters for the placebo group with a standard deviation of 50 meters, n = 26 per treatment group will provide approximately 80% power to detect the difference at 1-sided alpha = 0.10 level.

9.2. Populations for Analyses

Full Analysis Set (FAS): All randomized participants treated with correct treatment assignments.

Evaluable Population: All participants in the FAS who received at least 6 doses of the same dose during the Placebo-Controlled Treatment Period and have had their baseline and post-Placebo-Controlled Treatment Period PVR assessments (24 weeks/C9D1A) or EOT PVR assessment. Data from participants whose dose is down-titrated will be analyzed according to the dose received rather than the dose to which they were originally assigned.

Safety Population: All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

9.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before topline (24 weeks) database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data as needed. 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	ANCOVA will be used to compare the 24-week (C9D1A) change from baseline PVR data between sotatercept and placebo groups, with the randomization factor as the covariate. The primary analysis will be performed on the evaluable population. The non-evaluable rate will be blindly monitored, and adjustments to statistical methods may be considered based on this blinded data, as necessary. Gatekeeping method will be used to control the overall type 1 error rate, i.e., higher sotatercept dose group will be compared with the placebo group at 1-sided alpha = 0.10 first. If significant, then the lower sotatercept dose will be compared with the placebo group at 1-sided alpha = 0.10. If the sotatercept higher and lower dose groups data are similar, they may be combined together to compare with the placebo group.
Key Secondary	6MWD will be analyzed similarly as the primary endpoint of the evaluable population. ANCOVA will be used to compare the 24-week (C9D1A) 6MWD from baseline (C1D1) 6MWD data between sotatercept and placebo groups, with the randomization factor as the covariate. The gatekeeping method will be used to control the overall type 1 error rate If the sotatercept higher and lower dose groups data are similar, they may be combined together to compare with the placebo group.
Other Endpoints	In general, continuous data will be summarized descriptively with mean, standard deviation, median, min, max, and tested with ANCOVA method if applicable. Response rate data will be summarized with counts and percentages, tested with CMH method if applicable. Time to event data will be summarized with the Kaplan-Meier method, tested with the log-rank test, and the hazard ratio will be estimated with the Cox regression method.

6MWD = 6-minute-walk distance; ANCOVA = analysis of covariance; CMH = Cochran-Mantel-Haenszel; CxDy = Cycle x Day y; PVR = pulmonary vascular resistance.

9.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event listings will include the verbatim term and the MedDRA preferred term. TEAEs will be defined in the SAP and summarized by the worst severity grade, system organ class, and preferred term. TEAEs leading to death or discontinuation from treatment, TEAEs related to investigational product, and serious TEAEs will be summarized separately.

Clinical laboratory results will be summarized descriptively by treatment groups. Clinically significant laboratory abnormalities will be listed and summarized by treatment group. Renal function laboratory tests (creatinine and urine albumin-creatinine ratio) will be collected regularly during the Placebo-Controlled Treatment Period and may be limited to creatinine in the Extension Period. The descriptive statistics (mean, standard deviation, median, min, max) will be provided for each timepoint of the collection by the treatment group. One graph will be presented for the mean of each renal function test over time by treatment. A listing of abnormal

values will also be provided. Renal function related AEs will be summarized by treatment group. Change from baseline in renal function tests at each timepoint will be presented.

Vital sign measurements will be listed for each participant at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by treatment group.

Immunogenicity (incidence/titer of anti-drug antibody) will also be analyzed.

9.3.3. Other Analyses

Pharmacokinetic, PD, and biomarker exploratory analyses will be described in the SAP that will be finalized before database lock. Other analyses include the change in PVR from baseline, similar to the primary analysis, but on the FAS population and incorporating methods for handling missing data as detailed in SAP.

9.3.4. Data Monitoring Committee

The external, independent DMC will provide unblinded safety monitoring after at least 15 participants have been enrolled in the Treatment Period and completed Cycle 2, and at approximately 6-month intervals thereafter throughout the Extension Period.

A detailed charter will outline all activities of the DMC (including, but not limited to, the composition of the DMC, type of data to be reviewed, DMC responsibilities, and frequency of meetings).

9.3.5. Primary Endpoint Analysis

An analysis of the primary endpoint of change in PVR at 24 weeks (C9D1A) versus the screening PVR assessment will be performed on the evaluable population when all participants in the Placebo-Controlled Treatment Period have completed the 24-week (C9D1A) PVR assessment or EOT PVR for those participants who discontinue early in the Placebo-Controlled Treatment Period as described in Section 9.3.2.

9.3.6. Extension Period Analysis

A separate SAP will be developed for the details of the analyses in the Extension Period. Participants will have a total of 3 PVR assessments over the course of the study: PVR at Baseline (PVR0), PVR following completion of the 6-month Placebo-Controlled Treatment Period (PVR6), and PVR after 18 to 24 months post baseline (PVR-ext).

Table 11 provides notation for efficacy measurements at different timepoints.

Table 11: Notation: Efficacy Measurement at Different Timepoints

	PVR	6MWD	FC	FC Numeric Version
Month 0 (baseline)	PVR0	6MWD0	FC0	FCn0
Month 6	PVR6	6MWD6	FC6	FCn6
Months 18-24	PVR-ext	6MWD-ext	FC-ext	FCn-ext

6MWD = 6-minute-walk distance; FC = functional class; PVR = pulmonary vascular resistance.

Two Analysis Treatment Groups in the Extension Period:

- Continued sotatercept treatment group: Participants randomized to either dose group (0.3 and 0.7 mg/kg) of sotatercept at the beginning of the Placebo-Controlled Period. They continued to receive sotatercept in the Extension Period.
- Placebo-Crossed treatment group: Participants randomized to placebo at the beginning of the Placebo-Controlled Period and then randomized to either 0.3 or 0.7 mg/kg of sotatercept in the Extension Period.

Two Statistical Efficacy Analyses:

- Delayed-start efficacy analysis: Compare the efficacy endpoints between the 2 treatment groups in the Extension Period.
- Placebo-crossed efficacy analysis: Compare postbaseline (Months 18 to 24) versus baseline (Month 0) values of efficacy endpoints within the Placebo-Crossed treatment group.

The overall type I error rate will be 2-sided 0.05. Recycle method will be used to control the overall type I error rate.[14]

The set of Placebo-crossed efficacy analyses will be tested first at 2-sided 0.025 level. Gatekeeping method will be used to sequentially test each efficacy endpoint. PVR will be tested first at 0.025 level. If successful, 6MWD will be tested second at 0.025. If both PVR and 6MWD are successfully tested, FC improvement will then be tested at 2-sided 0.025 level.

If all 3 efficacy endpoints in the Placebo-crossed efficacy analyses are statistically significant, then the type I error rate of 0.025 will be recycled. The set of Delayed-start efficacy analysis will be tested at 0.025 + 0.025 = 0.05 2-sided level. Otherwise, if at least 1 of the 3 tests is not significant, they will be tested sequentially at 2-sided 0.025 level. Each endpoints in the Delayed-start efficacy analysis will be tested similarly as the placebo-crossed efficacy analyses.

The sotatercept 0.3- and 0.7-mg/kg groups will be pooled into 1 sotatercept group Extension Period analysis.

9.3.6.1. Delayed-start Efficacy Analysis

The primary analysis is to compare the change from baseline (PVR-ext – PVR0) between the Continued sotatercept treatment group and the Placebo-Crossed treatment group to evaluate disease-modifying effect with a type I error rate of 2-sided 0.025. ANCOVA will be used with PVR0 and FC0 as covariates. Normality will be tested using Shapiro-Wilk test. If normal distribution is rejected, a non-parametric Wilcoxon rank sum test stratified by FC0 will be used. Multiple imputation method will be used to handle the missing data.

The key secondary analysis is to compare change from baseline (6MWD-ext – 6MWD0) between the Continued sotatercept treatment group and Placebo-Crossed treatment group after the successful testing on primary PVR analysis with a type I error rate of 2-sided 0.025. ANCOVA will be used with 6MWD0 and FC0 as covariates. The normality check and missing data handling method will be similar to the primary analysis.

The other secondary analysis is to compare FC-ext improvement from baseline (FC0) between the Continued sotatercept treatment group and Placebo-Crossed treatment group after the successful testing on primary PVR and key secondary 6MWD analysis, with a type I error rate of 2-sided 0.025. Cochran-Mantel Haenszel (CMH) test will be used with FC0 as the stratum.

9.3.6.2. Placebo-Crossed Efficacy Analysis

The primary analysis is to evaluate PVR-ext – PVR0 in the Placebo-Crossed treatment group with a type I error rate of 2-sided 0.025. ANCOVA will be used to test the intercept with PVR0-average (PVR0) as the covariate. Normality will be tested using Shapiro-Wilk test. If normal distribution is rejected, a non-parametric Wilcoxon signed rank test will be used. Multiple imputation method will be used to handle the missing data.

The key secondary analysis is to evaluate 6MWD-ext - 6MWD0 in the Placebo-Crossed treatment group after the successful testing on primary PVR analysis, with a type I error rate of 2-sided 0.025. ANCOVA will be used to test the intercept with 6MWD0-average (6MWD0) as the covariate. The normality check and missing data handling method will be similar to the primary analysis.

The other secondary analysis is to evaluate FCn-ext – FCn0 in the Placebo-Crossed treatment group after the successful testing on primary PVR and key secondary 6MWD analysis, with a type I error rate of 2-sided 0.025. ANCOVA will be used to test the intercept with FCn0-average (FCn0) as the covariate. The FC categories are converted to numerical values, I = 1, II = 2, III = 3, and IV = 4. The numerical values will be used in this analysis. This conversion is made in order to increase the statistical power of the ANCOVA analysis.

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11. APPENDICES

ABBREVIATIONS AND SPECIALIST TERMS

Abbreviation or Specialist Term	Explanation
6MWD	Six-Minute-Walk Distance
6MWT	Six-Minute-Walk Test
ACE-011	Sotatercept
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMP	Bone Morphogenetic Protein
BMPR2	Bone Morphogenetic Protein Receptor type II
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CBC	Cell Blood Count
CFR	Code of Federal Regulations
CO	Cardiac Output
CxDy	Cycle x Day y
CMH	Cochran-Mantel-Haenszel (method)
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECHO	Echocardiogram
eGFR	Estimated Glomerular Filtration Rate
ERA	Endothelin-Receptor Antagonist
EOS	End of Study
EOT	End of Treatment
ETE	Embolic and Thrombotic Events
FAS	Full Analysis Set
FC	Functional Class
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
GDF	Growth and Differentiation Factor
GEE	Generalized Estimating Equation
Hgb	Hemoglobin
Hct	Hematocrit
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council For Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Medical Activities
MMP2	Matrix Metalloproteinase-2
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NI	Non-Inferiority
NOAEL	No-Observed-Adverse-Effect Level
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PBMC	Peripheral Blood Mononuclear Cell
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic(s)
PDE5	Phosphodiesterase 5
PK	Pharmacokinetic(s)
PPD	Pharmaceutical Product Development
PVR	Pulmonary Vascular Resistance
PVR0	Pulmonary Vascular Resistance at Baseline
PVR6	Pulmonary Vascular Resistance Following Completion of the 6-Month Placebo-Controlled Treatment Period
PVR-ext	Pulmonary Vascular Resistance After 12 to 18 Months on Treatment in the Extension Period
QTc	Corrected QT

Abbreviation or Specialist Term	Explanation
QTcF	Fridericia's Corrected QT formula
QoL	Quality of Life
QxW	Every X Weeks
RBC	Red Blood Cell
RHC	Right Heart Catheterization
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SMQ	Standardized MedDRA Queries
SOC	Standard of Care
SoE	Schedule of Events
sPAP	Systolic Pulmonary Artery Pressure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEAE	Treatment-Emergent Adverse Event
TGF-β	Transforming Growth Factor-βeta
UA	Urinalysis
UACR	Urine Albumin Creatinine Ratio
ULN	Upper Limit of Normal
VEGFR1	Vascular Endothelial Growth Factor Receptor 1
VQ	Ventilation-Perfusion (Scan)
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

APPENDIX 1. CLINICAL LABORATORY TESTS

The tests detailed in Table 12 will be performed by local laboratories at the timepoints specified in the Schedule of Events (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 12: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	CBC with differential: CBC includes RBCs, WBCs, Hgb, Hct, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count
Chemistry	Albumin, ALP, ALT, AST, blood urea nitrogen, calcium, chloride, carbon dioxide/bicarbonate, creatinine, glucose, phosphorus, potassium, sodium, total bilirubin, direct bilirubin
Urinalysis	UA, UACR
Seminal fluid collection	Sperm count, Sperm Motility, Sperm Morphology

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

Investigators must document their review of each laboratory safety report.

APPENDIX 2. STANDARD OF CARE THERAPY

Standard of care (SOC) therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with endothelin-receptor antagonists, phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. Standard of care therapy should remain stable throughout the study. 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 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 a participant may stay on study treatment.

During the Extension Period, PAH-specific medications can be modified (substituted, removed, or dose adjusted), including supplemental oxygen. Investigator discretion will be used to determine if sotatercept study treatment discontinuation is necessary.

APPENDIX 3. SIX-MINUTE-WALK TEST

A standardized 6-minute-walk test (6MWT) will be performed in accordance with the guidelines of the American Thoracic Society.[11-13] The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 meters in length. The length of the corridor should be marked every 3 meters. The turnaround points should be marked (e.g., with a cone). A starting line, which marks the beginning and end of each 60-meter lap, should be marked on the floor (e.g., using brightly colored tape).

The 6-minute-walk distance 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 adverse events (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 blood pressure, and make sure that clothing and shoes are appropriate. Record in the source documents.
4. Measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact.

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 1 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 4. 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 International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (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 serious adverse events (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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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 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 case report form (eCRF) 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 eCRF.
- 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 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 5. 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 follicle-stimulating hormone (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 1 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 1 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 a minimum of 112 days after the last dose of study treatment. Refrain from

donating blood or sperm for the duration of the study and for a minimum of 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 13. 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 13: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] Failure rate of < 1% per year when used consistently and correctly
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system 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.

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

Pregnancy Testing

- A Woman f Child-Bearing Potential should only be included in the study after 2 confirmed negative pregnancy tests.
- Additional pregnancy testing should be performed prior to study treatment administration at each dosing visit during the study and 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 6. GENETICS

Use/Analysis of Deoxyribonucleic Acid

- 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.
- Optional deoxyribonucleic acid (DNA) samples that are collected 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 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples that are collected will be analyzed for bone morphogenetic protein receptor type II (BMPR2; and other potential genes of interest) mutational status and variant allele frequency 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 optional genetic samples will be tested to characterize any associations between mutational status of pulmonary hypertension genes and the response of participants to study treatment, as well as potential susceptibility to, severity and progression of the disease in aggregate. Summary tables and figures will be generated to facilitate the understanding of the data. There is no analysis plan to focus on specific individual mutational information. The planned genetic analysis will help the future development of sotatercept in the indication of PAH.
- 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. All optional genetic samples collected will be analyzed at the bioanalytical laboratory shortly after receipt. Any remnants from the analysis will be stored until end of the study or as per local regulations. The information obtained from individual participants will be de-identified by labeling the samples with a unique participant identifier (participant number) prior to shipment to the analysis laboratory.

APPENDIX 7. NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 4.0

Currently active minor version of the National Cancer Institute-Common Terminology Criteria for Adverse Events , version 4.0:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

APPENDIX 8. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Tables

Substantive changes from Protocol Amendment 05D (12 August 2018) to Protocol Amendment 06D (18 December 2018) are detailed below. Minor edits are not included.

Protocol Location	Description of Change	Brief Rationale
Synopsis, Section 2., Schedule of Events, Section 4.1., Overall Design, Figure 1	Changed Double-Blind Treatment Period to Placebo-Controlled Treatment Period	Change in nomenclature of study periods to clarify that the difference between the study periods is defined by the presence of a placebo arm rather than the study blinding.
Synopsis, Section 3.1., Study Rationale, Section 4.1., Overall Design, Section 6.3., Dose Modification, Section 6.5., Randomization and Blinding; Section 8.2., Efficacy Assessments, Section 9.2., Populations for Analyses	Added cycle and day numbers to the descriptions of timepoints.	To align language in the protocol with the Schedule of Events and to clarify that the 24-week timepoint is Cycle 9 Day 1A (C9D1A).
Synopsis, Section 4.1., Overall Design, Figure 1, Section 9.1., Sample Size Determination	Changed sample size to approximately 100 participants to be enrolled in a 3:3:4 randomization ratio.	Added approximately 10 participants to be randomized to the 0.7 mg/kg sotatercept dose level group in order to ensure that a sufficient number of participants are evaluable in the higher dose level group.
Synopsis, Section 4.1., Overall Design, Section 5.2., Exclusion Criteria, Appendix 3: Standard of Care Therapy	Removed cap of 25% for the percentage of participants on monotherapy. Clarified definitions of SOC.	It is unnecessary to cap the percentage of participants who are receiving monotherapy to treat PAH.

Section 2., Schedule of Events	Separated the SOE into 2 distinct tables: The Placebo-Controlled Treatment Period (Table 3) and the Extension and Follow-Up Periods (Table 4). Cycle 9 Day 1 is split into Cycle 9 Day 1A and Cycle 9 Day 1B. Cycle 9 Day 1A is within the Placebo-Controlled Treatment Period and includes all assessments scheduled for the day. Cycle 9 Day 1B is the first column in the Extension Period and includes study treatment administration. Clarified timing and order of assessments, including 6MWT, ECHO, and RHC. Removed footnotes.	To improve readability and functionality of the SOE while maintaining the necessary level of detail. Footnotes composed of unnecessary or redundant information were removed.
Section 2., Schedule of Events, Section 8.4.2., Clinical Laboratory Assessments, Section 8.8., Seminal Fluid Analyses; Appendix 2: Clinical Laboratory Tests	Allowed seminal fluid collection to be optional for male participants. Added a section to explain seminal fluid collection and analyses (Section 8.8).	Comply with health authority request while allowing for operational feasibility. Clarified parameters to be evaluated for seminal fluid.
Section 4.1., Overall Design	Redundant and unnecessary language was removed from explanations of the study periods.	To improve clarity.
Section 5.1., Inclusion Criteria	Inclusion criterion 4: added language about the timing of RHC assessments Inclusion criterion 5: added language around pulmonary function tests for total lung capacity Inclusion criterion 6: added language regarding options for	To clarify when RHC assessments will be conducted. To clarify that pulmonary function test of total lung capacity may be substituted by a chest computed tomography scan showing no more than mild interstitial lung disease (ILD) by investigator interpretation.

	ventilation-perfusion scan if unavailable Inclusion criterion 8: 6MWD upper limit changed to 550 m Inclusion criterion 10: Contraceptive guidelines language clarified. Changed the timing of the requirement for effective contraception use prior to starting investigational product from 5 weeks to 28 days.	To clarify that pulmonary angiography result may be used. 6MWD distance upper threshold was increased to better reflect the patient population on treatment with SOC. To align inclusion criterion with the Appendix 6 guidelines and definitions. To align contraception guidelines with study timelines.
Section 5.2., Exclusion Criteria	Exclusion criterion 16: Clarified that if a historical ECHO is unavailable, a participant may receive 1 during the Screening Period. Exclusion criterion 20: 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 clarify timing of ECHO assessments. 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 adverse events and frequency of rescreening for screen failures.	To clarify that adverse event details are to be captured for screen failures and that rescreening is allowed only once.
Section 6.3., Dose Modification	Table 5: Changed the dose modification rules for AE, hemoglobin, and blood pressure.	To align with updated inclusion/exclusion criteria and to clarify when doses of study treatment should be delayed or reduced.
Section 6.5., Randomization and Blinding	Language added regarding timing of unblinding.	To clarify that unblinding will occur for everyone when all participants have had

		their post-Placebo-Controlled Period (C9D1) PVR assessment.
Section 8.2., Efficacy Assessments	Added information about the timing of the RHC (Section 8.2.1) and ECHO (Section 8.2.3) assessments.	To improve clarity of the timing of these assessments and to promote alignment with the SoE.
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.
Section 8.4., Safety Assessments	Weight was moved from the physical examination section (Section 8.4.1) to the vital signs section (Section 8.4.2).	Weight is collected and recorded in the eCRF as a part of the vital signs.
Section 8.4.3., Electrocardiograms	Added language regarding details of ECGs.	To clarify that single not triplicate ECGs are to be obtained and that manual calculations are to be made if automatic ones are not available.
Section 8.4.6., Clinical Safety Laboratory Assessments	Added, "If hemoglobin is ≥ 17 g/dL during Cycles 1-2 or Cycles 9-10, participants should return weekly for hemoglobin monitoring."	To ensure that participants whose hemoglobin levels become high are appropriately monitored.

6MWD = 6-minute-walk distance; 6MWT = 6-minute-walk test; AE = adverse event; AESI = adverse event of special interest; ANC = absolute neutrophil count; CKD = chronic kidney disease; CT = computed tomography; CxDy = Cycle x Day x; DMC = Data Monitoring Committee; ECG = electrocardiogram; ECHO = echocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOS = End of Study; Hgb = hemoglobin; ICF = informed consent form; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; QTcF = Fridericia's corrected QT formula; RHC = right heart catheterization; SOC = standard of care; SOE = Schedule of Events; TEAE = treatment-emergent adverse event; UA = urinalysis; UACR = urine albumin creatinine ratio; VQ = ventilation-perfusion; WBC = white blood cell.

Substantive changes from Protocol Amendment 04C (14 June 2018) to Protocol Amendment 5D (12 August 2018) are detailed below. Minor edits are not included.

Protocol Location	Description of Change	Brief Rationale
Synopsis Section 4.1 Overall Design, Section 5.2 Exclusion Criteria, and Appendix 3: Standard of Care Therapy	Removed any exclusion of prostacyclin treatment as part of standard of care	Sponsor acknowledges standard of care may include monotherapy with prostacyclin
Section 2., Schedule of Event, Section 8.4.2., Clinical Laboratory Assessments, Appendix 2: Clinical Laboratory Tests and Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information	Include seminal fluid collection pre-dose and post-dose and increase follow-up monitoring time	Comply with health authority request
Section 4.1., Overall Design	Remove interim analysis language.	Administrative change. Removal of interim analysis language that was inadvertently missed from last amendment.
Section 5.2., Exclusion Criteria number 32	Exclude patient with history of rare hereditary fructose intolerance and other genetic deficiencies of sugar metabolism	Comply with health authority request
Section 7.1., Discontinuation of Study Treatment	Add QTcF > 500ms during treatment period	Comply with health authority request
Section 8.4.2., Vital Signs	Add additional blood pressure measurements	To ensure accurate readings, for dose modifications rules pertaining to blood pressure as with all on – study blood pressure measurement 3 readings are required
Section 8.4.6., Clinical Safety Laboratory Assessments	Add all hematology findings	Clarify that all clinically significant abnormal hematology lab findings will be reported as adverse events

QTcF = Fridericia's corrected QT formula.

Substantive changes from Protocol Amendment 03B (24 May 2018) to Protocol Amendment 04C (14 June 2018) are listed below. Minor edits are not included.

Protocol Location	**Description of Change**	**Brief Rationale**
Synopsis Section 9.3.5 Interim Analysis	Interim analysis removed	Upon further review, the interim analysis was not expected to provide meaningful additional benefit over standard DMC monitoring.
Section 5.2 Exclusion Criteria.	Replaced exclusion criterion 20c with exclusion criterion 31: History of renal disease, including: a. Chronic renal disease at any time prior to screening; or b. Any episode of acute renal failure, with or without a prior history of renal disease, occurring within the 3 months prior to screening in which acute dialysis (e.g., intermittent hemodialysis or continuous veno-venous hemofiltration) was required	To reduce the risk of enrolling participants with baseline chronic renal impairment or a recent acute renal failure episode.
Section 6.3 Dose Modification	Added separate rows for leukopenia and thrombocytopenia.	To clarify actions to be taken whether these events were deemed related or not.
Section 9.3.2 Safety Analyses	Added language regarding creatinine and UACR.	To describe planned analyses for renal function tests.

DMC = Data Monitoring Committee; UACR = urine albumin creatinine ratio.

Substantive changes from the Protocol Amendment 02B (dated 30 April 2018) to amendment 03B (dated 24 May 2018) are listed below. Amendment 03B was approved internally and submitted to VHP but never implemented at any site. Minor edits are not included.

Protocol Location	**Description of Change**	**Brief Rationale**
Section 2., Schedule of Events	Added urinalysis (UA) and urine albumin creatinine ratio (UACR) assessments Edited timing of quality of life (QoL) assessments to be consistent with timing of 6-minute-walk test (6MWT)	UA and UACR added to provide additional renal function monitoring To provide for the opportunity to investigate any correlations of QoL with 6MWT
Section 5.2., Exclusion Criteria	Exclusion criterion 16: added timing around ECHO - to be historical within 6 months prior to Screening Exclusion criterion 20: added lower entry limits for white blood cell (WBC) count, platelets, and absolute neutrophil count (ANC). Edited eGFR threshold to < 45 ml/min/1.73m^2. Exclusion criterion 28: added "(auto)" in front of immune and "Autoimmune diseases are excluded with the exception of those related to PAH etiologies included in this study"	To clarify that historical ECHO (within 6 months) is to be used for eligibility (further clarified in Schedule of Events footnote 10) To limit baseline infection and bleeding risk of participants entering the study and to reduce the risk of enrolling participants with baseline significant renal impairment (i.e., CKD Stage 3B or worse excluded). To clarify that the presence of autoimmune conditions are also exclusionary, but not those which are associated with the particular subtypes of PAH disease included in this study.
Section 3.3., 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	Language regarding risks added to better synchronize between information presented in the Investigator's Brochure and informed consent form.

	thrombocytopenia have been described as treatment-emergent adverse events. As a consequence of the decrease in white blood cells, infection maybe a potential risk and as a consequence of thrombocytopenia, bleeding maybe a potential risk. Per health authority request, leukopenia, neutropenia, and thrombocytopenia have been identified as adverse events of special interest (AESI) in this study (see Section 6.3 Dose Modifications and 8.3 Adverse Events).	
Section 6.3. Dose Modifications	Guidance for AESI have been added to Table 5	To provide management of the events added to Section 3.3.
Section 8.3. Adverse Events	Added details regarding AESI	To provide details of the events added to Section 3.3.
Appendix 8: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0	Added link to NCI-CTCAE	For clarification purposes with additions to Sections 6.3 and 8.3.

6MWT = 6-minute-walk test; AESI = adverse event of special interest; ANC = absolute neutrophil count; CKD = chronic kidney disease; ECHO = echocardiogram; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PAH = pulmonary arterial hypertension; QoL = quality of life; UA = urinalysis; UACR = urine albumin creatinine ratio; WBC = white blood cell.

Substantive changes from the Protocol Amendment 01B (dated 15 February 2018) to amendment 02B (dated 30 April 2018) are listed below. Minor edits are not included.

Protocol Location	Description of Change	Brief Rationale
Section 2. Schedule of Events, footnote 13.	Added: "Additionally, PK will be collected on the following non-dosing days within the Treatment and Extension Periods: C1D8, C2D8, C9D8 and C10D8."	Clarification of PK collection visits (no assessments added or removed)
Section 5.1. Inclusion Criteria	Included information regarding sperm donation and oocyte donation into Inclusion Criteria 10	To provide more comprehensive information in the body of the document in addition to that in Appendix 6
Section 6.2. Treatment Administration and Schedule	Added: "Each injection will not exceed 1.0 mL; a minimum of 2 injections will be required per dose."	Clarified the number of injections in order to align with Exclusion Criteria 30 from the last protocol amendment and the Pharmacy Manual.
Section 9.3.5. Interim Analysis	"The first full interim analysis…" changed to "An interim analysis…" Removal of language detailing potential actions the sponsor could take after the interim analysis (IA).	Only one interim analysis is planned. Language was clarified to accurately express this intent. Simplification of the protocol text in order to clarify that if decisions are made post IA by the sponsor, any amendment to the protocol would take into consideration all operational and statistical requirements.
Section 11.7. Appendix 7. Genetics	Added descriptions for the use and long-term storage of genetic samples	To provide further details of the intent and logistics of the genetic testing

CxDy = Cycle x Day x; PK = pharmacokinetic.

Substantive changes from the original protocol (dated 15 December 2017) to amendment 01B (dated 15 February 2018) are listed below. Minor edits are not included.

Protocol Location	**Description of Change**	**Brief Rationale**
Synopsis. Overall Design. Section 4.1. Study Design. Section 11.3. Appendix 3. Standard of Care.	Deleted "SC/inhaled/PO" as a restriction on prostacyclin analogue or receptor agonist for Standard of Care.	Participants receiving IV prostanoids as part of their Standard of Care will be allowed.
Section 2. Schedule of Events	Added WHO functional class assessments at multiple timepoints	To be able to capture events of WHO functional class improvement as well as WHO functional class deterioration (already being assessed as part of clinical worsening).
Section 2. Schedule of Events, footnote 4	Added "If hemoglobin is ≥ 17 g/dL during Cycles 1-2 or Cycles 9-10, participant should return weekly for hemoglobin monitoring (and continue to follow Dose Modification rules for dosing days (Section 6.3)."	Additional monitoring for safety to ensure hemoglobin levels are not rising while participants are reaching steady state. Cycles 9-10 will be the first time placebo participants receive sotatercept.
Section 2. Schedule of Events, footnote 7 Section 8.7. Genetic Testing Appendix 7: Genetics	Added language to clarify that genetic testing is optional.	Genetic testing is now an optional procedure per protocol.
Section 2. Schedule of Events, footnote 14 Section 8.6. Pharmacodynamics	Updated list of PD biomarkers to: "activin A, BMPR2 (via PBMCs), GDF15, MMP2, NT-proBNP, TGF-β1, VEGFR1, and sex hormone metabolites".	PD biomarkers testing plan has been revised.
Section 5.2. Exclusion Criteria	Added exclusion criteria #30: "Weight > 140 kg at Screening"	The weight restriction ensures participants will receive 2 injections per dose, as detailed in the Pharmacy Manual.

Section 8.2.2. Six-Minute-Walk Distance	Added, "For assessment of clinical worsening, a decrease of ≥ 15% in 6MWD at any timepoint 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."	Clarification of the timing of the repeat 6MWT as needed for assessment of clinical worsening.
Section 8.4.4. Clinical Worsening	Added to the functional deterioration assessment, "…both of the below events occurring together at any time, even if they began at different times, as compared to their Screening values."	To clarify that the paired assessments for functional deterioration as part of the clinical worsening determination need not occur within the same cycle.

6MWD = six-minute-walk distance; 6MWT = six-minute-walk test; BMPR2 = bone morphogenetic protein receptor type II; GDF = growth and differentiation factor; IV = intravenous; MMP2 = matrix metalloproteinase-2; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PBMC = peripheral blood mononuclear cell; PO = oral; SC = subcutaneous; TGF-β1 = transforming growth factor-beta 1; VEGFR1 = vascular endothelial growth factor receptor 1; WHO = World Health Organization.