Official Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH
NCT number:	NCT04576988
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Protocol A011-11 (STELLAR)

PROTOCOL TITLE:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH
SHORT TITLE:	A Phase 3 Study of Sotatercept for the Treatment of PAH
REGULATORY AGENCY IDENTIFYING NUMBERS:	IND 136150 EudraCT 2020-004142-11
SPONSOR:	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 USA PPD
ORIGINAL PROTOCOL DATE:	12 September 2020
PROTOCOL AMENDMENT 01:	06 October 2021

Confidentiality Statement

This confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Acceleron Pharma Inc.

PROTOCOL SIGNATURE PAGE

Acceleron Pharma Inc. Approval

PPD

Investigator Agreement:

The information contained in this protocol and all other information relevant to sotatercept are the confidential and proprietary information of Acceleron Pharma Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Acceleron Pharma Inc.

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.

Signature: _____ **Date:** _____

Name (print): _____

Institution Name and Address:

_____

_____

_____

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Substantive changes from Revision 0.0 to Revision 1.0 are detailed below. Minor edits are not included.

Protocol Location	Description of Change	Brief Rationale
Title Page	Added "PROTOCOL AMENDMENT 01: 01 October 2021"	Updated protocol amendment identifier and release date
Table 1	Updated pharmacovigilance row	Added new contact information
	Updated Medical Monitor row	Changed phone number
Section 2, Schedule of Events	Changed the following in footnote d: "perform targeted cardiopulmonary and skin examinations."	Updated based on new information about the study treatment.
	Updated footnote j in Table 2 to indicate that RHC will be performed last "when possible." Similar changes were made in Section 9.2.1 Screening Period (up to 4 weeks prior to Visit 1) and Section 9.3.2 Right Heart Catheterization.	Clarified that sites have flexibility if it is not possible to schedule the RHC last
	Changed "CO_2" in footnote i in Table 2 and footnote k in Table 3 to "HCO_3" and added "albumin." A similar change was made to Section 9.3.16, Serum Chemistry	Correction
	Updated footnote n in Table 2 and footnote o in Table 3 to change "should be done prior to study drug administration" to "must be done prior to study drug administration."	Clarified the mandatory order of procedures
	Updated footnote m in Table 3 to remove the following: "If the PAH-SYMPACT cannot be completed at home on the 7 days prior to the EOS visit it should be completed once on-site at the EOT visit." A similar change was made to Section 9.3.8.2, Pulmonary Arterial Hypertension – Symptoms and Impact	Correction

Protocol Location	Description of Change	Brief Rationale
	Changed the row label "Serum Chemistry" to "Serum chemistry/FSH" in Table 3. Similar changes were made in Section 9.2 Study Procedures and Synopsis.	Improved consistency of row labels across Section 2
	Removed "hematology (complete blood count)" assessment from Visits 10-12, 14-16, 18-20, 22-24, 26-28, and 30-32 in Table 3. Similar changes were made in Section 9.2 Study Procedures.	Updated study assessments
Section 3.2, Risks and/or Benefits to Participants	Aligned text with A011-14 (ZENITH) Version 1.0 from 08 April 2021, updated text regarding the detection of anti-drug antibodies, and added text regarding the risk of telangiectasia.	Updated information for programmatic consistency and accuracy
Section 5.3 Secondary Efficacy Endpoints and Rationale; Section 11.5.2 Secondary Endpoints; and Synopsis	Changed Secondary Endpoints to clarify that the Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts domains of the PAH-SYMPACT will be evaluated. Removed EQ-5D-5L (added to the Exploratory Endpoints below).	Updates to endpoints
Section 5.4 Exploratory Endpoints; Section 11.5.3 Exploratory Endpoints; and Synopsis	Added evaluation of the Cardiovascular Symptoms domain of the PAH-SYMPACT®, EQ-5D-5L, and EQ-5D-5L VAS to the Exploratory Endpoints.	Updates to endpoints
Section 6.5, Home Health Care Visits	Removed the following: "For HHC visits, hematology results are not required to be evaluated prior to study drug administration. However, if results evaluated after dosing meet the criteria for dose modification, the following visit will be conducted on-site and the medical monitor consulted."	This text no longer applies because hematology will not be performed during the home health care visits
Section 6.6, Randomization and Blinding	Amended text starting in the middle of paragraph 2.	Clarified that participants will be discontinued after emergency unblinding and aligned the wording across the program

Protocol Location	Description of Change	Brief Rationale
Section 7.2, Background PAH Therapy	Removed the word "diuretics" from the description of background PAH therapy. Added a definition of stable diuretic therapy.	Correction and alignment with the Clarification letter sent 22 March 2021
Section 7.3, Inclusion Criteria and Synopsis	Added the following to criterion 4: "and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure of ≤ 15 mmHg." To avoid redundancy, the following was removed from exclusion criterion 20: "or PCWP > 15 mmHg as determined in the Screening Period RHC."	Improved consistency of entry criteria
Section 7.4, Exclusion Criteria and Synopsis	Added the following new criterion 4: "Baseline platelet count < 50,000/mm^3 (< 50.0 × 10^9/L) at screening"	Improved consistency with the criteria for dose delay and modification
	Changed the following in criterion 12: "If PFT is not available, a chest CT scan showing ~~no~~ more than mild interstitial lung disease (ILD) at the screening visit or 1 year prior to it"	Correction
	Modified criterion 8 in the following way: "> ~~1~~3 × ULN (bilirubin criterion waived if there is a documented history of Gilbert's syndrome)"	Correction
	Modified criterion 11 in the following way: "~~Have~~History of full ~~or partial~~ pneumonectomy."	Correction
Section 8.3.4, Dose Modifications Due to Adverse Events of Telangiectasia; Section 8.3.5, Dose Re-escalation following Dose Reduction; Section 10.9, Monitoring of Identified Risks, Potential Risks, and Adverse Events of Special Interest	Added language to describe dose modifications required for adverse events of telangiectasia.	Updated to provide guidance on dose modifications required for newly identified AESI of telangiectasia.

Protocol Location	Description of Change	Brief Rationale
Section 9.2.1 Screening Period (up to 4 weeks prior to Visit 1)	Added the following: "Upon discussion with the medical monitor, a historic RHC may be allowed as long as it was collected within 28 days prior to Visit 1."	Clarification of screening procedures
Section 9.3.1 Six-minute Walk Test	Added text describing the timing of 6MWT evaluations, criteria for screen failure related to the 6MWT, and criteria for performing an additional 6MWT. Added a reference to the Guidelines for the Six-Minute Walk Test (2002).	Provided additional guidance and aligned across the program
Section 9.3.2 Right Heart Catheterization	Removed "selected" as follows: "Right ventricle pressure data from the RHC with simultaneously recorded ECG recordings may be collected and digitally stored at the clinical ~~selected~~ sites."	Clarified the locations able to collect and store the specified data
Section 9.3.5, Borg Dyspnea Scale (Borg CR10 Scale)	Changed text to the following: "The Borg Dyspnea Scale (Borg CR10 Scale)…"	Correction
Section 9.3.9, Clinical Worsening Assessment	Removed "therapy" in the following statement: "Deterioration of PAH ~~therapy~~…"	Clarified the meaning of clinical worsening
Section 9.4.1, Participants Early Discontinuation	Modified the criteria for discontinuation due to a clinical worsening event and altered the instructions for further study visits.	Clarified that patients who experience clinical worsening that does not meet the criteria for discontinuation may continue on study drug up to the primary endpoint evaluation
	Modified the following text: "An increase in QTcF of > 60 ms that results in QTcF of > 500 ms (or > 550 ms if right bundle branch abnormality is present) during the treatment period."	Clarified the modified discontinuation criterion for patients with right bundle branch abnormality
Section 9.8, Criteria for Study Termination; Section 12, Direct Access to Source Data/Documents; Section 13, Ethics and Responsibilities;	Removed Appendix 3, Study Governance Considerations, and incorporated the information into the main body of the protocol.	Aligned protocol text across the program

Protocol Location	Description of Change	Brief Rationale
Section 14, Data Handling and Record Keeping; Section 16, Confidentiality; Section 18, Appendices		
Section 10, Safety Assessment, Reporting, and Monitoring	Aligned text with A011-14 (ZENITH) Version 1.0 from 08 April 2021. Updated Table 5 and the surrounding text to indicate that telangiectasia is the only AESI and provide monitoring parameters.	Updated information for programmatic consistency and accuracy
Section 11.5.1.1, Handling of Missing Data	Updated the 6MWD values to be used for participants with missing data.	Corrections

Abbreviations: 6MWD = six-minute walk distance; 6MWT = six-minute walk test; AESI = adverse event of special interest; CT = computed tomography; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; FSH = follicle-stimulating hormone; HCO_3 = bicarbonate; PAH = pulmonary arterial hypertension; PAH SYMPACT = Pulmonary Arterial Hypertension – Symptoms and Impact; PCWP = pulmonary capillary wedge pressure; PFT = pulmonary function test; QTcF = Fridericia's corrected QT interval; RHC = right heart catheterization; ULN = upper limit of normal; VAS = visual analog scale.

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1. PROTOCOL SYNOPSIS

Protocol Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH
Short Title	A Phase 3 Study of Sotatercept for the Treatment of PAH.
Protocol Number	A011-11 (STELLAR)
Study Type	Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study.
Rationale	Pulmonary arterial hypertension is a progressive, fatal disease that causes marked limitations in physical activity and quality of life, even when treated with approved therapies. This Phase 3 study is supported by data from the PULSAR study (Phase 2, NCT03496207), in which participants taking any approved single or combination therapy for PAH were randomized to receive additional sotatercept or placebo for 24 weeks. The PULSAR study demonstrated a statistically significant improvement in its primary endpoint, pulmonary vascular resistance (PVR). Additionally, improvement was observed in 6-Minute Walk Distance (6MWD), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and other endpoints.
Study Objective	The objective of this study is to evaluate the efficacy and safety of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH.
Study Population	Participants diagnosed with symptomatic PAH (World Health Organization [WHO] functional class [FC] II or III) who present with idiopathic or heritable PAH, PAH associated with connective tissue diseases (CTD), drug or toxin induced, post shunt correction PAH, or PAH presenting at least 1 year following the correction of congenital heart defects, and currently on background PAH therapy.

Number of Participants	Approximately 284 participants will be randomly assigned in a 1:1 ratio to the two study treatment groups (142 participants per arm).
Study Design	The study is divided into a Screening Period (up to 4 weeks), Double-Blind Placebo-Controlled (DBPC) Treatment Period (24 weeks), a Long-Term Double-Blind (LTDB) Treatment Period (until last participant completes the DBPC treatment period, up to approximately 72 weeks), and a Follow-Up Period (at least 8 weeks) (Figure 1). Each study eligible participant will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms for the duration of the DBPC and LTDB Treatment Periods. • Arm 1: Placebo administered subcutaneously (SC) every 21 days plus background PAH therapy • Arm 2: Sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered SC every 21 days plus background PAH therapy The LTDB treatment period will last until the last participant randomized completes the DBPC Treatment Period and the study is unblinded. During this period, select study visits may be performed as home health care (HHC) visits as described in Section 6.5. After the study is unblinded, participants who complete the DBPC Treatment Period and are currently on treatment (sotatercept or placebo) in the LTDB Treatment Period may be eligible to participate in a separate open-label long-term follow-up (LTFU) study. Participants who complete the DBPC and LTDB treatment periods and do not wish to participate in the LTFU study will complete the Follow-up Period as described in Section 6.2. Participants who discontinue the DBPC Treatment Period early will complete the end of treatment (EOT) visit at the time of discontinuation. These participants will be invited to come for limited study assessments at selected visits (Period 1 Follow-up Visits 1 and 2) depending on the timing of their discontinuation. In addition, they will complete the end of study (EOS) visit (described in Section 9.2.6), provided that consent is not withdrawn.

Estimated Duration of the Study	Study duration for a given participant in A011-11 will be up to approximately 108 weeks as follows: • Screening Period (for up to 4 weeks) • DBPC Treatment Period (Period 1) (24 weeks, which includes 9 study visits [Visit 1 to Visit 9]) • LTDB Treatment Period (Period 2) (up to approximately 72 weeks, [Visit 10 up to Visit 33], depending on when the last participant randomized into the study completes the DBPC Treatment Period) • Follow-up Period (at least 8 weeks, which may include Period 1 Follow-up Visits 1 and 2 and EOT and EOS visits)
Inclusion Criteria	Eligible participants must meet all of the following inclusion criteria to be enrolled in the study: 1. Age ≥ 18 years 2. Documented diagnostic right heart catheterization (RHC) at any time prior to screening confirming the diagnosis of WHO PAH Group 1 in any of the following subtypes: • Idiopathic PAH • Heritable PAH • Drug/toxin-induced PAH • PAH associated with CTD • PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair 3. Symptomatic PAH classified as WHO FC II or III 4. Baseline RHC performed during the Screening Period documenting a minimum PVR of ≥ 5 Wood units (WU) and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure of ≤ 15 mmHg 5. On stable doses of background PAH therapy and diuretics (i.e., patient-specific dose goal for each therapy already achieved) for at least 90 days prior to screening; for infusion prostacyclins, dose adjustment within 10% of optimal dose is allowed per medical practice. Background PAH therapy is defined in Section 7.2 6. 6MWD ≥ 150 and ≤ 500 m repeated twice at screening (measured at least 4 hours apart, but no longer than 1 week),

	and both values are within 15% of each other (calculated from the highest value) 7. Females of childbearing potential must: • Have 2 negative urine or serum pregnancy tests as verified by the investigator prior to starting study therapy; she must agree to ongoing urine or serum pregnancy testing during the study and until 8 weeks after the last dose of the study drug • If sexually active, have used, and agree to use, highly effective contraception without interruption, for at least 28 days prior to starting the investigational product, during the study (including dose interruptions), and for 16 weeks (112 days) after discontinuation of study treatment • Refrain from breastfeeding a child or donating blood, eggs, or ovum for the duration of the study and for at least 16 weeks (112 days) after the last dose of study treatment 8. Male participants must: • Agree to use a condom, defined as a male latex condom or nonlatex condom NOT made out of natural (animal) membrane (e.g., 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 16 weeks (112 days) following investigational product discontinuation, even if he has undergone a successful vasectomy • Refrain from donating blood or sperm for the duration of the study and for 16 weeks (112 days) after the last dose of study treatment 9. Ability to adhere to study visit schedule and understand and comply with all protocol requirements 10. Ability to understand and provide written informed consent
Exclusion Criteria	1. Diagnosis of pulmonary hypertension WHO Groups 2, 3, 4, or 5 2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus (HIV)-associated PAH and PAH associated with portal hypertension. Exclusions in PAH Group 1 should also include schistosomiasis-associated PAH and pulmonary veno-occlusive disease

	3. Hemoglobin (Hgb) at screening above gender-specific upper limit of normal (ULN), per local laboratory test 4. Baseline platelet count < 50,000/mm^3 (< 50.0 × 10^9/L) at screening 5. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure > 160 mmHg or sitting diastolic blood pressure > 100 mmHg during screening visit after a period of rest 6. Baseline systolic blood pressure < 90 mmHg at screening 7. Pregnant or breastfeeding women 8. Any of the following clinical laboratory values at the screening visit: • Estimated glomerular filtration rate (eGFR) < 30 mL/min/m^2 (as defined by the Modification of Diet in Renal Disease [MDRD] equation) • Serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels > 3 × ULN (bilirubin criterion waived if there is a documented history of Gilbert's syndrome) 9. Currently enrolled in or have completed any other investigational product study within 30 days for small-molecule drugs or within 5 half-lives for biologics prior to the date of signed informed consent 10. Prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536) and/or excipients or known allergic reaction to either one 11. History of full pneumonectomy 12. Pulmonary function test (PFT) values of forced vital capacity (FVC) < 60% predicted at the screening visit or within 6 months prior to the screening visit. If PFT is not available, a chest CT scan showing more than mild interstitial lung disease at the screening visit or 1 year prior to it. 13. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to the screening visit 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). 14. History of more than mild obstructive sleep apnea that is untreated

	15. 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) 16. History of restrictive, constrictive, or congestive cardiomyopathy 17. History of atrial septostomy within 180 days prior to the screening visit 18. Electrocardiogram (ECG) with Fridericia's corrected QT interval (QTcF) > 500 ms during the Screening Period 19. Personal or family history of long QT syndrome (LQTS) or sudden cardiac death 20. Left ventricular ejection fraction < 45% on historical echocardiogram within 6 months prior to the screening visit 21. Any symptomatic coronary disease events (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the screening visit. Note: Anginal pain can be ignored as an exclusion criterion if coronary angiography shows no obstructions. 22. Cerebrovascular accident within 3 months prior to the screening visit 23. Acutely decompensated heart failure within 30 days prior to the screening visit, as per investigator assessment 24. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease 25. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the screening visit
Efficacy Endpoints	**Primary Efficacy Endpoints** The primary efficacy endpoint is the change in 6MWD at Week 24 versus baseline. **Secondary Efficacy Endpoints** Ranked as below: 1. Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline: • Improvement in 6MWD (increase ≥ 30 m)

	• Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L • Improvement in WHO FC or maintenance of WHO FC II 2. Change from baseline in PVR at Week 24 3. Change from baseline in NT-proBNP levels at Week 24 4. Proportion of participants who improve in WHO FC at Week 24 from baseline 5. Time to death or the first occurrence of any of the following clinical worsening events: • Worsening-related listing for lung and/or heart transplant • Need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more • Need for atrial septostomy • Hospitalization for worsening of PAH (≥ 24 hours) • Deterioration of PAH defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: – Worsened WHO FC – Decrease in 6MWD by ≥ 15% confirmed by 2 tests at least 4 hours apart, but no more than 1 week 6. Proportion of participants who maintain or achieve a low risk score at Week 24 versus baseline using the simplified French Risk score calculator 7. Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) at Week 24 8. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24 9. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24 **Exploratory Endpoints** The following indices will also be evaluated: • Change in echocardiogram parameters at Week 24 versus baseline

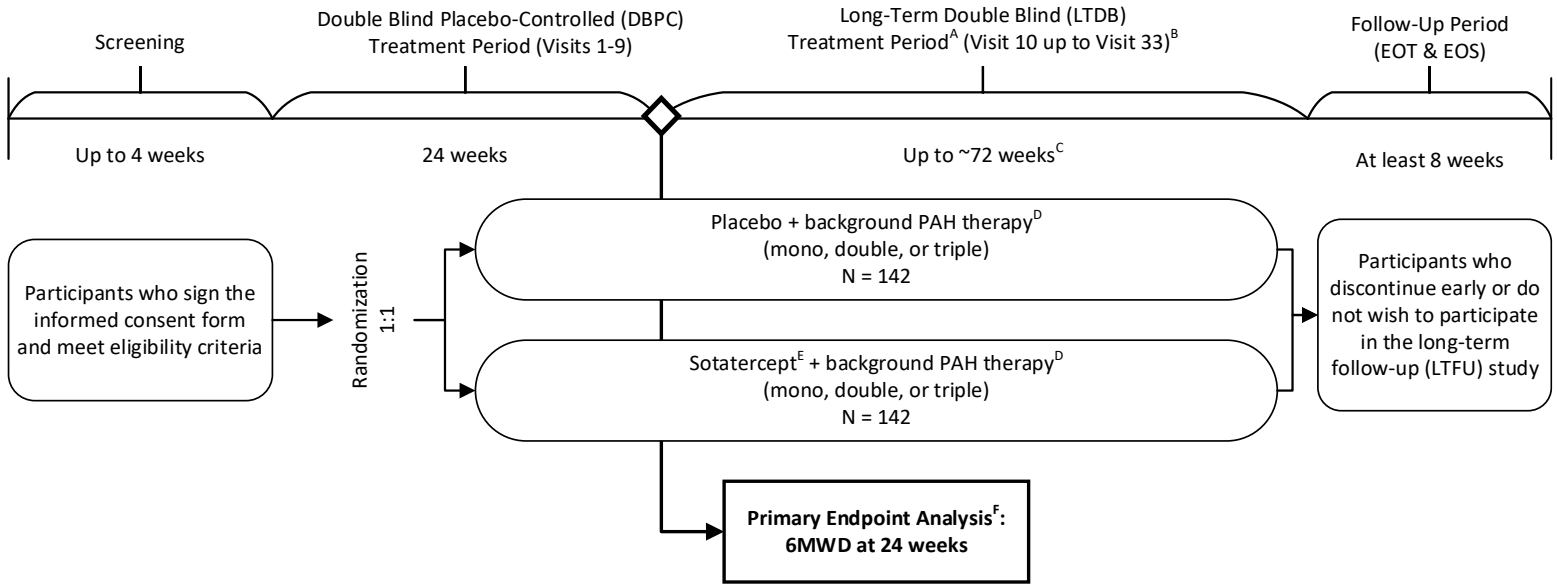
	• Change in dyspnea score (assessed by Borg CR10 scale®) at Week 24 versus baseline • Proportion of participants who achieve PVR < 3 WU at Week 24 • Proportion of participants who achieve mean pulmonary arterial pressure (mPAP) < 25 mmHg at Week 24 • Change from baseline in mPAP at Week 24 • Change from baseline in the Cardiovascular Symptoms domain score of PAH-SYMPACT® at Week 24 • Change from baseline in the EuroQoL – 5 Dimension – 5 Level (EQ-5D-5L) index score at Week 24 • Change from baseline in the EQ-5D-5L visual analog scale (VAS) at Week 24
Safety Endpoints	Safety will be evaluated by collecting the following information: • Adverse events • Anti-drug antibodies • Laboratory assessments (hematology, serum chemistry/FSH, urinalysis) • Vital signs • Physical examination • 12-Lead ECG
Sample Size Determination and Power Calculations	The sample size determination is based on the primary efficacy endpoint and the secondary endpoint of improvement in WHO FC. Assumptions for the desired treatment effect and estimate of variability (6MWD endpoint) are based on data from the PULSAR study (Phase 2, NCT03496207) and from a published clinical trial in PAH participants.[1] For 6MWD, assuming a 1:1 randomization, a 2-sided 0.05 Type I error rate, a 25-m improvement in sotatercept treatment compared to placebo, a common standard deviation (SD) of 50 m, and 121 participants per arm, the statistical power is approximately 96%, under the Wilcoxon rank sum test using N-Query®. For the secondary endpoint, "proportion of participants who improve in WHO FC at Week 24," assuming the proportion of participants treated with placebo and sotatercept is 0.11 and 0.25, respectively, 1:1 randomization, a 2-sided 0.05 Type I error rate, and 121 participants

	per arm, the statistical power is approximately 80% based on the 2-sample chi-square test. Assuming a 15% dropout rate, the total sample size will be n = 284 (n = 142 participants per arm).
Stratified Randomization Factors	Randomization will be stratified by: • Baseline WHO FC (Class II or III) • Background PAH therapy (mono/double or triple therapy)
Statistical Methods	**Efficacy Analyses:** All efficacy analyses will be based on the Full Analysis Set (FAS), which is defined as all randomized participants. All participants will be analyzed according to the treatment arm to which the participant is randomized. Efficacy analyses will also be performed on the Per-Protocol Set (PPS), which is defined as all participants randomized who receive at least 1 dose of study treatment with no data or study procedural-related issues that would otherwise impact the interpretation of the efficacy data. Analyses on the FAS will be considered primary for reporting purposes. **Safety Analyses:** All safety analyses are based on the Safety Set, which is defined as all participants who receive at least 1 dose of study medication. All participants will be analyzed according to the treatment they are administered. **Pharmacokinetic Analyses:** The Pharmacokinetic (PK) Population is defined as all participants who receive at least 1 dose of study drug and have sufficient PK samples collected and assayed for PK analysis. **Primary Endpoint:** The change in 6MWD at Week 24 from baseline will be analyzed using the stratified Wilcoxon test with the randomization factors as strata. The Hodges-Lehmann location-shift estimate of the treatment group difference with 95% confidence interval (CI) will be provided. **Secondary Endpoints:** The multicomponent improvement endpoint will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization factors. The change in NT-proBNP and PVR at Week 24 versus baseline will be analyzed using an analysis of covariance (ANCOVA) model with randomization factors and baseline values as covariates. The proportion of participants who improve in WHO FC at Week 24 from baseline will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization factors.

	Time to first clinical worsening event or death will be analyzed using log-rank test with randomization factors as strata. The proportion of participants who maintain or achieve a low risk score using the simplified French Risk score calculator at Week 24 versus baseline will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization factors. The change from baseline at Week 24 in the Physical Impacts domain score of PAH-SYMPACT® will be analyzed using an ANCOVA model with randomization factors and baseline value as covariates. The change from baseline at Week 24 in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® will be analyzed using an ANCOVA model with randomization factors and baseline value as covariates. The change from baseline at Week 24 in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® will be analyzed using an ANCOVA model with randomization factors and baseline value as covariates. A gatekeeping method will be used to control the Type I error rate in secondary endpoints by testing in the order of the secondary endpoints listed above, after successful testing for the primary endpoint. Secondary endpoint testing will be performed using a 2-sided alpha = 0.05 level proceeding successively in the order of the secondary endpoints listed above after each of the preceding endpoints is tested to be statistically significant. **Exploratory Endpoints:** For continuous variables, ANCOVA will be used with the randomization factors and baseline as covariates. For dichotomous variables, the Cochran-Mantel-Haenszel test will be used, stratified by the randomization factors. No adjustments for multiplicity will be performed. **Safety Endpoints** Safety data will be summarized descriptively by treatment arm.
Safety and Pharmacovigilance	An unblinded, external, independent Data Monitoring Committee (DMC) will monitor participant safety throughout the course of the study. A detailed charter will outline all activities of the DMC (including but not limited to the composition of the DMC, the type of data to be reviewed, the DMC responsibilities, and the frequency of meetings). Internal data review of safety-related data will occur in a blinded manner at a preplanned frequency throughout the study duration.

1.1. STUDY SCHEMATIC

Figure 1: Schematic of Study Periods for Study A011-11



[A] During the LTDB treatment period, select study visits may be performed as home health care (HHC) visits.
[B] LTDB treatment period will last until the last participant randomized completes the DBPC treatment period, at which point the study will be unblinded and participants may rollover into the LTFU study
[C] LTDB treatment period duration is estimated based on projected enrollment duration and time required for the last participant to complete the DBPC treatment period.
[D] Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists.
[E] Sotatercept at a starting dose of 0.3 mg/kg SC with a target dose of 0.7 mg/kg SC
[F] Primary endpoint analysis will be completed after the last participant randomized completes the DBPC treatment period.

6MWD = 6-minute walk distance; EOS = end of study; EOT = end of treatment; PAH = pulmonary arterial hypertension.

2. SCHEDULE OF EVENTS

The schedule of events (SoE), which provides an overview of the study periods and procedures, is presented in Table 2 and Table 3.

Specific information on visits and assessments during the Screening Period, Double-Blind Placebo-Controlled (DBPC) Treatment Period, and Follow-up Period is discussed in Section 9.

Table 2: Schedule of Events Period 1 – Double-Blind Placebo-Controlled Treatment Period and Follow-Up

Study Procedure/ Assessment	Screening Period (up to 4 weeks prior to Visit 1)	Double-Blind Placebo-Controlled (DBPC) Treatment Period[a] (24 weeks)						Period 1 Follow-Up Visits[b] (early discontinuation during DBPC period only)	
		Visit 1 ±3 days	Visit 2 ±3 days	Visits 3, 4 ±3 days	Visit 5 ±3 days	Visits 6, 7, 8 ±3 days	Visit 9 (1°EP Evaluation) ±3 days	Follow-Up Visit 1 (12 weeks after Visit 1) ±3 days	Follow-Up Visit 2 (24 weeks after Visit 1) ±3 days
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history review[c]	X								
Physical examination[d]	X	X			X		X	X	X
12-lead ECG	X				X		X		
Pulmonary function test or Chest CT scan[e]	X								
Vital signs including weight[f]	X	X	X	X	X	X	X	X	X
Pregnancy test (urine or serum)[g]	X	X	X	X	X	X	X	X	X
Hematology (complete blood count)[h]	X		X	X	X	X	X	X	X
Serum chemistry/FSH[i]	X				X		X	X	X
Urinalysis (dipstick)	X						X		
Right heart catheterization[j]	X						X		X
6MWT[k]	X		X		X		X	X	X
Borg Dyspnea Scale (pre- and post-6MWT)	X		X		X		X	X	X
WHO FC assessment	X		X		X		X	X	X
Clinical worsening assessment			X		X		X	X	X
QoL assessments[l]		X					X		X
NT-proBNP sample collection	X	X	X	X	X		X	X	X

Study Procedure/ Assessment	Screening Period (up to 4 weeks prior to Visit 1)	Double-Blind Placebo-Controlled (DBPC) Treatment Period[a] (24 weeks)						Period 1 Follow-Up Visits[b] (early discontinuation during DBPC period only)	
		Visit 1 ±3 days	Visit 2 ±3 days	Visits 3, 4 ±3 days	Visit 5 ±3 days	Visits 6, 7, 8 ±3 days	Visit 9 (1°EP Evaluation) ±3 days	Follow-Up Visit 1 (12 weeks after Visit 1) ±3 days	Follow-Up Visit 2 (24 weeks after Visit 1) ±3 days
ADA sample collection	X	X	X	X	X		X	X	X
PK sample collection	X	X	X	X	X		X	X	X
Randomization		X							
Echocardiogram[m]	X				X		X		X
Study drug administration[n]		X	X	X	X	X	X		
AE/SAE review	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X

Abbreviations: 6MWT = 6-Minute Walk Test; ADA = anti-drug antibody; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; DBPC = double-blind placebo-controlled; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQoL - 5 Dimension - 5 Level; FC = functional class; FSH = follicle-stimulating hormone; Hgb = hemoglobin; NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension - Symptoms and Impact; PFT = pulmonary function test; PK = pharmacokinetic(s); QoL = quality of life; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

[a] Each dosing visit will be 21 days (± 3 days) from the previous dosing visit unless a dose delay is required. If a dose delay is required per the dose modification guidelines (Section 8.3), the participant will not be dosed and will return every 3 weeks for assessment of hematology results and AEs until eligible to receive the next dose of study drug. The participant should resume treatment at the next planned dosing visit (e.g., if the participant missed a dose at Visit 4, then they would resume dosing at Visit 5).

[b] Participants discontinuing study treatment prior to Visit 5 are asked to complete EOT (Table 3), Follow-up Visits 1 and 2, and EOS (Table 3) visits (and in that order). Participants discontinuing study treatment after Visit 5 but before Visit 9 are asked to complete only EOT (Table 3), Follow-up Visit 2, and EOS (Table 3) visits (and in that order).

[c] Medical history review includes confirmation of disease history associated with PAH.

[d] Perform full physical examination at the screening visit only. For all other visits, perform targeted cardiopulmonary and skin examinations.

[e] A PFT will be done if the most recent test was performed more than 6 months prior to the screening visit. If a PFT is not possible, a chest computed tomography scan at the screening visit or a scan result within 1 year prior should be assessed for exclusion of interstitial lung disease.

[f] Height measurement will be required for the collection of vital signs at screening.

[g] Two serum or urine pregnancy tests are required for female participants of childbearing potential at the screening visit. One urine or serum pregnancy test is required prior to study drug administration at all other visits.

[h] Complete blood (cell) count includes red blood cells, absolute white blood cells, Hgb, hematocrit, and platelet count. Results are evaluated at the screening visit and then prior to study drug administration (or up to 3 days prior if available) for each visit except for Visit 1. Refer to Section 8.3 for dose modification guidelines based on Hgb levels and platelet count

[i] Blood urea, creatinine, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorus, glucose, magnesium, HCO_3, albumin, and FSH will be measured.

[j] In order to reduce invasive procedures for participants prior to confirming eligibility, RHC during the Screening Period should be performed last and after all screening clinical laboratory tests are done for eligibility, when possible. The RHC performed after screening may be performed on the day of study visit or within 1 week prior to study drug administration. If other assessments are performed on the same day, RHC should be performed last, when possible.

[k] 6MWT during the Screening Period must be performed twice, at least 4 hours but no longer than 1 week apart. 6MWT can be performed on the day of the study visit and has to be performed before study drug administration.

[l] QoL assessments include EQ-5D-5L and PAH-SYMPACT®. EQ-5D-5L should be completed before performing other study assessments (6MWT, blood draws, AE discussions, and RHC). PAH-SYMPACT should be completed at home daily on the 7 days prior to the study visit.

[m] Echocardiogram can be performed on the day of the study visit or up to 1 week prior to study drug administration.

[n] All study procedures must be done prior to study drug administration. Dose must be calculated based on the participant's weight on the day of dosing during the DBPC treatment period. Dose modification guidelines based on Hgb levels and platelet count must be reviewed and implemented prior to dosing (Section 8.3).

Table 3: Schedule of Events Period 2 – Long-Term Double-Blind Treatment Period and Follow-Up

Study Procedure/ Assessment	Long-Term Double-Blind (LTDB)[a] Treatment Period[b] (Up to ~ 72 weeks)[c]			Follow-Up Period	
	Visits 10-12, 14-16, 18-20, 22-24, 26-28, and 30-32[d] ±3 days	Visit 13, 21, and 29 ±3 days	Visit 17, 25, and 33 ±3 days	EOT[e] ±3 days	EOS[e, f] (At least 56 ±7 days after EOT)
Physical examination[g]		X	X	X	X
12-lead ECG		X	X	X	
Weight[h]		X	X		
Vital signs	X	X	X	X	
Pregnancy test (urine or serum)[i]	X	X	X	X	
Hematology (complete blood count)[j]		X	X	X	
Serum chemistry/FSH[k]		X	X	X	
Urinalysis (dipstick)			X	X	
6MWT[l]		X	X	X	X
Borg Dyspnea Scale (pre- and post-6MWT)		X	X	X	X
WHO FC assessment		X	X	X	X
Clinical worsening assessment		X	X	X	X
QoL assessments[m]				X	
NT-proBNP sample collection		X	X	X	X
ADA sample collection		X	X	X	X
PK sample collection		X	X	X	X
Echocardiogram[n]			X	X	
Study drug administration[o]	X	X	X		
AE/SAE review	X	X	X	X	X
Concomitant medication review	X	X	X	X	X

Abbreviations: 6MWT = 6-Minute Walk Test; ADA = anti-drug antibody; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; DBPC = double-blind placebo-controlled; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQoL - 5 Dimension - 5 Level; FC = functional class; FSH = follicle-stimulating hormone; Hct = hematocrit; Hgb = hemoglobin; HHC = Home health care; LTDB = long-term double-blind; LTFU = long-term follow-up; NT-proBNP

= N-terminal proB-type natriuretic peptide; PAH-SYMPACT® = Pulmonary Arterial Hypertension - Symptoms and Impact; PK = pharmacokinetic(s); QoL = quality of life; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

[a] The LTDB treatment period is applicable until the last randomized participant completes Visit 9 in the DBPC treatment period and the study is unblinded, at which point participants can rollover into a separate open label LTFU study.

[b] Each dosing visit will be 21 days (± 3 days) from the previous dosing visit unless a dose delay is required. If a dose delay is required per the dose modification rules (Section 8.3), the participant will not be dosed and will return every 3 weeks for assessment of hematology results and AEs until eligible to receive the next dose of study drug. The participant should resume treatment at the next planned dosing visit (e.g., if the participant missed a dose at Visit 4, then he/she would resume dosing at Visit 5) if eligible per dose modification rules.

[c] Estimate is based on projected enrollment duration and time required for the last participant to complete the DBPC treatment period.

[d] These select visits may be conducted as HHC visits for eligible participants. See Section 6.5 for further details.

[e] Once the study is unblinded, participants who complete the DBPC treatment period and are currently on treatment in the LTDB treatment period may roll over from this study into a separate open-label LTFU study. For these participants, the EOS visit can be waived and Visit 1 of the LTFU study will take place 21 (± 7) days after the last dose administered in this study, which may coincide with this study's EOT visit. Participants who discontinue treatment early for reasons other than clinical worsening should complete the EOT visit at the time of discontinuation and complete the EOS visit at least 56 days (± 7 days) after the EOT visit.

[f] EOS visit is applicable to participants who do not wish to participate in the LTFU study and for participants who discontinue treatment early for reasons other than clinical worsening.

[g] Perform targeted cardiopulmonary and skin examinations.

[h] For dosing visits at which weight is not collected, the most recently collected weight should be utilized for dose calculation.

[i] Two serum or urine pregnancy tests are required for female participants of childbearing potential at the screening visit. One urine or serum pregnancy test is required prior to study drug administration at all other visits.

[j] Complete blood (cell) count includes red blood cells, absolute white blood cells, Hgb, Hct, and platelet count. Results are evaluated prior to study drug administration (or up to 3 days prior if available) for each visit conducted on-site. For HHC visits, results are not required to be evaluated prior to study drug administration. Refer to Section 8.3 below for dose modification guidelines based on Hgb levels and platelet count.

[k] Blood urea, creatinine, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, HCO_3, albumin, and FSH will be measured.

[l] 6MWT can be performed on the day of the study visit and has to be performed before study drug administration.

[m] QoL assessments include EQ-5D-5L and PAH-SYMPACT®. EQ-5D-5L should be completed before performing other study assessments (6MWT, blood draws, AE discussions, and RHC). PAH-SYMPACT® should be completed at home daily on the 7 days prior to the study visit.

[n] Echocardiogram can be performed on the day of the study visit or up to 1 week prior to study drug administration.

[o] All study procedures must be done prior to study drug administration.

3. INTRODUCTION: BACKGROUND AND STUDY RATIONALE

3.1. Background

Pulmonary arterial hypertension (PAH) applies to a group of diseases causing a progressive increase in pulmonary vascular resistance (PVR), resulting in right ventricular dysfunction and ultimately failure as well as premature death.[2,3] 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 vascular smooth muscle cells (VSMCs) in pulmonary arterioles, which results in progressive pulmonary vascular remodeling, increased PVR and, eventually, right-sided heart failure.[4] In the absence of treatment, the majority of patients succumb to heart failure within a few years of diagnosis.[5] There is currently no pharmacological cure for PAH. Current background PAH therapy involves increasing blood flow through the pulmonary vasculature via pharmacologic manipulation of various pathways to relieve symptoms and slow clinical worsening of the disease. In addition to general supportive care agents (e.g., anticoagulants, diuretics, digoxin), current disease-specific treatments for PAH include vasodilator-type agents such as endothelin-receptor antagonists (ERAs), phosphodiesterase 5 (PDE5) inhibitors, and prostanoids.

Genetic mutations in the bone morphogenetic protein (BMP) type II receptor (BMPR2) are associated with the majority of the familial form of PAH[6,7] and approximately 25% of idiopathic PAH. Specifically, impairment of the BMPR2-associated signal pathway appears to lead to uncontrolled proliferation of pulmonary VSMCs, the principal cause of PAH. These data strongly suggest a key role of transforming growth factor (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.[8]

Sotatercept is a novel first-in-class fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1.[9] It has previously been tested in chemotherapy-induced anemia,[10] multiple myeloma,[11] bone loss,[9] myelodysplastic syndromes,[12] β-thalassemia,[13] end-stage kidney disease,[14] and as an erythropoietic agent,[15] and has been well tolerated in more than 350 participants exposed to the drug. Sotatercept binds select ligands in the TGF-β superfamily, such as activins A and B and GDF-8 and -11, to suppress their signaling and restore balance between the opposing growth-promoting activin/GDF and growth-inhibiting BMP pathways.[16,17]

Recent preclinical data suggest that sotatercept (murine analogue, RAP-011) may positively affect vascular remodeling in animal models of PAH. 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 were either comparable or superior to agents approved for 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. Taken together, these data indicate that RAP-011 can attenuate the development and progression

of PAH, even when administered to animals with established disease. These preclinical data suggest that sotatercept is a mechanism-targeted nonvasodilator therapy that may positively affect vascular remodeling associated with PAH.[8] Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of sotatercept are provided in the Investigator's Brochure (IB).

3.2. Risks and/or Benefits to Participants

The evidence for potential benefits of sotatercept is supported by data observed in preclinical studies in rodent models of PAH and clinical results from the PULSAR study (Phase 2, NCT03496207).

Preclinical studies in rodent models of PAH have shown reduced muscularization and thickness of pulmonary vessel walls, reduced right-sided heart pressures, and reduced right-to-left ventricle weight ratios. These improvements observed in rodent models are thought to be associated with reductions in PVR as well as increases in functional capacity and quality of life (QoL) in humans, which have been assessed in the PULSAR study, a Phase 2 Study of Sotatercept for the Treatment of PAH (NCT03496207), in which participants taking any approved single or combination therapy for PAH were randomized to receive additional sotatercept or placebo for 24 weeks.

Results from the PULSAR study demonstrated a statistically significant improvement in PVR at 24 weeks when compared to baseline (the study's primary endpoint).[18] Pulmonary vascular resistance was reduced in both sotatercept dose groups versus placebo (least squares mean difference [standard error[1]]) (sotatercept 0.3 mg/kg: −145.8 [48.6] dyn·s/cm^5, p = 0.0027; sotatercept 0.7 mg/kg: −239.5 [45.8] dyn·s/cm^5, p < 0.0001).

Six-Minute Walk Distance (6MWD) was the key secondary endpoint at 24 weeks. The least squares mean increase from baseline in 6MWD was 58.1 m for sotatercept 0.3 mg/kg, 50.1 m for sotatercept 0.7 mg/kg, and 28.7 m for placebo. Combined, sotatercept produced a least squares mean difference versus placebo of 24.9 m (95% confidence interval [CI]: 3.1, 46.6 m). Sotatercept also improved N-terminal proB-type natriuretic peptide (NT-proBNP) levels.

In addition, a greater proportion of participants in the sotatercept treatment groups improved in World Health Organization (WHO) functional class (FC) compared with placebo.

Risks of sotatercept to participants that were observed in previous clinical studies included increases in hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, and blood pressure (BP). Leukopenia, neutropenia (including febrile neutropenia), granulocytopenia, and thrombocytopenia have been described as treatment-emergent adverse events (TEAEs) in clinical oncology studies in chemotherapy-induced anemia and osteolytic bone disease in multiple myeloma. Infection may be a consequence of the decrease in white blood cells, and bleeding may be a consequence of the decrease in platelets. As of the preplanned interim data cutoff of 14 January 2020, increased Hgb and thrombocytopenia were the most common drug-related adverse effects. By Week 24 of the PULSAR study, Hgb levels had not changed from baseline in the placebo group (0.0 ± 1.1 g/dL) but had increased in the sotatercept 0.3 mg/kg (1.2 ± 1.2 g/dL) and sotatercept 0.7 mg/kg (1.5 ± 1.1 g/dL) groups. Change from baseline in platelet counts at Week 24 were −6.3 ± 29.1, 12.1 ± 47.7, and −12.1 ± 49.8 × 10^9/L in the

placebo, sotatercept 0.3 mg/kg, and sotatercept 0.7 mg/kg groups, respectively. No events of bleeding were deemed related to a treatment-emergent reduction in platelet counts, and no participant presented with platelet counts below 50×10^9/L.

Each of the risks of sotatercept was monitored during the PULSAR study, and dosing adjustments were made as necessary to mitigate these risks. Potential risks of reproductive effects and renal injury were also monitored, and no clinically meaningful changes were observed. Anti-drug antibodies (ADAs) were detected but without associated adverse effects.

Cutaneous telangiectasia emerged as a late-onset adverse event in the open-label extension period of PULSAR.

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

3.3. Study Rationale

This is a Phase 3, randomized, double-blinded, placebo-controlled study to compare the efficacy and safety of sotatercept versus placebo when added to background PAH therapy for the treatment of PAH.

This Phase 3 study is supported by data from the PULSAR study (Phase 2, NCT03496207) as described in Section 3.2.

In the PULSAR study, more than 90% of patients at baseline were receiving double or triple background PAH therapy, targeting multiple existing therapeutic pathways. Sotatercept was able to demonstrate hemodynamic and functional improvements in these patients, including those receiving maximal PAH therapy with double/triple drug combinations and intravenous (IV) prostacyclin.

Treatment with sotatercept in addition to background PAH therapies was well tolerated, with thrombocytopenia and increased Hgb levels being the most commonly reported drug-related side effects. The treatment-induced increases in Hgb levels and decrease in platelet count observed in the PULSAR study are consistent with effects of sotatercept in previous clinical studies described in Section 3.1.[9-15]

There is an unmet need for additional PAH therapies because, despite available therapeutic options, the disease continues to progress in most patients. Through a novel mechanism of action, sotatercept targets an imbalance in activin/GDF and BMP pathway signaling, opening a new treatment paradigm for PAH. This Phase 3 study is being conducted to definitively assess the risk:benefit profile of sotatercept in PAH.

4. STUDY OBJECTIVES

The objectives of this study are to evaluate the efficacy and safety of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH.

5. STUDY ENDPOINTS AND RATIONALE

5.1. Endpoints Reported in Previous Pulmonary Arterial Hypertension Studies

Pivotal clinical trials for many drugs approved for PAH used 6MWD as a primary endpoint to assess exercise capacity. Secondary endpoints commonly measured include invasive hemodynamics to demonstrate improvement in PVR, WHO FC to assess symptoms, and NT-proBNP to assess cardiac function.

However, these endpoints did not consistently correlate with indicators of disease progression such as hospitalization and death. This led to the preference toward morbidity and mortality as primary endpoints, which were used in the more recent clinical trials for PAH.[19-22] Despite the limitations of 6MWD and improvement in WHO FC as standalone endpoints, it is noteworthy that all 4 trials utilizing morbidity and mortality as endpoints include 6MWD and FC in the definition of clinical worsening.

While the use of clinical worsening or disease progression had been endorsed by the World Symposium on Pulmonary Hypertension (PH) in previous meetings, at their last meeting in 2018, the Task Force on Endpoints in Clinical Trial Design recommended identifying endpoints that reflect "improvement of patients' ability to live more functional and fulfilled lives," such as time to clinical improvement instead of worsening and utilization of change in risk as marker of efficacy.[23-26]

Assessment of risk in PAH has been proposed using variables that are routinely measured in PAH, with a recommendation first issued by the European Society for Cardiology and European Respiratory Society, followed by validation and simplified versions using registry data.[21] The indices that consistently show the most significant predictive effect across the different risk scores are 6MWD, WHO FC, and NT-proBNP.

Please refer to Section 11 for details on study endpoints calculations.

5.2. Primary Efficacy Endpoint and Rationale

The primary efficacy endpoint is the change from baseline in 6MWD at Week 24.

5.2.1. 6-Minute Walk Distance Rationale

The 6MWD has been the most commonly used primary endpoint in clinical trials of PH therapies, beginning with the first randomized controlled trial (RCT) for regulatory approval of epoprostenol.[27] However, the utility of improvement in 6MWD as a primary outcome measure in clinical trials became limited particularly in more contemporary trials involving sequential, add-on therapies, in which the change from baseline in 6MWD was smaller than the clinically relevant thresholds of around 30 m,[28] despite the significance achieved by morbidity and mortality outcomes.[19-21] The 6MWD remains an important prognostic factor in the risk scores but as absolute thresholds (< 165 m, 165 to 440 m, and > 440 m)[23] instead of changes from baseline. Based on these scores, patients who walk > 440 m have a low (< 5%) risk of mortality in 1 year.

5.3. Secondary Efficacy Endpoints and Rationale

The secondary endpoints will be assessed as ranked below:

1. Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline:
   - Improvement in 6MWD (increase ≥ 30 m)
   - Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L
   - Improvement in WHO FC or maintenance of WHO FC II
2. Change from baseline in PVR at Week 24
3. Change from baseline in NT-proBNP levels at Week 24
4. Proportion of participants who improve in WHO FC at Week 24 from baseline
5. Time to death or the first occurrence of any of the following clinical worsening events (time to clinical worsening [TTCW])
   - Worsening-related listing for lung and/or heart transplant
   - Need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more
   - Need for atrial septostomy
   - Hospitalization for worsening of PAH (≥ 24 hours)
   - Deterioration of PAH defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values:
     - Worsened WHO FC
     - Decrease in 6MWD by ≥ 15% confirmed by 2 tests at least 4 hours apart, but no more than 1 week
6. Proportion of participants who maintain or achieve a low risk score (Section 5.3.6) at Week 24 versus baseline using the simplified French Risk score calculator
7. Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) at Week 24
8. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24
9. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24

5.3.1. Multicomponent Improvement Endpoint Rationale

The components of the endpoint are considered important and relevant to the medical management of patients with PAH in that they encompass functional assessments (6MWD and WHO FC) and a prognostic biomarker and indicator of cardiac strain (NT-proBNP).

The justification for the proposed multicomponent secondary endpoint takes into consideration the following:

- Assessment of risk in PAH is currently based upon recommendations initially issued by the European Society of Cardiology and the European Respiratory Society, with subsequent validation and simplified versions using robust registry data. The variables that have consistently been the most significant prognostic indicators of disease progression and survival are NT-proBNP, 6MWD, and WHO FC.
- Four of the most recent clinical trials in PAH that relied upon morbidity and mortality events as a primary endpoint nevertheless utilized 6MWD and WHO FC in the composite endpoint of "clinical worsening."
- NT-proBNP, as described in Section 5.3.3, has been consistently shown to be an independent predictor of survival in PAH

5.3.2. Pulmonary Vascular Resistance Rationale

The term PAH describes a group of PH patients characterized hemodynamically by the presence of precapillary PH, defined by a pulmonary artery wedge pressure ≤ 15 mmHg and a PVR > 3 WU.[29] Generally, PVR values < 5 WU are considered to be of good prognostic value. This parameter is in fact part of the calculation of the REVEAL risk score.[26]

Earlier trials have used PVR as part of their endpoints, mostly as the key secondary endpoint, or in substudies, as in the pivotal trials of the more recently approved PAH therapies.

Decreases in PVR in response to treatment have been associated with long-term transplant-free survival.[29]

5.3.3. N-Terminal Pro-Hormone B-type Natriuretic Peptide Rationale

N-Terminal pro-hormone B-type natriuretic peptide (NT-proBNP) is secreted by cardiomyocytes in response to ventricular stretch and is an established noninvasive marker of ventricular dysfunction in patients with PAH. Plasma NT-proBNP levels correlate with functional capacity, right ventricular function, and echocardiographic and hemodynamic variables, and it has been consistently shown to be an independent predictor of survival in PAH.[29-31] In addition, the 2 largest studies of investigational new therapies in PAH to date, which used an outcomes-based primary endpoint, have shown that improvement in NT-proBNP correlated with lower risk of morbidity/mortality.[32,33]

5.3.4. World Health Organization Functional Class Rationale

The WHO FC, despite its interobserver variability,[34] remains one of the most powerful predictors of survival, not only at diagnosis but also during follow-up.[35-37] A worsening FC is one of the most alarming indicators of disease progression, which should trigger further diagnostic studies to identify the causes of clinical deterioration.[36-38]

The WHO FC is also a powerful predictor of survival, as the WHO FC categories (I to IV) represent a scale to measure the severity of PAH. Studies have shown that a poor WHO FC status at presentation is associated with a lower 5-year survival rate and is therefore an important prognostic factor in the risk scores.

5.3.5. Time to Clinical Worsening Rationale

Time to clinical worsening can be used to assess disease progression associated with PAH and therefore presents a relevant measurement to patients, clinicians, and regulatory agencies. The majority of clinical trials in PAH have included TTCW as a secondary endpoint. Some of the more recent clinical trials have demonstrated a treatment-related delay in TTCW, and while others have not,[39] recent results suggest that TTCW shows promise in detecting disease progression.[19-22]

5.3.6. Simplified French Risk Score Calculator Rationale

The simplified French risk scoring system is based on the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH. In this study, the noninvasive parameters will be used to determine the score. "Low risk" is defined as attaining or maintaining all 3 low-risk criteria: WHO FC I or II, 6MWD > 440 m, and NT-proBNP < 300 ng/L.[32]

5.3.7. Quality-of-Life Assessments Rationale

Disease-specific patient-reported outcome (PRO) instruments are essential tools to evaluate disease, treatment and the QoL. QoL for PAH participants in this study will be assessed using 2 PRO measures: the EuroQoL – 5 Dimension – 5 Level (EQ-5D-5L) index score and the PAH-SYMPACT®.

The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. It is designed for self-completion and therefore captures information directly from the respondent, thereby generating data that conforms to the general requirement of all PRO measures.

The PAH-SYMPACT draft consists of 16 symptom and 25 impact items within 4 domains. It was developed based on interviews with patients with PAH. It is the only PAH-specific instrument developed and validated in accordance with the United States Food and Drug Administration guidance on PRO development process therefore providing a validated insight of disease impact in PAH patients.

5.4. Exploratory Endpoints

In addition to the primary and secondary endpoints, the following will be analyzed:

- Change in echocardiogram (ECHO) parameters at Week 24 versus baseline
- Change in dyspnea score (assessed by Borg CR10 scale) at Week 24 versus baseline
- Proportion of participants who achieve PVR < 3 wood units (WU) at Week 24
- Proportion of participants who achieve mean pulmonary arterial pressure (mPAP) < 25 mmHg at Week 24
- Change from baseline in mPAP at Week 24
- Change from baseline in the Cardiovascular Symptoms domain score of PAH-SYMPACT® at Week 24
- Change from baseline in the EQ-5D-5L index score at Week 24

- Change from baseline in the EQ-5D-5L visual analog scale (VAS) at Week 24

5.5. Safety Endpoints

Safety will be evaluated by collecting the following:

- AEs
- ADAs
- Laboratory assessments (hematology, serum chemistry/follicle-stimulating hormone (FSH), urinalysis)
- Vital signs
- Physical examination
- 12-Lead electrocardiogram (ECG)

6. STUDY DESIGN

6.1. Study Description

This is a Phase 3, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of sotatercept versus placebo when added to background PAH therapy for the treatment of PAH.

Participants enrolled in the study will have a diagnosis of PAH (Pulmonary Hypertension WHO Group 1) associated with idiopathic/heritable, drug-induced, connective tissue diseases (CTD), or post shunt correction PAH, within WHO FC II or III.

6.2. Duration of Study

Each participant will be enrolled in the study for up to approximately 108 weeks as follows:

- The Screening Period is up to 4 weeks (28 days).
- The DBPC Treatment Period (Period 1) (24 weeks, which includes 9 study visits [Visit 1 to Visit 9]).
- The Long-Term Double Blind (LTDB) Treatment Period (Period 2) (up to approximately 72 weeks, [Visit 10 up to Visit 33], depending on when the last participant randomized into the study completes the DBPC Treatment Period).
- The Follow-up Period will be at least 8 weeks, which may include Period 1 Follow-up Visits 1 and 2 and end of treatment (EOT) and end of study (EOS) visits.

6.3. Rationale for Dose Selection

The PULSAR study demonstrated that both the 0.3 and 0.7 mg/kg sotatercept doses are pharmacologically active and that both resulted in statistically significant improvements across a number of study endpoints compared to placebo. However, comprehensive exposure-response (E-R) analyses demonstrated that a concentration-effect relationship exists for PVR, 6MWD, and NT-proBNP for efficacy and Hgb for safety. Simulations based on these E-R models suggest a higher probability of achieving clinically meaningful targets for 6MWD, PVR, and NT-proBNP with the 0.7 mg/kg dose level compared to 0.3 mg/kg. Consistent with these, in PULSAR data, 55% of patients in the 0.7 mg/kg group achieved a ≥ 30% reduction in PVR (PULSAR primary endpoint) compared to 25% in the 0.3 mg/kg dose group.

Acceleron Pharma Inc.'s interpretation of the PULSAR safety data is that both dose levels are generally safe and well tolerated in patients with PAH, which is consistent with previous experience with sotatercept in other indications. While a concentration-effect relationship was also demonstrated for Hgb increases, no significant difference at steady state was observed between sotatercept dose levels in the PULSAR study; mean change from baseline in Hgb at Week 24 was 1.2 and 1.5 g/dL in the 0.3 and 0.7 mg/kg groups, respectively. The PULSAR study demonstrated that excursions in Hgb concentration above the upper limit of normal (ULN) can be effectively managed by sotatercept dose modification guidelines. Simulations based on the E-R model for Hgb suggest a very low probability (< 10%) of crossing Hgb safety thresholds defined in the PULSAR study.

Clinical trial simulations from the pharmacokinetic (PK)/pharmacodynamic (PD) model for Hgb suggested that the probability of having Hgb ≥ 18 g/dL and an increase in Hgb ≥ 2 g/dL is higher during the first 21 days after a dose of 0.7 mg/kg than after a dose of 0.3 mg/kg. Therefore, for this study, a starting dose of 0.3 mg/kg was selected and will be administered at Visit 1 and a target dose of 0.7 mg/kg will be administered at Visit 2 and for the remainder of the treatment period. All doses will be administered subcutaneously (SC) every 3 weeks with appropriate dose modification guidelines (see Section 8.3).

6.4. Study Design, Stratification and Treatment Assignment

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Participants who have provided signed informed consent and meet all eligibility criteria will be stratified by:

- WHO Functional Class (FC) (Class II or III)
- Background PAH therapy (mono/double or triple therapy)

Approximately 284 participants will be randomly assigned in a 1:1 ratio to receive SC injections of either placebo or sotatercept at a starting dose of 0.3 mg/kg SC at Visit 1. Participants will then be escalated to the target dose level of 0.7 mg/kg SC at Visit 2 and at will remain at this target dose level for all subsequent DBPC Treatment Period and LTDB Treatment Period visits (Visits 2 to 9 and Visits 10 to 33). Randomization is described below (see Section 6.5).

Dosing will be once every 21 days for a total consecutive period of 24 weeks during the DBPC Treatment Period and up to 72 weeks during the LTDB Treatment Period. During all study periods, all participants will remain on background PAH therapy.

The study is divided into a screening period (up to 4 weeks), a DBPC Treatment Period (24 weeks), a LTDB Treatment Period (until the last participant randomized completes the DBPC Treatment Period [up to approximately 72 weeks]), and a Follow-up Period (at least 8 weeks).

The LTDB Treatment Period will last until the last participant randomized completes the DBPC Treatment Period and the study is unblinded. During this period, selected study visits may be performed as home health care (HHC) visits as described in Section 6.5. After the study is unblinded, participants who complete the DBPC Treatment Period and are currently on treatment (sotatercept or placebo) in the LTDB Treatment Period may be eligible to participate in the separate open-label long-term follow-up (LTFU) study. For these participants, the EOS visit can be waived and Visit 1 of the LTFU study will take place 21 (± 7) days after the last dose administered in this study, which may coincide with this study's EOT visit.

Participants who complete the DBPC and LTDB treatment periods and do not wish to participate in the LTFU study will complete the EOT and EOS visits of the Follow-up Period as described in Section 6.2.

Participants who discontinue the DBPC Treatment Period early will complete the EOT visit at the time of discontinuation. These participants will be invited to come for limited study assessments at selected visits (Period 1 Follow-up Visits 1 and 2) depending on the timing of

their discontinuation. In addition, they will complete the EOS visit (described in Section 9.2.6) provided that consent is not withdrawn.

6.5. Home Health Care Visits

Select study visits (Visits 10, 11, 12, 14, 15, 16, 18, 19, 20, 22, 23, 24, 26, 27, 28, 30, 31, and 32) may be performed at the participant's home during the LTDB treatment period by a qualified health care professional if permitted by local and institutional regulations requested by study participant.

Participants are eligible for HHC visits if dose modification/delays did not occur in the previous 2 consecutive visits. Participants can opt to start HHC at Visit 10, provided that dose modification was not performed at Visits 8 and 9. Guidelines for dose modification are described in Section 8.3.

If a dose modification is required, at any time during the LTDB treatment period, the following 2 visits will be performed on-site. The participant will be eligible for HHC visits again once 2 consecutive visits without dose modification have occurred.

For example, if a dose modification is required at Visit 13, then Visits 14 and 15 must be performed on-site. If no further dose modifications are required at Visits 14 and 15, then Visit 16 may be performed as a HHC visit.

6.6. Randomization and Blinding

Participants who have signed the informed consent and meet all eligibility criteria will be stratified by baseline WHO FC and background PAH therapy and then randomized to receive placebo plus background PAH therapy or sotatercept plus background PAH therapy. Randomization assignments will be generated through a computerized system, provided by an Interactive Response Technology (IRT) (see IRT Manual for details). Recruitment will be controlled to ensure that at least 50% of enrolled participants are PAH in WHO FC III.

In the event of a medical emergency for an individual participant in which knowledge of the study drug is critical to the participant's medical management, the investigator may break the blind for that participant via the IRT (see IRT user Manual for further instruction). If the nature of the emergency does not permit time to consult with the medical monitor prior to breaking the blind, the investigator must inform the medical monitor that the blind has been broken at the earliest opportunity.

In non-urgent situations, the investigator must consult with the study medical monitor prior to breaking the blind. Only if knowledge of the participant's treatment assignment is necessary for the medical management of that participant should the blind be broken. If the blind is broken, the participant will be discontinued from the study and will not be eligible to enroll in the LTFU study. The investigator should not inform the participant of their treatment assignment under any circumstances.

7. STUDY POPULATION

7.1. Rationale for Selected Population

Participants diagnosed with symptomatic PAH (WHO FC II or III) who present with idiopathic or heritable PAH, PAH associated with CTD, drug/toxin induced, post shunt correction PAH, or PAH presenting at least 1 year following the correction of congenital heart defects, and currently on background PAH therapy will be eligible for this study.

PAH is considered a relatively rare condition, with approximately 80% of PAH patients presenting as WHO FC II-III. Typically, WHO FC I PAH patients are excluded from interventional studies due to the relatively low rate of identification, low prevalence, and mild symptomatology. Similarly, there is a low prevalence of PAH patients with WHO FC IV, and given their severe disease burden, these patients have a limited ability to participate in longer interventional studies. Eligibility criteria (Section 7.3 and Section 7.4) for this study are consistent with those of other studies in this population.

7.2. Background Pulmonary Arterial Hypertension Therapy

Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. Background PAH therapy should be stable at least 90 days prior to screening and remain stable throughout the study.

Stable diuretic therapy is defined as no addition of a new diuretic and no switching of a pre-existent oral diuretic to parenteral administration; however, dose adjustments (up or down) in pre-existent oral diuretics are acceptable.

7.3. Inclusion Criteria

Eligible participants must meet these criteria (and others) to be enrolled in the study:

1. Age ≥ 18 years
2. Documented diagnostic right heart catheterization (RHC) at any time prior to screening confirming the diagnosis of WHO PAH Group 1 in any of the following subtypes:
   - Idiopathic PAH
   - Heritable PAH
   - Drug/toxin-induced PAH
   - PAH associated with CTD
   - PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
3. Symptomatic PH classified as WHO FC II or III
4. Baseline RHC performed during the Screening Period documenting a minimum PVR of ≥ 5 WU and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure of ≤ 15 mmHg

5. On stable doses of background PAH therapy and diuretics (i.e., patient-specific dose goal for each therapy already achieved) for at least 90 days prior to screening; for infusion prostacyclins, dose adjustment within 10% of optimal dose is allowed per medical practice. Background PAH therapy is defined in Section 7.2.
6. 6MWD ≥ 150 and ≤ 500 m repeated twice at screening (measured at least 4 hours apart, but no longer than 1 week), and both values are within 15% of each other (calculated from the highest value).
7. Females of childbearing potential (as defined in Appendix 3) must:
   - Have 2 negative urine or serum pregnancy tests as verified by the investigator prior to starting study drug administration; she must agree to ongoing pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug
   - If sexually active, have used, and agree to use, highly effective contraception without interruption, for at least 28 days prior to starting the investigational product, during the study (including dose interruptions), and for 16 weeks (112 days) after discontinuation of study treatment
   - Refrain from breastfeeding a child or donating blood, eggs, or ovum for the duration of the study and for at least 16 weeks (112 days) after the last dose of study treatment
8. Male participants must:
   - Agree to use a condom, defined as a male latex condom or non-latex condom NOT made out of natural (animal) membrane (e.g., 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 16 weeks (112 days) following investigational product discontinuation, even if he has undergone a successful vasectomy
   - Refrain from donating blood or sperm for the duration of the study and for 16 weeks (112 days) after the last dose of study treatment
9. Ability to adhere to study visit schedule and understand and comply with all protocol requirements
10. Ability to understand and provide written informed consent

7.4. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria are met:

1. Diagnosis of PH WHO Groups 2, 3, 4, or 5
2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus (HIV)-associated PAH and PAH associated with portal hypertension. Exclusions in PAH Group 1 should also include schistosomiasis-associated PAH and pulmonary veno-occlusive disease
3. Hemoglobin at screening above gender-specific ULN, per local laboratory test
4. Baseline platelet count < 50,000/mm^3 (< 50.0 × 10^9/L) at screening

5. Uncontrolled systemic hypertension as evidenced by sitting systolic BP > 160 mmHg or sitting diastolic BP > 100 mmHg during screening visit after a period of rest
6. Baseline systolic BP < 90 mmHg at screening
7. Pregnant or breastfeeding women
8. Any of the following clinical laboratory values at the screening visit:
   - Estimated glomerular filtration rate (eGFR) < 30 mL/min/m^2 (as defined by the Modification of Diet in Renal Disease [MDRD] equation)
   - Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels > 3 × ULN (bilirubin criterion waived if there is a documented history of Gilbert's syndrome)
9. Currently enrolled in or have completed any other investigational product study within 30 days for small-molecule drugs or within 5 half-lives for biologics prior to the date of signed informed consent
10. Prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536) or known allergic reaction to either one
11. History of full pneumonectomy
12. Pulmonary function test (PFT) values of forced vital capacity (FVC) < 60% predicted at the screening visit or within 6 months prior to the screening visit. If PFT is not available, a chest CT scan showing more than mild interstitial lung disease at the screening visit or 1 year prior to it.
13. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to the screening visit 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).
14. History of more than mild obstructive sleep apnea that is untreated
15. 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).
16. History of restrictive, constrictive, or congestive cardiomyopathy
17. History of atrial septostomy within 180 days prior to the screening visit
18. Electrocardiogram (ECG) with Fridericia's corrected QT interval (QTcF) > 500 ms during the Screening Period
19. Personal or family history of long QT syndrome (LQTS) or sudden cardiac death
20. Left ventricular ejection fraction (LVEF) < 45% on historical ECHO within 6 months prior to the screening visit
21. Any symptomatic coronary disease events (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain)

within 6 months prior to the screening visit. Note: Anginal pain can be ignored as an exclusion criterion if coronary angiography shows no obstructions

22. Cerebrovascular accident within 3 months prior to the screening visit
23. Acutely decompensated heart failure within 30 days prior to the screening visit, as per investigator assessment
24. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease.
25. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the screening visit

7.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to receive study treatment. Electronic case report forms (eCRFs) must be completed for all participants who sign the informed consent form (ICF). 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, reason for screen failure, and AEs.

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.

8. STUDY DRUG TREATMENT

8.1. Study Drug Description

Sotatercept is a homodimeric recombinant fusion protein consisting of the extracellular domain of the human activin receptor type IIA (ActRIIA) linked to the human IgG1 Fc domain. Sotatercept is the generic name assigned to ActRIIA-IgG1Fc. The laboratory code is ACE-011. The Chemical Abstracts Service (CAS) Registry number for sotatercept is 1001080-50-7; the United States Adopted Name (USAN) and the International Nonproprietary Name (INN) is sotatercept.

8.1.1. Clinical Drug Product

The clinical drug product consists of sotatercept (60 mg/vial) in 10 mM citrate buffer, pH 5.8, 8% w/v sucrose, and 0.02% w/v polysorbate 80. The matching placebo consists of 10 mM citrate buffer, pH 5.8, 2% w/v sucrose, 3% w/v mannitol, and 0.02% w/v polysorbate 80. Both the clinical drug product containing sotatercept and its matching placebo are supplied as a lyophilized powder in labeled, rubber-stoppered, type I glass vials. Both the investigator and the participant will be blinded as described in Section 6.5.

PAH background therapy will not be provided as study medication during the study. To be enrolled in the study, participants must be on stable PAH background therapy according to local practice. Participants must remain on the same PAH background therapy during the course of the study. More details on PAH background therapy are provided in Section 7.2.

8.1.2. Formulation

Sotatercept (60 mg/vial) clinical drug product and placebo will be provided by Acceleron Pharma Inc. as a lyophilized powder.

8.2. Study Drug Management

8.2.1. Storage

The recommended storage temperature for sotatercept lyophilized drug product and matching placebo is 2°C to 8°C. Refer to the Pharmacy Manual for additional details.

8.2.2. Packaging and Shipment

Sotatercept or its matching placebo will be packaged in single-use kits. Each kit will contain 1 vial of sotatercept (60 mg/vial) or its matching placebo product and 1 prefilled syringe of sterile water for injection (sWFI) for reconstituting the lyophilized sotatercept or its matching placebo. Each kit also contains ancillary components as follows:

- A swabbable vial adapter to aid reconstitution and withdrawal of required drug or placebo solution from the vial
- A syringe and needle for SC injection
- Alcohol swabs

Each vial, prefilled syringe, and kit will be labeled for clinical trial use only, with country-specific required label text. Each kit will be assigned a serialized Medication ID number for identification. The kit will be tamper sealed. Kits will be stored at a depot and shipped under refrigerated conditions until the time of dispensation.

8.2.3. Dose and Administration

Each eligible participant will be randomly assigned in a 1:1 ratio to one of the two treatment arms:

- Arm 1: Placebo administered subcutaneously (SC) every 21 days plus background PAH therapy
- Arm 2: Sotatercept at a starting dose of 0.3 mg/kg SC with a target dose of 0.7 mg/kg administered subcutaneously (SC) every 21 days plus background PAH therapy

Prior to administration, the lyophilized sotatercept drug product (60 mg/vial) or matching placebo will be reconstituted with 1.3 mL of sWFI. Reconstituted sotatercept yields a 50-mg/mL solution of sotatercept.

8.3. Dose Modification

Dose delay, reduction, or discontinuation may be performed in any treatment arm (sotatercept or placebo). Dose delays should always precede dose reductions, as summarized in Figure 2, Figure 3 and Figure 4. While guidance for dose modifications and dose delay are summarized in Figure 3 and Figure 4, dose delays or reductions can be implemented for safety reasons at any time per the investigator's assessment and are not limited to the dose modification guidance provided.

Blood samples must be taken and assessed for Hgb and platelet count levels on the same day of study drug administration or up to 3 days prior to that day if available.

8.3.1. Escalation to Target Dose (0.7 mg/kg)

All participants will begin treatment at a starting dose of 0.3 mg/kg at Visit 1. At Visit 2, the dose will be escalated to the target dose of 0.7 mg/kg and remain at 0.7 mg/kg for the duration of the treatment period, unless dose reduction criteria as described in Section 8.3.2 and Section 8.3.3 are met. However, if at Visit 2 Hgb increases by more than 2.0 g/dL from baseline and this value is above the gender-specific ULN per local laboratory test, dosing should be delayed. All other study procedures, with the exception of study drug administration, should be performed. At Visit 3, if Hgb has increased by less than 2.0 g/dL from baseline or Hgb value is below the gender-specific ULN per local laboratory test, dosing should be restarted at 0.3 mg/kg. At Visit 4, if Hgb has increased by less than 2.0 g/dL from baseline or Hgb value is below the gender-specific ULN per local laboratory test, the dose will be escalated to the target dose of 0.7 mg/kg. Refer to Figure 3 for additional details.

8.3.2. Dose Modifications Due to Hemoglobin Increase

From Visit 3 onward, if Hgb level increases by more than 2 g/dL from the previous dosing visit, and this value is above the gender-specific ULN per local laboratory test, then a maximum of 3

consecutive dose delays are allowed during the study treatment period. After the third dose delay, if Hgb level persists at more than 2 g/dL above the previous dosing visit, and this value is above the gender-specific ULN per local laboratory test then the dose should be reduced to 0.3 mg/kg. If the participant is already at a dose of 0.3 mg/kg, the study medical monitor should be consulted, and study drug discontinuation should be considered.

If Hgb level increases more than 4 g/dL above the participant's baseline value, the study medical monitor should be consulted, and study drug discontinuation should be considered.

8.3.3. Dose Modifications Due to Low Platelet Count

If platelet count is less than 50,000/mm^3, dose delay is allowed for up to 3 visits. If platelet count remains less than 50,000/mm^3 after 3 consecutive dose delays, then study drug treatment should be discontinued/not restarted. At the visit following each dose delay, if platelet count is more than 50,000/mm^3, then the dose should be reduced to 0.3 mg/kg and study drug treatment should be restarted. If the participant is already at a dose of 0.3 mg/kg, study treatment should be restarted at 0.3 mg/kg. Refer to Figure 4 for additional details.

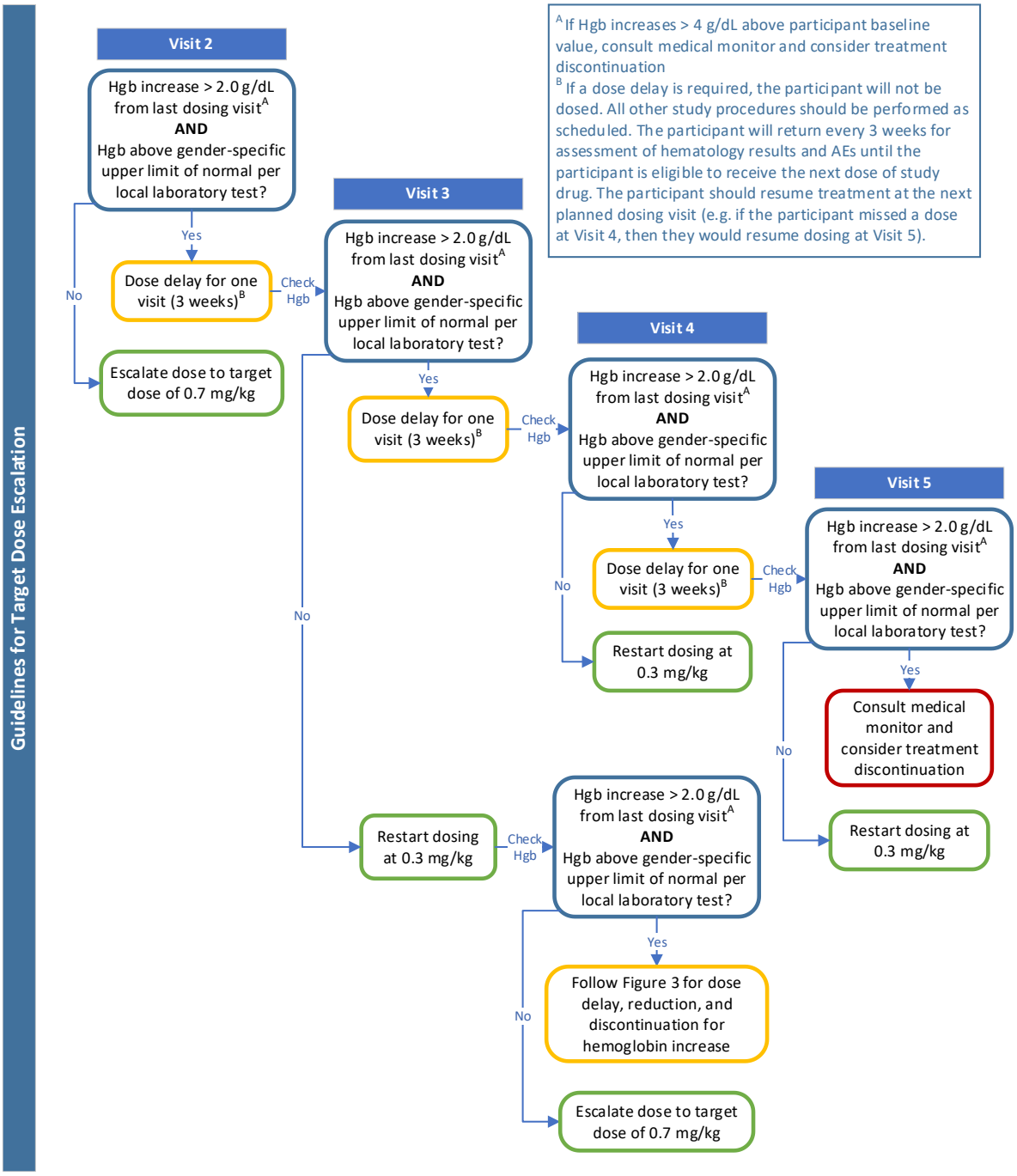
8.3.4. Dose Modifications Due to Adverse Events of Telangiectasia

In cases of the identification of new events of telangiectasia that are of moderate or greater severity/intensity, or for the progression of a telangiectasia event from mild to moderate, the dose of study drug should be delayed for one visit if the participant was receiving 0.7 mg/kg study drug, or for three visits if the participant was receiving 0.3 mg/kg at the time of the event. If, following the dose hold(s), there has been no progression in the severity of the event of telangiectasia, dosing of study drug may be resumed at a dose level of 0.3 mg/kg. If the event of telangiectasia progresses during the time in which study drug dosing has been delayed, the investigator should consult the medical monitor and consider discontinuation from study drug.

8.3.5. Dose Re-escalation Following Dose Reduction

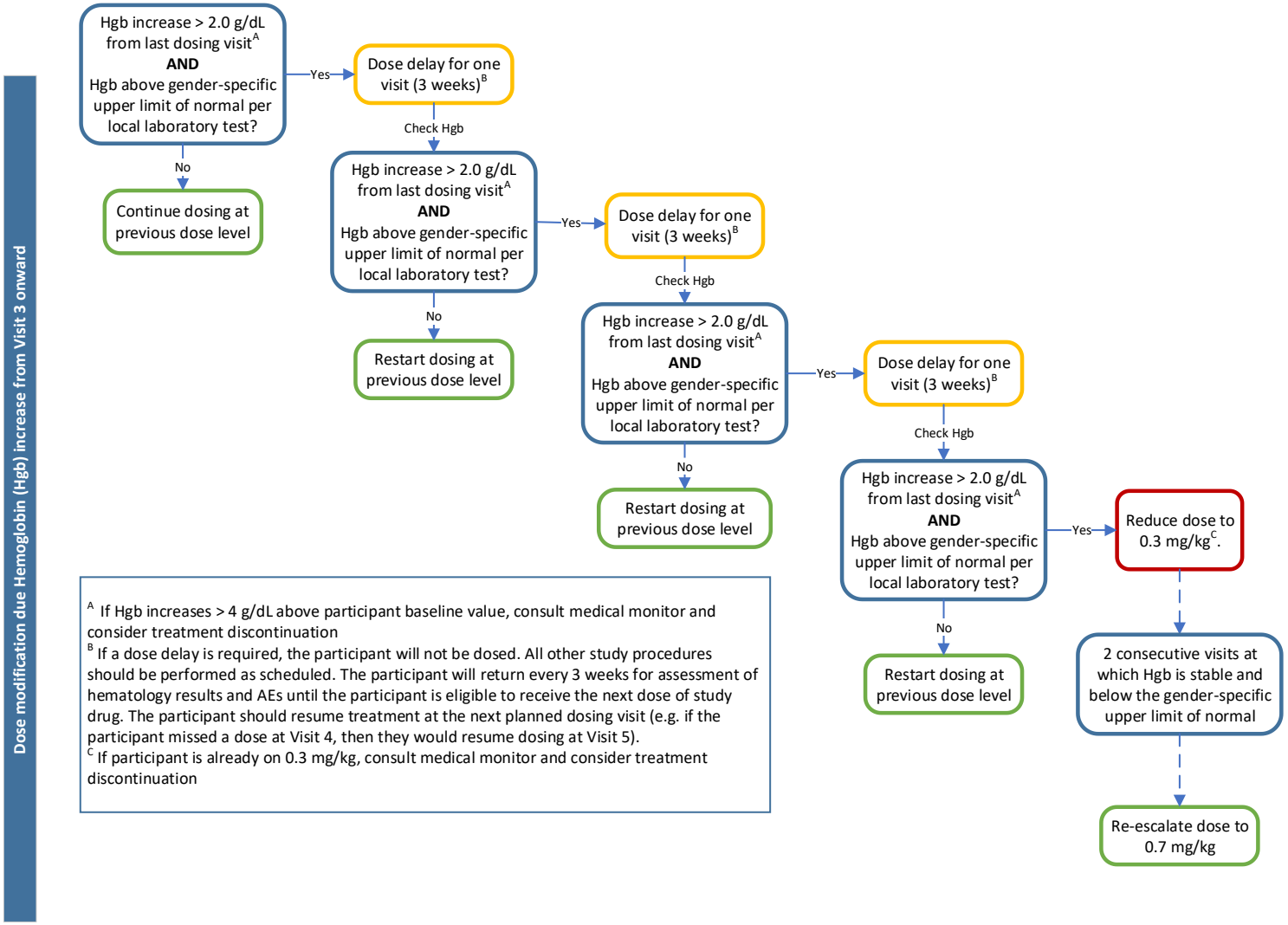
In cases of dose reduction due to an AE not related to study drug, the dose can be re-escalated when the AE is resolved. In cases of dose reduction due to increases in Hgb, the dose will be re-escalated to 0.7 mg/kg after 2 consecutive visits at which Hgb values are stable and equal or lower than the ULN normal (refer to Figure 3). Similarly, in cases of dose reduction due to decrease in platelet count, the dose will be re-escalated to 0.7 mg/kg after 2 consecutive visits at which platelet counts are stable and more than 50,000/mm^3, with no association with AEs of bleeding (refer to Figure 4). In cases of dose reduction due to events of telangiectasia, the dose may be re-escalated to 0.7 mg/kg only if the event has completely resolved.

Figure 2: Guidelines for Target Dose Escalation (0.7 mg/kg)



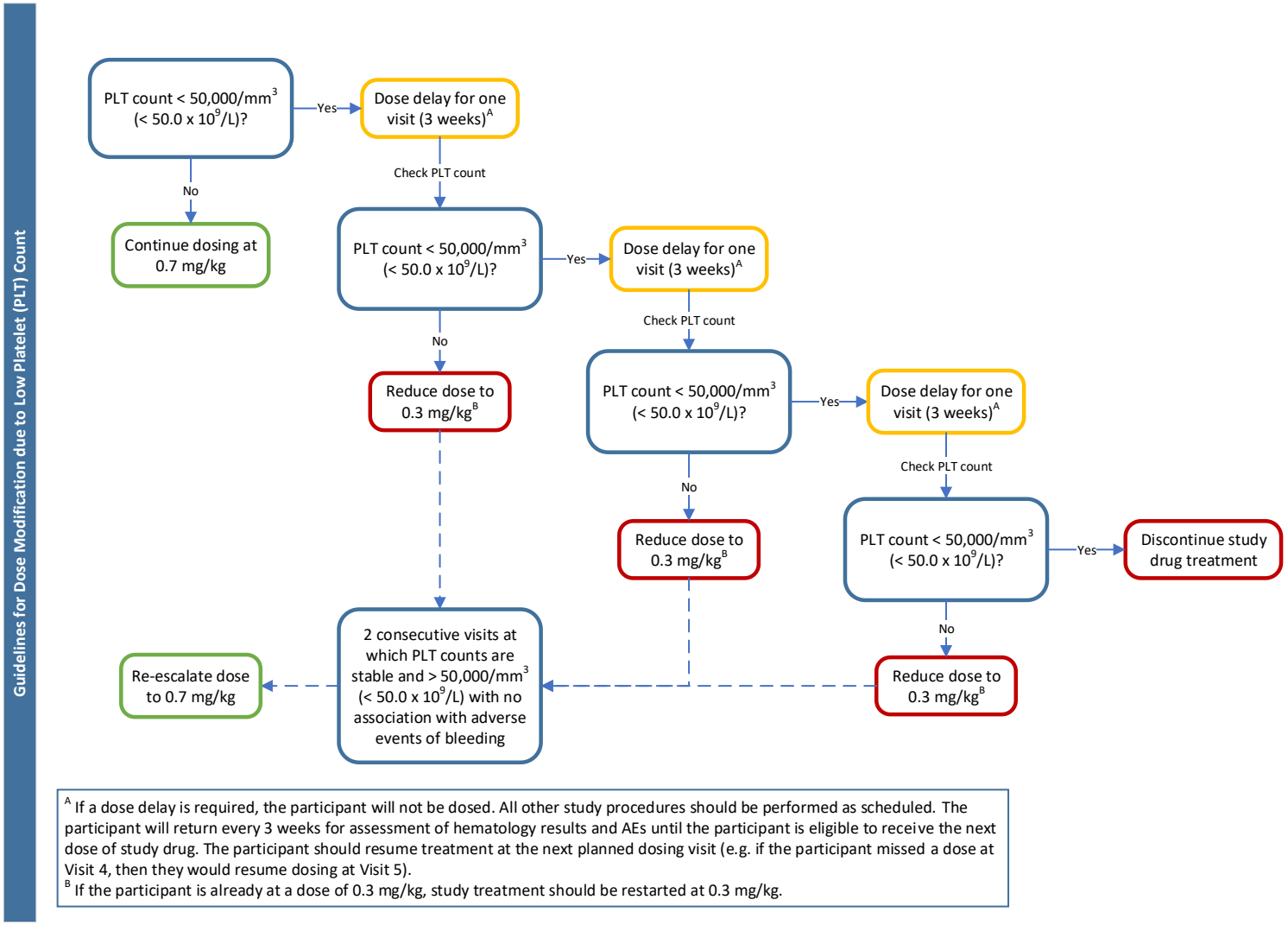
Abbreviations: AE = adverse event; Hgb = hemoglobin.

Figure 3: Guidelines for Dose Modification Due to Hemoglobin Increase From Visit 3 Onward



Abbreviations: AE = adverse event; Hgb = hemoglobin.

Figure 4: Guidelines for Dose Modification Due to Low Platelet Count



[A] If a dose delay is required, the participant will not be dosed. All other study procedures should be performed as scheduled. The participant will return every 3 weeks for assessment of hematology results and AEs until the participant is eligible to receive the next dose of study drug. The participant should resume treatment at the next planned dosing visit (e.g. if the participant missed a dose at Visit 4, then they would resume dosing at Visit 5).
[B] If the participant is already at a dose of 0.3 mg/kg, study treatment should be restarted at 0.3 mg/kg.

Abbreviations: AE = adverse event; PLT = platelet.

8.3.6. Accountability

Accountability for study drug during 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 with dates and amounts of study drug received, to whom it was administered (participant-by-participant accounting), and accounts of any study drug accidentally or deliberately damaged, destroyed, or returned. Accurate recording of all study drug administration must be made in the appropriate section of the participant's eCRF and source documents. Unless otherwise notified, all vials of study drug, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The investigator must return all unused vials of study drug to Acceleron Pharma Inc. at the end of the study, or the study drug may be destroyed at the clinical site after Acceleron Pharma Inc. approval. Either method must be documented on the drug accountability log.

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

9. STUDY CONDUCT

9.1. General Instructions

- Study procedures and their timing are summarized in the Schedule of Events (SoE) (Section 2).
- Prospective approval of protocol deviations to recruitment and eligibility criteria, also known as protocol waivers or exemptions, are not permitted.
- Assessments performed outside of their defined windows must be handled as protocol deviations.
- Immediate safety concerns must be discussed with the medical monitor immediately upon occurrence or awareness to determine whether 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 protocol assessment data must be recorded in the participant's source documentation.

9.2. Study Procedures

9.2.1. Screening Period (up to 4 weeks prior to Visit 1)

Potential participants must sign an ICF before any study-specific screening tests are conducted. Informed consent must be provided before any screening procedures are undertaken.

All screening procedures must be performed per the SoE (Section 2) and are to be completed and reviewed by the investigator to confirm participant eligibility prior to dosing.

The investigator will maintain a screening log to record details of all participants screened to confirm eligibility and record reasons for screening failure, as applicable.

Any screening clinical laboratory values considered abnormal may be repeated once during the screening period but prior to the RHC (RHC should be performed last and after all other screening procedures are done, when possible, as described below and in the SoE). Upon discussion with the medical monitor, a historic RHC may be allowed as long as it was collected within 28 days prior to Visit 1.

Screening procedures may be performed and completed over more than 1 screening visit as long as all screening procedures are completed within the 28 days immediately preceding Visit 1.

Screening will include a review of the participant's medical, surgical, and family history, collecting of demographics, race, ethnicity, and medical record requests for relevant external procedures.

Screening procedures include:

- Informed consent
- Inclusion/ exclusion criteria

- Medical history review
- Physical examination
- 12-Lead ECG
- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (complete blood cell [CBC] count)
- Serum chemistry/FSH
- Urinalysis (dipstick)
- Pulmonary function test if the last test results are done over 6 months prior to the screening visit (or if PFT is not available, a chest CT scan at the screening visit or a scan result within 1 year prior)
- RHC
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC Assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- AE/SAE review
- Concomitant medication review

Measurements/assessments taken during Screening Period will be recorded as the baseline values for study assessment of endpoints unless described otherwise. The RHC should be performed last and after all other screening procedures are performed, when possible.

9.2.2. Double-Blind, Placebo-Controlled Treatment Period (Visits 1 to 9)

Study procedures for Visits 1 to 9 vary dependent on the visit number. All study procedures/assessments should be performed prior to the administration of the study drug.

Visit 1 (± 3 days)

Visit 1 procedures include:

- Targeted cardiopulmonary and skin physical examinations
- Vital signs including weight
- A serum or urine pregnancy test (where applicable)

- QoL assessments
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- Randomization
- Study drug administration
- AE/SAE review
- Concomitant medication review

Visit 2 (± 3 days)

Visit day windows are relative to the date of the previous dose of study drug: every 21 days (± 3 days). Visit 2 procedures include:

- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- 6MWT
- Borg Dyspnea Scale (pre- and post- 6MWT)
- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

Visit 3 and Visit 4 (± 3 days)

Visit 3 and Visit 4 procedures include:

- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- NT-proBNP sample collection
- ADA sample collection

- PK sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

Visit 5 (± 3 days)

Visit 5 procedures include:

- Targeted cardiopulmonary and skin physical examinations
- 12-Lead ECG
- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- Study drug administration
- AE/SAE review
- Concomitant medication review

Visits 6, 7, and 8 (± 3 days)

The procedures at Visits 6, 7, and 8 include:

- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Study drug administration
- AE/SAE review

- Concomitant medication review

Visit 9 (± 3 days)

The first primary endpoint evaluation occurs at Visit 9. The procedures include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-Lead ECG
- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- Urinalysis (dipstick)
- RHC
- 6MWT
- Borg Dyspnea Scale (pre- and post- 6MWT)
- WHO FC assessment
- Clinical worsening assessment
- QoL assessments
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.3. Period 1 Follow-up Visits 1 and 2

Period 1 Follow-up Visits are applicable for participants who discontinue study early during the DBPC Treatment Period. For participants discontinuing prior to Visit 5, Follow-up Visits 1 and 2 should be performed. For participants discontinuing after Visit 5 and prior to Visit 9, only Follow-up Visit 2 should be performed. Please refer to the SoE (Section 2) for details on assessments during these visits.

Follow-up Visit 1 (12 weeks After Visit 1, ± 3 days)

Follow-up Visit 1 procedures include:

- Targeted cardiopulmonary and skin physical examinations

- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- AE/SAE review
- Concomitant medication review

Follow-up Visit 2 (24 weeks After Visit 1, ± 3 days)

Follow-up Visit 2 procedures include:

- Targeted cardiopulmonary and skin physical examinations
- Vital signs including weight
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- RHC
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- QoL assessments
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- AE/SAE review

- Concomitant medication review

9.2.4. Long-Term Double-Blind Treatment Period (Visit 10 up to Visit 33)

The LTDB period can last up to approximately 72 weeks depending on enrollment duration for study participants and the time required for the last participant to complete the DBPC Treatment Period. During this period, select study visits may be performed as HHC visits as described in Section 6.5.

Once the last randomized participant completes the last visit in DBPC Treatment Period, the study will be unblinded and eligible participants can rollover to the LTFU study. These participants will forgo the EOS visit to begin the LTFU study. For these participants, Visit 1 of the LTFU study will take place 21 (± 7) days after the last dose administered in this study, which may coincide with this study's EOT visit.

Participants who discontinue during the LTDB Treatment Period for reasons other than clinical worsening will complete EOT and EOS visits as described in Section 9.2.6.

Visits 10, 11, 12, 14, 15, 16, 18, 19, 20, 22, 23, 24, 26, 27, 28, 30, 31, and 32 (± 3 days)

These visits may be performed as HHC visits for eligible participants. The procedures include the following:

- Vital signs
- A serum or urine pregnancy test (where applicable)
- Study drug administration
- AE/SAE review
- Concomitant medication review

Visits 13, 21, and 29 (± 3 days)

When possible, participants are required to be on-site for these visits. Procedures/assessments include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-Lead ECG
- Weight
- Vital signs
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment

- Clinical worsening assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

Visits 17, 25, and 33 (± 3 days)

When possible, participants are required to be on-site for these visits. Procedures/assessments include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-Lead ECG
- Weight
- Vital signs
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- Urinalysis (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.5. End of Treatment Visit (± 3 days)

The EOT visit should occur 21 days (± 3 days) after the last study drug administration. Participants who discontinue early should complete the EOT visit at the time of discontinuation. Discontinuation of study drug administration can occur at any visit during the DBPC Treatment Period or the LTDB period. Reasons for early discontinuation are described in Section 9.4.1. The procedures at the EOT visit include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-Lead ECG
- Vital signs
- A serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry/FSH
- Urinalysis (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- QoL assessments
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- AE/SAE review
- Concomitant medication review

9.2.6. End of Study (± 3 days)

The EOS visit will be completed by participants who do not wish to participate in the LTFU study and for participants who discontinue treatment early for reasons other than clinical worsening. These participants should also complete their EOT visit assessments as described in Section 9.2.5 as long as consent is not withdrawn. Details on EOS assessments are in Section 2.

The procedures include the following:

- Targeted cardiopulmonary and skin physical examinations
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)

- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP sample collection
- ADA sample collection
- PK sample collection
- AE/SAE review
- Concomitant medication review

9.3. Description of Study Procedures

9.3.1. Six-Minute Walk Test

The 6MWD will be measured by the 6MWT during the Screening Period and at multiple timepoints throughout the study as per the SoE. During Screening, the 6MWT is to be performed twice-at least 4 hours and no more than 1 week apart; 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 that 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.

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course should be 30 m in length (or at least 15 m) and should be at the same location that is used for all study visits[40,41]. The length of the corridor should be marked every 3 m. The turnaround points should be marked (e.g., with a cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor (e.g., using brightly colored tape).

The distance walked in 6 minutes (the 6MWD) will be calculated and recorded. If the participant discontinues the test prematurely, the time (mm:ss) and distance walked will be recorded. Requirement of acute supportive rescue medication (e.g., oxygen therapy) and any adverse events occurring during the 6MWT must be recorded. If a participant is on chronic oxygen therapy, oxygen should be administered at their standard rate, or as directed by the investigator. During the study, the 6MWT should be performed at approximately the same time of day to avoid diurnal variation. The 6MWT should be performed under the same conditions at least between Screening and Visit 9, including chronic oxygen therapy, use of walking aids or face coverings (the latter as required by local regulations). All 6MWTs performed from Visit 1 onward can be performed at the study visit day or within 10 days prior to study drug administration. Refer to Appendix 2 for additional details.

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.

9.3.2. Right Heart Catheterization

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, mPAP, mean PCWP, mixed venous saturation of oxygen (SvO_2), and cardiac output. The following hemodynamic parameters will be assessed when the participant is in a stable hemodynamic rest state (as demonstrated by 3 consecutive cardiac output measurements within 10% of each other) while the participant is breathing ambient air or oxygen:

- Right atrial pressure, mPAP, mean PCWP, systolic PAP, diastolic PAP, SvO_2, and heart rate (HR)
- Cardiac output 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)

The PVR 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 the clinical sites.

In order to reduce invasive procedures for participants prior to confirming eligibility, RHC in the Screening Period should be performed last and after all screening tests are done for eligibility, when possible. The RHC performed after screening may be performed on the day of study visit or within 1 week prior to study drug administration. If other assessments are performed on the same day, RHC should be performed last, when possible.

9.3.3. 12-Lead Electrocardiogram

A single 12-lead ECG will be obtained at each study visit as outlined in the SoE (Section 2) and will be transferred to a central laboratory for reading and interpretations. Parameters obtained will be HR, QRS, and QT:QTcF.

- Clinically significant abnormal findings will be reported as AEs
- ECGs should be performed prior to 6MWT

9.3.4. Echocardiogram Parameters

Two-dimensional echocardiogram (2-D ECHO) parameters will include but not limited to tricuspid annular plane systolic excursion (TAPSE), PAP, right ventricular fractional area change (RVFAC), and right ventricular end diastolic area (RVEDA). The ECHO performed during the Screening Period is used as the baseline for this study. All ECHOs performed after screening can be performed on the day of study visit or within 1 week prior to study drug administration. The ECHO parameters review process will be performed by a central vendor, according to the study manual.

9.3.5. Borg Dyspnea Scale (Borg CR10 Scale)

The Borg Dyspnea Scale (Borg CR10 Scale) will be used pre- and post-6MWT.

9.3.6. World Health Organization Functional Class Assessment for Pulmonary Hypertension

The WHO class system is used to provide information about how affected an individual is by their disease. The 4 FCs that are used to rate how ill a PAH participant is are detailed in Table 4.

Table 4: World Health Organization Functional Class Assessment for Pulmonary Arterial Hypertension[a]

WHO Class	Description
Class I	Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PAH resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PAH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Any physical activity leads to increased discomfort.

Abbreviations: PAH = pulmonary arterial hypertension; WHO = World Health Organization.
[a] Modified after New York Heart Association (NYHA) functional assessment.

9.3.7. N-Terminal pro-B-type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a hormone produced by the heart. NT-proBNP is a non-active prohormone that is released from the same molecule that produces BNP. Both BNP and NT-proBNP are released in response to changes in pressure inside the heart. NT-proBNP levels are primarily used to help detect, support diagnosis, and, in some instances, evaluate the severity of heart failure. Samples for NT-proBNP analysis will be collected as described in the SoE and will be shipped and analyzed by a central laboratory.

9.3.8. Patient-Reported Outcomes (QoL Assessments)

9.3.8.1. EuroQol – 5 Dimension – 5 Level Assessment

The EQ-5D-5L scale is a standardized measure of health status developed to provide a simple generic measure of health for clinical and economic appraisal. EQ-5D-5L is designed for self-completion and, as such, captures information directly from the respondent, thereby generating data that conform to the general requirement of all PRO measures.

The EQ-5D questionnaire has 2 components: health state description and evaluation.

In the description part, health status is measured in terms of 5 dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The “mobility” dimension asks about the person’s walking ability. The “self-care” dimension asks about the ability to wash or dress by oneself, and “usual activities” dimension measures performance in “work, study, housework, family or leisure activities.” The “pain/discomfort” dimension asks how much pain or discomfort an individual has, while the “anxiety/depression” dimension asks how anxious or depressed the individual is. Respondents self-rate their level of severity for each dimension using the 5-level (EQ-5D-5L) scale.

In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS).

Participants will complete the EQ-5D-5L questionnaire prior to study drug administration during the study visits outlined in the SoE. Refer to the study manual for more details.

9.3.8.2. Pulmonary Arterial Hypertension – Symptoms and Impact

PAH-SYMPACT® is a PRO instrument; the draft consists of 16 symptom and 25 impact items within 4 domains. The PRO was developed based on interviews with patients with PAH following the process outlined in the FDA's PRO guidance.

Participants will complete the PAH-SYMPACT® questionnaire at home, once daily on the 7 days prior to the study visits outlined in the SoE. Refer to the study manual for more details.

9.3.9. Clinical Worsening Assessment

Clinical worsening must be assessed by the investigator and recorded on the CRF.

Clinical worsening must be assessed using the following criteria:

- Death
- Worsening-related listing for lung and/or heart transplant
- Need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more
- Need for atrial septostomy
- Hospitalization for worsening of PAH (≥ 24 hours)
- Deterioration of PAH defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values:
  - Worsened WHO FC (II to III, III to IV, II to IV, etc.)

    and
  - Decrease in 6MWD by ≥ 15% (confirmed by two 6MWTs at least 4 hours apart, but no more than 1 week)

An independent blinded adjudication committee will adjudicate all clinical worsening events up to the end of the study, including death, to determine whether these events are due to PAH.

All other clinically significant abnormal findings that do not meet the above criteria will be reported as AEs.

9.3.10. Physical Examination

- A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, skin, and neurological systems. A full physical examination will be completed at the Screening Visit only.
- A targeted physical examination will include, at a minimum, assessments of the cardiovascular and pulmonary systems, as well as the skin, and will be completed at all other visits after screening.

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

9.3.11. Vital Signs

Vitals signs to be collected before blood collection and study treatment administration include the following:

- Temperature, pulse rate (PR), respiratory rate, and BP will be assessed at every visit. Height will be measured once during the Screening Period. Weight will be measured (in indoor clothing but without shoes) and recorded at each dosing visit during the DBPC treatment period. Weight will be measured on selected visits during the LTDB treatment period. Dose will be calculated based on the participant's most recently recorded weight.
- Blood pressure and pulse measurements will be assessed while seated after a period of rest in a quiet setting with no distractions (e.g., television, cell phones). The same method of collection (manual or automated) should be used throughout the study. Manual techniques will be used only if an automated device is not available.
- Clinically significant abnormal findings will be reported as AEs (Section 10.1).

9.3.12. Pharmacokinetics Measurements

Serum samples will be collected for measurement of serum concentrations of sotatercept as specified in the SoE (Section 2). Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and Acceleron Pharma Inc.

Instructions for the collection and handling of biological samples will be provided by the Acceleron Pharma Inc. 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 the 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. Samples collected for analyses of sotatercept serum concentration may also be used to determine concentrations of concomitant medications in the background PAH therapy.

9.3.13. Anti-Drug Antibody (ADA) Assessments

The ADA samples will be collected as outlined in the SoE and will be analyzed by a central lab. Participants who have a new or higher titer-positive ADA result at their last visit may be asked to return for additional ADA testing approximately every 3 months until response is negative or titer is stable.

9.3.14. Pharmacodynamics

Venous blood samples will be collected for the measurement of PD biomarkers including N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at timepoints listed in the SoE.

Samples collected for NT-proBNP analyses will be used to evaluate the study drug safety and/or efficacy aspects during the study.

9.3.15. Clinical Laboratory Tests

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF.

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 and/or 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 Acceleron Pharma Inc. notified.

All protocol-required laboratory assessments must be conducted in accordance with the SoE.

Please refer to the SoE (Section 2) for the timing and frequency of clinical laboratory tests.

9.3.16. Serum Chemistry/Follicle-Stimulating Hormone

A central laboratory will be used for the analysis of all chemistry laboratory specimens collected.

Blood samples for laboratory evaluations will be collected per the SoE table and should be drawn prior to dosing. Blood urea, creatinine, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorus, glucose, magnesium, HCO_3, albumin, and FSH will be measured. Investigators must review the results to monitor the participant's safety.

9.3.17. Urinalysis (Dipstick)

Urinalysis will be performed per the SoE using dipsticks provided to sites by the central laboratory to evaluate pH, specific gravity, protein, glucose, bilirubin, ketones, blood, leukocytes, urobilinogen, and nitrite.

9.3.18. Pregnancy Testing

Pregnancy testing (urine or serum) will be performed per the SoE for all females of childbearing potential prior to each dose administration. See Appendix 3 for further information.

9.3.19. Hematology

Hematology (CBC) laboratory assessments will be collected and analyzed locally at the investigator sites and will be measured at the visits specified in the SoE. Hematology (CBC) includes RBCs, absolute white blood cells, Hgb, Hct, and platelet count.

9.4. Discontinuation and Withdrawal Criteria

9.4.1. Participants Early Discontinuation

The reason for early discontinuation must be recorded in the corresponding participant's eCRF. The investigator must notify Acceleron Pharma Inc. and medical monitor when a participant has discontinued treatment or has withdrawn from the study. All participants who are discontinued from the study prior to the EOT visit should complete the assessments scheduled for the EOT visit at the time of discontinuation and will be asked to return to the clinic to complete the remaining follow-up EOS visit.

Early discontinuation of study treatment refers to permanently stopping study drug administration before completing the DBPC or before the trial has been unblinded for participants to rollover into the LTFU study. Reasons that may lead to discontinuation from the study drug include the following:

- AE: If a participant discontinues due to a drug-related serious adverse event (SAE) or other medical reason(s), the participant should be followed at regular intervals until the AE normalizes or the participant returns to their baseline condition, as per Section 10.6.
- Participant request (withdrawal of consent): If the participant withdraws from the study and withdraws consent for disclosure of future information, no further evaluations are to be performed and no additional data are to be collected and this will be recorded as the EOS visit; Acceleron Pharma Inc. may retain and continue to use any data collected before such withdrawal of consent.
- Participant's unwillingness or inability to comply with the protocol
- A clinical worsening event that occurs prior to Visit 9 and is accompanied by initiation of rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more.
- An increase in QTcF of > 60 ms that results in QTcF of > 500 ms (or > 550 ms if right bundle branch abnormality is present) during the treatment period.
- More than 3 dose delays required per dose adjustment guidelines (Section 8.3)
- Pregnancy
- Women of childbearing potential not using adequate combination of effective contraception methods throughout the study
- Men with a partner of childbearing potential not accepting to use contraceptive methods throughout the study
- Study terminated by Acceleron Pharma Inc.
- Lost to follow-up

Participants who discontinue study treatment during the DBPC Treatment Period prior to Visit 5 will be asked to return to complete limited study assessments (specified in the SOE, Section 2) at Follow-up Visit 1 and Follow-up Visit 2. Participants who discontinue study treatment during

the DBPC Treatment Period after Visit 5 will be asked to return to complete limited study assessments (specified in the SOE, Section 2) at Follow-up Visit 2. These participants will complete the relevant EOT visit assessments in addition to the EOS visit assessments described in Section 9.2.6. Details on EOT and EOS assessments are in Section 2.

Participants who discontinue study treatment during the LTDB Treatment Period will complete the EOT and EOS visits as specified in the SoE (Section 2).

Participants who experience an event of clinical worsening prior to Visit 9 (during the DBPC treatment period) that is accompanied by the initiation of rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more will discontinue immediately. These participants will complete the EOT visit at the time of discontinuation as specified in the SoE (Section 2). They will be asked to return to complete the EOS visit, provided that consent is not withdrawn. These participants will not be eligible to enroll in the LTFU study.

Participants who experience a clinical worsening event prior to Visit 9 (during the DBPC treatment period) that does not meet the criteria for study treatment discontinuation (ie, is NOT accompanied by the initiation of rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more) will continue to receive study treatment and complete study visits up to Visit 9. Thereafter, they will be eligible to roll over into the open-label LTFU study. These participants will complete the EOT visit, which may coincide with the first dosing visit in the LTFU study.

Participants who discontinue study treatment due to any clinical worsening event during the LTDB Treatment Period may roll over directly into the LTFU study after completing the EOT visit, which may coincide with the first dosing visit in the LTFU study.

Acceleron Pharma Inc. may terminate the study after consultation with the investigator and the DMC at any time for safety or administrative reasons. Acceleron Pharma Inc. will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the participants.

9.4.2. 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/or EOS visits.

The EOS visits are only required for participants who discontinue the study early or decline transition to a future sotatercept LTFU study. The EOS is defined as when the last participant completes the last visit.

9.5. Participants Lost to Follow-up

A participant will be considered lost to follow-up if he/she stops attending scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant stops attending study visits:

- 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). Each attempt at contact must be documented in the participant's study record.
- If the participant continues to be unreachable after the mentioned attempts, 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.

9.6. Concomitant Medication and Therapy During Study Conduct

During screening and throughout the study, participants may take stable doses of medications for chronic conditions. 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 preexisting condition, concurrent therapy may be administered at the discretion of the investigator. The investigator may consult the medical monitor regarding what constitutes a stable dose or a chronic condition. Information regarding concomitant medications will be collected in the eCRF beginning after signing the ICF and will include all medications taken during Screening Period to EOS.

9.7. Treatment Compliance

Each dose of study treatment will be administered by SC injection(s) and must be documented in the study record. Accurate recording of all study drug administration must be made in the appropriate section of the participant's eCRF and source documents.

Background PAH therapy compliance will be the responsibility of each participant and his/her treating physician. The investigator should promote compliance by instructing the participant to take their background PAH therapy exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant is expected to adhere to their background PAH therapy throughout the study and should be instructed to contact the investigator if he/she is unable for any reason to take their background PAH therapy as prescribed.

9.8. Criteria for Study Termination

Both Acceleron Pharma Inc. and the Principal Investigator reserve the right to terminate the study at any time. Should this be necessary, Acceleron Pharma Inc. or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the same. In terminating the study, Acceleron Pharma Inc. and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

9.8.1. Study and Site Closure

Acceleron Pharma Inc. or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Acceleron Pharma Inc. 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 Acceleron Pharma Inc. or investigator may include but are not limited to the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Acceleron Pharma Inc.'s procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

10. SAFETY ASSESSMENT, REPORTING, AND MONITORING

10.1. Adverse Events

10.1.1. Definitions of Adverse Event

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

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

10.1.1.1. Unexpected Adverse Events

An unexpected AE is an event the nature, severity, or outcome of which is not consistent with the Reference Safety Information in the current IB.

10.1.1.2. Events Not Considered as Adverse Events

Preexisting medical conditions/signs/symptoms present 30 days prior to the initial study drug administration (Visit 1) 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 preexisting conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

10.2. Serious Adverse Events

10.2.1. Definition of Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death
- Life threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

10.2.2. Definition of Serious Adverse Event Terms

Death: An AE that results in death.

Life threatening: An AE in which the participant was at risk of death at the time of the event; it does not refer to an event that, hypothetically, might have caused death if it were more severe.

Hospitalization: An AE that requires inpatient hospitalization or prolongation of existing hospitalization; however, a hospitalization for an elective procedure will not be considered an SAE.

Hospitalization for planned surgery prior to signing the ICF or routine clinical procedures that are not the result of an AE are not to be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either "serious" or "nonserious" according to the usual criteria.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Events not to be considered as SAEs are hospitalizations related to any of the following:

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

Disability/incapacitating: 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.

Congenital anomaly/birth defect: Congenital anomaly/birth defect in a child of a participant or its partner that was exposed to study drug prior to conception or during pregnancy.

Important medical event: An important medical event is an event that may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the 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.

10.3. Assessment of Severity

Investigators must evaluate the severity/intensity of AEs and SAEs. If there is a change in severity of an AE, it must be recorded as a separate event.

Mild: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Usually transient in nature and generally not interfering with normal activities.

Moderate: 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.); sufficiently discomforting to interfere with normal activities.

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

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 participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning.

10.4. Assessment of Causality

The investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as "not suspected" or "suspected" as defined below. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of study drug including PK properties of sotatercept, known side effects of study drug, medical history, concomitant therapy, course of the underlying disease, and pertinent study procedures. Median time to reach maximum sotatercept (T_{max}) ranged from 5 to 8 days since first dose. After every 21-day dosing, sotatercept concentrations are expected to reach 95% steady state by Week 15 and t_{max} at steady state can occur relatively early in the first few days after dose.

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

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

10.5. Documenting 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 nonleading 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 that are either volunteered by participants or observed during or following the course of investigational product administration on the appropriate CRF page. All clearly related signs, symptoms, and abnormal results from diagnostic procedures 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 CRF. Any clinically relevant changes in laboratory assessments or other clinical findings as described are considered AEs and must be recorded on the AE eCRF.

It is important that each AE report includes a description of the event, duration (onset and resolution dates), severity, relationship with study drug, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of study drug), and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria should be documented.

Specific guidance can be found in the eCRF Completion Guidelines provided by Acceleron Pharma Inc. or designee.

For all SAEs, an SAE form must be completed with as much information as possible and submitted within the timeframe described in Section 10.6.

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

10.6. Reporting Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately, within a maximum 24 hours after becoming aware of the event, inform Acceleron Pharma Inc. via the contract research organization (CRO) by entry on the eCRF or, if not available, by telephone or email.

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, for SAE reporting are located on the SAE Report Form, and in the completion, instructions are 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

email. Reporting procedures and timelines for follow-up information are the same as for the initially reported SAE.

Relevant pages from the CRF 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 CRF.

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

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

For all SAEs, an SAE form must be completed with as much information as possible and submitted within the timeframe described in Section 10.6.

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

10.6.1. Reporting Period and Monitoring of Participants with Adverse Events

All AEs must be recorded in the eCRF from the signing of the ICF up until the EOS Visit. All participants who took at least 1 dose of study drug, whether they completed the DBPC Treatment Period or not, should complete the EOS Visit unless they are transitioning into the LTFU Study, provided that consent is not withdrawn.

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.

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

Acceleron Pharma Inc. 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 safety events involving his/her participants to the IEC that approved the study.

In accordance with International Council for Harmonisation (ICH) GCP guidelines, Acceleron Pharma Inc. 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.

Acceleron Pharma Inc. will inform the investigator of AEs that are both serious and unexpected and are considered to be related to study drug (suspected unexpected serious adverse reactions [SUSARs]). The investigator should place copies of these Safety Reports in the Investigator Site File, if applicable. National regulations with regard to Safety Report notifications to investigators will be followed.

When specifically required by regulations and guidelines, Acceleron Pharma Inc. will provide appropriate Safety Reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting by Acceleron Pharma Inc. 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, Acceleron Pharma Inc.'s responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related Detailed Guidances.

10.7. Overdose

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

Sotatercept dosing is weight-based. Therefore, for the purpose of this trial, an overdose is defined as any dose that has exposures in excess of the monkey no-observed-adverse-event level dose of 1 mg/kg (see current IB), which was also the highest dose tested in the human volunteers 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 Pharma Inc. or a specified designee within 24 hours and be fully documented as an AE in the CRF.

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 potential risks as described in the IB.

10.8. 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 to 16 weeks (112 days) after last dose of study drug treatment. The pregnancy information will be recorded on the appropriate form and must be submitted to Acceleron Pharma Inc. 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 Acceleron Pharma Inc. 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 16 weeks (112 days) after the last dose.

If a pregnancy is reported, the investigator must inform Acceleron Pharma Inc. within 24 hours of learning of the pregnancy. If pregnancy is reported, the participant will be discontinued from the study treatment.

10.9. Monitoring of Identified Risks, Potential Risks, and Adverse Events of Special Interest

The adverse events of special interest (AESIs) are considered important parameters to be monitored in order to assess the overall safety of the PAH population and therefore be added for safety monitoring in the sotatercept clinical trial. For further information, consult the IB.

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 study schedule or upon an unscheduled visit if applicable. Details regarding dose modifications due to decreases in platelets, increases in Hgb, and events of moderate or severe telangiectasia are provided in Section 8.3.

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 study participants. An independent blinded adjudication committee will adjudicate clinical events up to the end of the study, including death, to determine whether these events are due to PAH.

10.9.1. Adverse Events of Special Interest

The monitoring of AESIs is detailed in Table 5.

Based on review of safety data from the PULSAR study, and the adequacy of routine safety monitoring described above, hepatic toxicity, leukopenia, and neutropenia are no longer considered as AESIs and will be followed as events of medical interest in routine medical monitoring and signal detection activities. Thrombocytopenia, suppression of FSH, and thromboembolic events, formerly designated as AESIs, are now considered as potential risks.

Table 5: Monitoring of Adverse Events of Special Interest

Description	Monitoring Parameters
Telangiectasia	Any investigator who reports a patient with an AE of telangiectasia (spider veins, spider naevi) must complete a customized page in the eCRF

Abbreviations: AE = adverse event; eCRF = electronic case report form.

11. STATISTICAL ANALYSES

11.1. Overview

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study to determine the efficacy and safety of sotatercept versus placebo.

Planned statistical analyses to be conducted are outlined in the sections that follow. Additional detail will be described in the statistical analysis plan (SAP) and will include but not necessarily be limited to the analysis populations to be used in the analyses as well as additional details of procedures for accounting for missing data as needed. Modifications and/or clarifications to protocol-specified statistical analyses as well as any other additional statistical analyses will be added to the SAP. The SAP will be developed and finalized before the study is unblinded and the database is locked.

11.2. Sample Size Determination

Sample size determination is based on the primary efficacy endpoint and the secondary endpoint of improvement in WHO FC (see Section 5.2). Assumptions for the desired treatment effect and estimate of variability (6MWD endpoint) are based on data from the PULSAR study (Phase 2, NCT03496207) and from a published clinical trial in PAH participants.

For 6MWD, assuming a 1:1 randomization, a 2-sided 0.05 type I error rate, a 25-m improvement in sotatercept treatment compared to placebo, a common standard deviation (SD) of 50 m, and 121 participants per arm, the statistical power is approximately 96% under the Wilcoxon rank-sum test using N-Query®.

For the secondary endpoint, "proportion of participants who improve in WHO FC at Week 24," assuming the proportion of participants treated with placebo and sotatercept is 0.11 and 0.25, respectively, 1:1 randomization, a 2-sided 0.05 type I error rate, and 121 participants per arm, the statistical power is approximately 80% based on the 2-sample chi-square test.

Assuming a 15% dropout rate, the total sample size will be n = 284 (n = 142 participants per arm) (see Section 5.2).

11.3. Populations for Analysis

The populations to be used for statistical analyses are listed below.

- **Full Analysis Set (FAS):** All participants will be analyzed according to the treatment arm to which the participant is randomized.
- **Safety Set:** All participants who receive at least 1 dose of study treatment. All participants will be analyzed according to the treatment they actually received.
- **Per-Protocol Set (PPS):** All participants randomized who receive at least 1 dose of study treatment with no data or study procedural-related issues that would otherwise impact the interpretation of the efficacy data.
- **Pharmacokinetic Population:** All participants who receive at least 1 dose of study drug and have sufficient PK samples collected and assayed for PK analysis.

11.4. Statistical Methods

The SAP will be developed and finalized before database lock and will describe the populations to be used in the analyses, and additional details of procedures for accounting for missing, unused, and spurious data as needed. In general, analysis of covariance (ANCOVA) or the stratified Wilcoxon test will be used for continuous variables; Cochran-Mantel-Haenszel test will be used for dichotomous variables; log-rank test and Kaplan-Meier method will be used for time to event variables. Statistical analyses of efficacy data will be performed on the FAS and PPS. Analyses with the FAS will be considered primary for reporting purposes.

11.5. Study Endpoints

11.5.1. Primary Endpoint

The change in 6MWD at Week 24 from baseline will be analyzed using the stratified Wilcoxon test with the randomization factors as strata. The Hodges-Lehmann location-shift estimate of the treatment group difference with 95% CI will be provided.

11.5.1.1. Handling of Missing Data

For the analysis of change in 6MWD at Week 24 from baseline, the following primary method will be used in the event that a participant's Week 24 assessment is missing:

For participants who missed the 6MWT at Week 24 for reasons other than death or a clinical worsening event (other than death), a standard multiple imputation method will be used to impute missing data. For participants who die, the worst-rank score will be used to impute the missing data. For participants who experience a clinical worsening event (other than death), the next worst-rank score will be used to impute the missing data.[42]

The following additional sensitivity analyses will be performed:

a. Use the same standard multiple imputation method as described above for participants who missed the 6MWT at Week 24 for reasons other than death or a clinical worsening event (other than death) for missing data. For participants who missed the 6MWT at Week 24 due to death, the worst-rank score will be used to impute the missing data under the untied worst-rank score approach with the participant's baseline 6MWD being used to break ties for deaths.[42] In this case, participants who die will be considered to have a 6MWD at Week 24 of -2000 meters. Ties will be broken by subtracting the individual participant's baseline 6MWD value from the imputed Week 24 6MWD value. In this case, participants with higher baseline 6MWD values will have larger negative imputed Week 24 changes from baseline resulting in lower ranks among those who die. For participants who missed the 6MWT at Week 24 due to a clinical worsening event (other than death), the participant will be considered to have a 6MWD at Week 24 of -1000 meters. Ties will be broken by subtracting the individual participant's baseline 6MWD from the imputed Week 24 6MWD value. In this case, participants with higher baseline 6MWD values will have larger negative imputed Week 24 changes from baseline resulting in lower ranks among those who experience a clinical worsening event (other than death).

b. Use the same standard multiple imputation method as described above for participants who missed the 6MWT at Week 24 for reasons other than death or a clinical worsening event (other than death) for missing data. For participants who missed the 6MWT at Week 24 due to death or a clinical worsening event (other than death), the worst rank score will be used to impute the missing data under the tied worst rank score approach[42]. In this case, participants who die or experience a clinical worsening event (other than death) will receive the same worst rank value.
c. Use the same standard multiple imputation method as described above for participants who missed the 6MWT at Week 24 for reasons other than death or a clinical worsening event (other than death) for missing data. For participants who missed the 6MWT at Week 24 due to death or a clinical worsening event (other than death), the worst rank score will be used to impute the missing data. In this case, participants will be considered to have a 6MWD at Week 24 of -2000 meters. Ties will be broken by subtracting the individual participant's baseline 6MWD from the imputed Week 24 6MWD value. Participants with higher baseline 6MWD values will have larger negative imputed Week 24 changes from baseline resulting in lower ranks among those who die or have a clinical worsening event (other than death).
d. The primary analysis described in Section 11.5.1 will be repeated with participants who have non-missing change in 6MWD at Week 24 from baseline data.
e. An ANCOVA model with randomization factors and baseline 6MWD as covariates. The least squares mean of the treatment effect with corresponding 95% CI will be provided. The least squares mean and standard error of the mean (SEM) for each treatment arm will also be provided. Standard multiple imputation will be used for participants who missed the 6MWT at Week 24 for reasons other than death or a clinical worsening event (other than death) for missing data. For participants who missed the 6MWT at Week 24 due to death or a clinical worsening event, the worst change from baseline will be used to impute the missing data.
f. A tipping point analysis will be performed in the event that the p-value for the treatment effect is highly significant at a 2-sided 0.05 significance level.

Additional sensitivity analyses may be performed. These will be described in the SAP.

11.5.2. Secondary Endpoints

There are 8 secondary endpoints ranked as below:

1. Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline:
   - Improvement in 6MWD (increase ≥ 30 m)
   - Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L
   - Improvement in WHO FC or maintenance of WHO FC II
2. Change from baseline in PVR at Week 24
3. Change from baseline in NT-proBNP levels at Week 24
4. Proportion of participants who improve in WHO FC at Week 24 from baseline

5. Time to the first occurrence of any of the following clinical worsening events or death (TTCW):
    - Worsening-related listing for lung and/or heart transplant
    - Need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more
    - Need for atrial septostomy
    - PAH-specific hospitalization (≥ 24 hours)
    - Deterioration of PAH defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values:
        - Worsened WHO FC
        - Decrease in 6MWD by ≥ 15% confirmed by 2 tests at least 4 hours apart, but no more than 1 week apart
6. Proportion of participants who achieve a low-risk score (Section 5.3.6) at Week 24 using the simplified French Risk score calculator
7. Change from baseline in the Physical Impacts domain score of PAH-SYMPACT® at Week 24
8. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24
9. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24

The multicomponent improvement endpoint will be analyzed using Cochran-Mantel-Haenszel test, stratified by the randomization factors.

The change from baseline in PVR and NT-proBNP at Week 24 will be analyzed using an ANCOVA model with randomization factors and baseline values as covariates.

The proportion of participants who improve in WHO FC at Week 24 from baseline will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization factors.

Time to first clinical worsening event or death will be analyzed using the log-rank test with randomization factors as strata. In addition, Kaplan-Meier curves will be generated for each arm with randomization factors as strata.

The proportion of participants who maintain or achieve a low-risk score (Section 5.3.6) using the simplified French Risk score calculator at Week 24 versus baseline will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization factors.

The change from baseline in the Physical Impacts domain score of PAH-SYMPACT® at Week 24 will be analyzed using an ANCOVA model with randomization factors and baseline value as covariates.

The change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24 will be analyzed using an ANCOVA model with randomization factors and baseline value as covariates.

The change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24 will be analyzed using an ANCOVA model with randomization factors and baseline value as covariates.

A gatekeeping method will be used to control the Type I error rate in secondary endpoints by testing in the order of the secondary endpoints listed above, after successful testing for the primary endpoint. Secondary endpoint testing will be performed using a 2-sided alpha = 0.05 level by proceeding successively in the order of the secondary endpoints listed above only after each of the preceding endpoints is tested to be statistically significant.

The handling of missing data for missing secondary endpoints will be described in the SAP.

11.5.3. Exploratory Endpoints

Other endpoints of interest are the following:

- Change in ECHO parameters at Week 24 versus baseline
- Change in dyspnea score (assessed by Borg CR10 scale) at Week 24 versus baseline
- Proportion of participants that achieve PVR < 3 WU at Weeks 24 and 48
- Proportion of participants that achieve mPAP < 25 mmHg at Week 24
- Change from baseline in mPAP at Week 24
- Change from baseline in the Cardiovascular Symptoms domain score of PAH-SYMPACT® at Week 24
- Change from baseline in the EQ-5D-5L index score at Week 24
- Change from baseline in the EQ-5D-5L VAS at Week 24

They will be analyzed using appropriate statistical methods as mentioned in Section 11.4. The SAP will provide more details.

11.6. Analysis of Safety

All safety analyses will be performed on the Safety Set.

Adverse events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events are defined as an AE that starts after the first administration of study drug up to 8 weeks after the last dose and summarized by worst severity grade, system organ class, and preferred term. Treatment-emergent adverse events 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 arm. Clinically significant laboratory abnormalities will be listed and summarized by treatment arm. Chemistry and hematology laboratory tests will be collected regularly and reviewed periodically.

Descriptive statistics (mean, SD, SEM, median, min, max) will be provided for each timepoint of the collection by treatment arm for each timepoint analyzed.

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 ADA) will also be analyzed.

11.7. Pharmacokinetic Analysis

Population PK analysis will be performed using nonlinear mixed effect modeling. Concentration data obtained from this study and other studies will be combined to develop a population PK model that describes the PK exposure data and the associated variability. Participant-specific factors (demographics, baseline characteristics, markers for organ function, ADAs against sotatercept, etc.) will be explored as covariates for their potential to influence sotatercept PK parameters. Empiric individual Bayesian estimates of PK parameters will be generated, and using the final population PK model, appropriate measures of sotatercept exposure (area under the curve [AUC], maximum plasma concentration [C_{max}], or other exposure metrics of interest) will be computed for each participant. The relationship between serum sotatercept exposure and the primary efficacy endpoint, AEs of interest, or other selected secondary endpoints will be explored as appropriate.

Full details will be included in a separate PK/PD Data Analysis Plan.

11.8. Interim Analysis

No interim analyses are planned.

11.9. Subgroup Analysis

Appropriate subgroup analyses by randomization factors and other baseline characteristics for clinical activity may be conducted as exploratory analyses. Full details will be included in the SAP.

11.10. Critical-Event Adjudication Committee and Data Monitoring Committee

An independent blinded critical-event external adjudication committee will adjudicate all clinical worsening events up to the end of the study, including death, to determine whether these are due to PAH. An external, independent Data Monitoring Committee (DMC) will review unblinded safety data after at least 15 participants have been enrolled and have completed Visit 2, and at approximately 3-month intervals thereafter. A detailed charter will outline all activities of the DMC (including, but not limited to, DMC responsibilities, frequency of meetings, and type of data to be reviewed).

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

Acceleron Pharma Inc. personnel (or designee) will monitor each site throughout the study at predetermined intervals to check for study progress, to identify any problems, and to ensure compliance with the protocol, GCP, and other regulations.

Source document verification will be performed against entries on the eCRFs according to the study monitoring plan (see Section 14.1 for additional details on source documentation).

12.2. Audits and Inspections

Acceleron Pharma Inc., the CRO, and/or the IRB may audit the investigator's records both during and after the study. The purpose of the audit is to ensure that ethics, regulatory, and quality requirements are fulfilled in all studies performed by the Acceleron Pharma Inc. See Section 14.2 for additional information about audits and inspections.

13. ETHICS AND RESPONSIBILITIES

13.1. Good Clinical Practice

This study will be conducted in accordance with the standard of ICH GCP, an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. All applicable country and local regulations will also be observed. Compliance with these standards provides assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles in the Declaration of Helsinki, and that the clinical study data are credible.

13.2. Regulatory and Ethical Considerations

The following regulatory and ethical considerations will be applied:

- 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
  - ICH GCP guidance and regulations
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations Part 312, ICH guidelines, IRB/IEC, European Regulation 536/2014 for clinical studies (when applicable), European Union Clinical Trials Directive 2001/20/EC (when applicable), and all other applicable local regulations

13.3. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to ensure that the appropriate IRB/IEC has reviewed and approved this protocol prior to initiating the study. The investigator must provide Acceleron

Pharma Inc. or Acceleron Pharma Inc.'s representative with current and revised IRB/IEC membership rosters that include the members' occupations and qualifications. Sites within the US may provide a copy of the US Department of Health and Human Services Assurance Number.

The IRB/IEC must also review and approve the clinical site's ICF, other written information provided to the participant, and all advertisements that may be used for study recruitment. The investigator will provide the study monitor with copies of these documents and of dated IRB/IEC approval(s) prior to the start of the study.

If the protocol or the ICF is amended during the study, the investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. Approval of the amended documents must be obtained from the IRB/IEC before implementation and before new participants are consented to participate in the study using the amended version of the ICF. The investigator must provide Acceleron Pharma Inc. with the dated IRB/IEC approval of the amended documents as soon as available.

13.4. Informed Consent

Prior to study entry, the investigator or designee will explain the nature, purpose, benefits, and risks of participation in the study to each participant, participant's legally acceptable representative, or impartial witness. Participants must be informed that their participation is voluntary. Written and signed informed consent must be obtained prior to the participant entering the study (before initiation of any study-related screening procedure). Sufficient time will be allowed to discuss any questions raised by the participant. The ICF, which will contain all US federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act authorization information in a language that is understandable to the participant, must be signed by all participants. The authorized person obtaining the informed consent must also sign and date the ICF. A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative, and such action must be documented according to local requirements. The process of obtaining consent will be in compliance with all applicable local and country regulations and ICH requirements.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to IRB/IEC approval of the amended form. The clinical site must use the amended ICF for all new participants and must reconsent any ongoing participants with the amended ICF, if instructed to do so by the IRB/IEC.

The consent and reconsent process must be properly documented in the source documentation. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study as well as the time and date the written consent was obtained.

14. DATA HANDLING AND RECORD KEEPING

14.1. Source Documentation

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available for source data verification.

14.2. Data Quality Assurance

The following data quality assurance considerations will be applied:

- All participant data relating to the study will be recorded on an eCRF unless transmitted to Acceleron Pharma Inc. or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by 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.
- Acceleron Pharma Inc. 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 Acceleron Pharma Inc. No records may be transferred to another location or party without written notification to Acceleron Pharma Inc.

15. STUDY REPORT AND PUBLICATIONS

Acceleron Pharma Inc. is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of Acceleron Pharma Inc. is discussed in the investigator's Clinical Research Agreement.

All information concerning sotatercept is considered confidential and shall remain the sole property of Acceleron Pharma Inc. The investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without the written approval of Acceleron Pharma Inc. The investigator agrees not to disclose 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 Acceleron Pharma Inc. 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 Acceleron Pharma Inc. 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 Acceleron Pharma Inc. and the investigator.

Acceleron Pharma Inc. will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Acceleron Pharma Inc. will generally support the 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.

16. CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Acceleron Pharma Inc. However, authorized regulatory officials, IRB/IEC personnel, Acceleron Pharma Inc., and its authorized representatives are allowed full access to the study records.

Identification of participants and CRFs shall be by initials and screening and treatment numbers only. If required, the participant's full name may be made known to an authorized regulatory agency or other authorized official.

16.1. Data Protection

The following data protection considerations will be applied:

- Participants will be assigned a unique identifier by Acceleron Pharma Inc. Any participant records or datasets that are transferred to Acceleron Pharma Inc. will contain the identifier only; participant names or any information that 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 Acceleron Pharma Inc. 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 Acceleron Pharma Inc., by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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18. APPENDICES

APPENDIX 1. ABBREVIATIONS AND SPECIALIST TERMS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
CBC	Complete blood cell (count)
CI	Confidence interval
C_{max}	Maximum plasma concentration
(e)CRF	(Electronic) case report form
CRO	Contract research organization
CTD	Connective tissue disease
DBPC	Double-Blind Placebo-Controlled
DMC	Data monitoring committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EOS	End of study
EOT	End of treatment
E-R	Exposure-response
ERAs	Endothelin-receptor antagonists
EQ-5D-5L	EuroQoL – 5 Dimension – 5 Level
FAS	Full Analysis Set
FC	Functional class
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GDF	Growth and differentiation factor(s)
Hct	Hematocrit

Hgb	Hemoglobin
HHC	Home health care
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
LTDB	Long-Term Double-Blind
LTFU	Long-term follow-up
mPAP	Mean pulmonary arterial pressure
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDE5	Phosphodiesterase 5
PH	Pulmonary hypertension
PK	Pharmacokinetic
PPS	Per-Protocol Set
PR	Pulse rate
PRO	Patient-reported outcome
PVR	Pulmonary vascular resistance
QoL	Quality of life
QTcF	Frederica's corrected QT interval
RBC	Red blood cell
RCT	Randomized controlled trial
RHC	Right heart catheterization

SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SoE	Schedule of Events
sWFI	Sterile water for injection
TAPSE	Tricuspid annular plane systolic excursion
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TTCW	Time to clinical worsening
ULN	Upper limit of normal
VSMC	Vascular smooth muscle cell
WHO	World Health Organization
WU	Wood unit

APPENDIX 2. SIX-MINUTE WALK TEST

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 m in length (or at least 15 m) and should be at the same location that is used for all study visits. The length of the corridor should be marked every 3 m. The turnaround points should be marked (e.g., with a cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor (e.g., using brightly colored tape).

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 the 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.

5. Have the participant stand and rate their baseline dyspnea using the Borg dyspnea scale (Borg CR10 Scale).
    a. Show the scale to the participant and ask the participant this: "Please grade your level of shortness of breath using this scale." Record the pre-walk Borg dyspnea level.
    b. At the end of the exercise, remind the participant of the breathing number that they chose before the exercise and ask the participant to grade their breathing level again.

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. Remind the participant of their breathing number pretest and ask the participant to rate their level of shortness of breath again. Record the post-walk Borg dyspnea level.
2. Measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
3. Record the number of laps from the counter.
4. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides.
5. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
6. Congratulate the participant on good effort and offer a drink of water.

APPENDIX 3. 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 6.1):

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

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

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 6. 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 6: 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] • 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.

Abbreviations: IUD = intrauterine device; WOCBP = woman of childbearing potential.
[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.

Pregnancy Testing

- A Woman of Childbearing 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 10.8. 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.