Official Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality
NCT number:	NCT04896008
Document Date:	23-Apr-2024

PROTOCOL A011-14 (ZENITH)

PROTOCOL TITLE:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality
SHORT TITLE:	A Phase 3 Study of Sotatercept in Participants with PAH WHO FC III or FC IV at High Risk of Mortality
REGULATORY AGENCY IDENTIFYING NUMBERS:	IND 136150 EudraCT 2021-001498-21
SPONSOR:	Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA 126 East Lincoln Avenue P.O. Box 2000 Rahway, NJ 07065 USA
ORIGINAL PROTOCOL DATE:	08 April 2021
PROTOCOL AMENDMENT 01 DATE (MK-7962-006-01):	16 June 2022
PROTOCOL AMENDMENT 02 DATE (MK-7962-006-06):	29 June 2023
PROTOCOL AMENDMENT 03 DATE (MK-7962-006-07):	23 April 2024

See Appendix 5 for nomenclature mapping

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Acceleron Pharma Inc. Approval

Signature: _____ **Date:** _____

Name (print): _____

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 with current United States (US) Food and Drug Administration (FDA) regulations, International Council for Harmonisation (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

Signature: _____ **Date:** _____

Name (print): _____

Institution Name and Address:

_____

_____

_____

PROCEDURES IN CASE OF EMERGENCY

Table 1 Emergency Contact Information

Role in Study	**Name**	**Contact Information**
Medical Monitor	Details provided in the Regulatory Binder	Details provided in the Regulatory Binder
Pharmacovigilance	Acceleron Safety Reporting Hotline	EMEA/Asia Tel #: +44 1223 374 240 EMEA/Asia Fax #: +44 1223 374 102 Emeaasiasafetycentral.sm@ppd.com LA Tel #: +55 11 4504 4801 LA Fax #: +55 11 4504 4802 LATSafety@ppd.com RTP Tel #: +1 888 483 7729 RTP Fax #: +1 888 529 3580 RTPSafety@ppd.com Wilmington Tel #: +1 800 201 8725 Wilmington Fax #: +1 888 488 9697 WILSafety@ppd.com

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

This protocol amendment was created primarily to add dose modification instructions due to serious bleeding events, add event adjudication language, and update the risk/benefit section. Changes from the Version 3.0 (29 June 2023) to Version 4.0 (23 April 2024) are detailed below. Minor edits are not included.

Protocol Location	Description of Change	Brief Rationale
Section 2, Table 2	Added details to footnote 'h' stating that hematology assessments are required after a dose modification prior to the next dose administration for participants on HHC and non-quarterly site visits (full text not shown).	To facilitate hematology assessments after dose modification and before the next dose for participants on HHC and non-quarterly visits.
Section 2, Table 3	Changed footnote 'e' to read, "Participants may be asked to return for additional ADA testing after their last visit if there is any indication of potential immunogenicity-related safety concern." The previous statement was deleted.	To provide flexibility in post-study ADA sampling across all Sotatercept studies.
Section 3.2	Updated the language on the important risks of sotatercept.	To reflect the potential risk of serious bleeding as added to the sotatercept core risk profile.
Section 8.3	Changed text, "Dose delays should always precede dose reductions~~, as summarized in Figure 3 and Figure 4~~. ~~While g~~ Guidance for dose modifications and dose delays are summarized in Figure 3 and Figure 4~~,~~ . For safety reasons other than those listed in Figure 3 and Figure 4, dose delays ~~or~~followed by dose reductions can be implemented ~~for safety reasons~~ at any time per the investigators assessment ~~and are not limited to the dose modification guidance provided~~."	To facilitate the correct application of the dose modification guidelines.

Protocol Location	Description of Change	Brief Rationale
Section 8.3.2	Changed the text to read, "If Hgb level increase more than 4 g/dL above the participant's baseline value, the study Medical Monitor should be consulted, and treatment discontinuation should be considered;…"	To align the body text with Figure 3.
Section 8.3.5	Added a new section (Dose Delays due to SAEs of Bleeding) and the text, "In cases of serious active bleeding, the dose of study intervention should be delayed until the event resolves. If more than one dose delay due to a serious bleeding event occurs, then the Medical Monitor should be consulted." The subsequent section headings increased by one sequential number as a result.	See Section 3.2 rationale.
Section 9.2.1	Deleted text, "Measurements/assessments taken during Screening Period will be recorded as the baseline values for study assessment of endpoints unless described otherwise."	To indicate that Section 9.2.1 is not intended for defining analysis details.
Section 9.3.14	Changed text, "Participants ~~who have a new or higher titer-positive ADA result at their last visit~~ may be asked to return for additional ADA testing after their last visit if there is any indication of potential immunogenicity-related safety concern ~~approximately every 3 months until response is negative or result is considered stabilized~~."	See Section 2, Table 3 rationale.
Section 9.3.18	Added a new section (Clinical Event Information) to describe the collection of clinical events (full text not shown).	To add details regarding how clinical event information will be collected before an eDMC review or an interim/final analysis.

Protocol Location	Description of Change	Brief Rationale
Section 10.5, Section 10.6	Changed text, "For overdose and cancer (serious and non-serious) and all SAEs, a paper SAE Report Form must be completed with a concise account of the event ~~as much information as possible~~ and submitted within the timeframe described in this section."	To emphasize overdose and cancer as reportable events.
Section 10.7	Added text, "Additionally, the Serious Adverse Event Reporting Form must be submitted within the same timeframe. This form is to be submitted to the PPD PVG at the email address found at the bottom of the form.".	To clarify that overdose should be reported using the Serious Adverse Event Reporting Form within 24 hours.
Section 10.9.1	Removed the risk language from this section (full text not shown).	To prevent redundancy with Section 3.2.
Section 11.10	Added a paragraph detailing the adjudication of events (full text not shown).	To provide specific information on the adjudication of events.

ADA = anti-drug antibodies; eDMC = external data monitoring committee; Hgb = hemoglobin; HHC = home health care; IB = Investigator's Brochure; PAH = pulmonary arterial hypertension; PVG = pharmacovigilance; SAE = serious adverse event.

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1 PROTOCOL SYNOPSIS

Protocol Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality
Short Title	A Phase 3 Study of Sotatercept in Participants With PAH WHO FC III or FC IV at High Risk of Mortality
Protocol Number	A011-14/MK-7962-006-06 (ZENITH)
Study Type	Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study.
Rationale	PAH 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 Phase 2 Study A011-09 (PULSAR; 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, improvements were observed in 6-minute walk distance (6MWD), N-terminal prohormone B-type natriuretic peptide (NT-proBNP), and other endpoints.
Study Objective	The objective of this study is to evaluate the effects of sotatercept treatment (plus maximum tolerated background PAH therapy) versus placebo (plus maximum tolerated background PAH therapy) on time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of $\geq$ 24 hours, in participants with WHO FC III or FC IV PAH at high risk of mortality.
Study Population	Participants with symptomatic PAH (WHO FC III or FC IV at high risk of mortality) 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 defect (CHD). Participants must have a Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2.0 risk score of $\geq$ 9 and be on maximum tolerated combination background PAH therapy.
Number of Participants	Up to 166 participants will be randomly assigned in a 1:1 ratio to the 2 study treatment groups (83 participants per arm).

Study Design	The study is divided into a Screening Period (up to 4 weeks) followed by a Double-blind Placebo-controlled (DBPC) Treatment Period. Participants who experience an event of PAH worsening-related hospitalization of ≥ 24 hours will complete an End of Treatment (EOT) Visit and may be eligible to enroll in the open-label, long-term follow-up (LTFU) study, A011-12 (SOTERIA). At the end of the DBPC Treatment Period, which will occur when the required number of participants have experienced a primary endpoint event (time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours), all participants who do not experience a primary endpoint event will complete an EOT Visit and may be eligible to enroll into the open-label, LTFU Study A011-12 SOTERIA. If the participant does not choose to enroll into the SOTERIA study, they will complete the Follow-up Period of the study that will include both the EOT and the End of Study (EOS) Visits (Figure 1). Each study-eligible participant will be randomized in a 1:1 ratio to 1 of the 2 treatment arms prior to starting the DBPC Treatment Period. • 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 Each participant will remain in the DBPC Treatment Period until 1 of the following occurs, whichever comes first: 1) they experience the first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours; 2) the time when the required number of primary events are accrued for the final analysis; 3) the study is stopped early at the interim analysis (IA) for either efficacy or futility. The planned IA will occur when approximately 59 participants have experienced a primary endpoint event (roughly 50% of the required number of events). Study participants who have not experienced an event will remain in the DBPC Treatment Period until the required number of participants have experienced a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization. Upon experiencing an event of PAH worsening-related hospitalization of ≥ 24 hours or at the time of study unblinding, participants will complete an EOT Visit and may enroll into the LTFU study, A011-12 (SOTERIA). If the SOTERIA study is not yet activated at study site, participants will remain in the ZENITH DBPC Treatment Period until SOTERIA has been activated.

	Participants who experience an event of lung transplantation or who elect not to continue into the LTFU study, A011-12 (SOTERIA), will complete the Follow-up Period including both EOT and the EOS Visits. Participants who discontinue from the DBPC Treatment Period early without experiencing a primary endpoint event, or before the trial is unblinded, should complete the EOT Visit at the time of discontinuation as specified in the SoE (Section 2) and EOS Visit (described in Section 9.2.3.2), provided that consent is not withdrawn. Following the EOT and EOS, or if the participant refuses to attend additional study visits, they will receive quarterly telephone contacts for vital status until the study is unblinded. These participants will not be eligible to enroll into the LTFU study A011-12 (SOTERIA).
Estimated Duration of the Study	Maximum study duration for a given participant in this study will be up to approximately 43 months as follows: • Screening Period (up to 4 weeks) • DBPC Treatment Period (up to approximately 40 months) • Follow-up Period (up to 8 weeks)
Inclusion Criteria	Eligible participants must meet all of the following inclusion criteria to be enrolled in the study: 1. Age 18 to 75 years, inclusive 2. Documented diagnostic right heart catheterization 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 III or IV 4. REVEAL Lite 2.0 risk score of ≥ 9 5. Right heart catheterization performed during screening (or within 2 weeks prior to screening, if done at the clinical study site) documenting a minimum PVR of ≥ 5 Wood units and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of ≤ 15 mmHg

	6. Clinically stable and on stable doses of maximum tolerated (per investigator's judgment) double or triple background PAH therapies for at least 30 days prior to screening 7. Females of childbearing potential must: • Have 2 negative urine or serum pregnancy tests as verified by the investigator prior to starting study therapy; must agree to ongoing urine or serum pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug • If sexually active with a male partner - Used highly effective contraception without interruption; for at least 28 days prior to starting the investigational product AND - Agree to use the same highly effective contraception in combination with a barrier method 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 PH WHO Groups 2, 3, 4, or 5 2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus-associated PAH and PAH associated with portal hypertension 3. Diagnosis of pulmonary veno-occlusive diseases or pulmonary capillary hemangiomatosis or overt signs of capillary and/or venous involvement 4. Hemoglobin at screening above gender-specific upper limit of normal (ULN), per local laboratory test 5. Baseline platelet count < 50,000/mm^3 (< 50.0 × 10^9/L) at screening 6. Baseline systolic blood pressure < 85 mmHg at Screening 7. Pregnant or breastfeeding women 8. Serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels > 3.0 × ULN 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 or known allergic reaction to sotatercept, its excipients, or luspatercept 11. History of pneumonectomy 12. This criterion has been removed 13. Untreated more than mild obstructive sleep apnea 14. History of known pericardial constriction 15. History of restrictive or congestive cardiomyopathy 16. Electrocardiogram (ECG) with Fridericia's corrected QT interval (QTcF) > 500 ms during the Screening Period 17. Personal or family history of long QT syndrome or sudden cardiac death 18. Left ventricular ejection fraction < 45% on historical echocardiogram within 1 year prior to the Screening Visit 19. Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) in the past 6 months prior to the Screening Visit 20. Cerebrovascular accident within 3 months prior to the Screening Visit 21. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease

	22. Currently on dialysis or anticipated need for dialysis within the next 12 months
Efficacy Endpoints	**Primary Efficacy Endpoint** The primary efficacy endpoint is the time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours. All events will be adjudicated by a blinded, independent committee of clinical experts. **Secondary Efficacy Endpoints** The secondary endpoints are ranked as follows: 1. Overall survival 2. Transplant-free survival 3. Proportion of participants who experienced a mortality event at EOS 4. Change from baseline in REVEAL Lite 2.0 risk score at Week 24 5. Proportion of participants achieving a low or intermediate (≤ 7) REVEAL Lite 2.0 risk score at Week 24 6. Change from baseline in NT-proBNP levels at Week 24 7. Change from baseline in mean pulmonary artery pressure (mPAP) at Week 24 8. Change from baseline in PVR at Week 24 9. Proportion of participants who improve in WHO FC at the end of the DBPC Treatment Period 10. Change from baseline in 6MWD at Week 24 11. Change from baseline in cardiac output (CO) at Week 24 12. Change from baseline in EuroQoL-5 dimensions scale 5 levels (EQ-5D-5L) index score at Week 24 **Exploratory Endpoints** • Number of PAH-related hospital days during the study • Change from baseline in right ventricular (RV)-pulmonary artery (PA) coupling at Week 24 • Change from baseline in biomarkers; including, but not limited to, serum biomarkers such as C-reactive protein (CRP) and Activin A at Week 24 • Proportion of participants achieving a low or intermediate-low COMPERA 2.0 4-strata risk score (Section 9.3.6) at Week 24

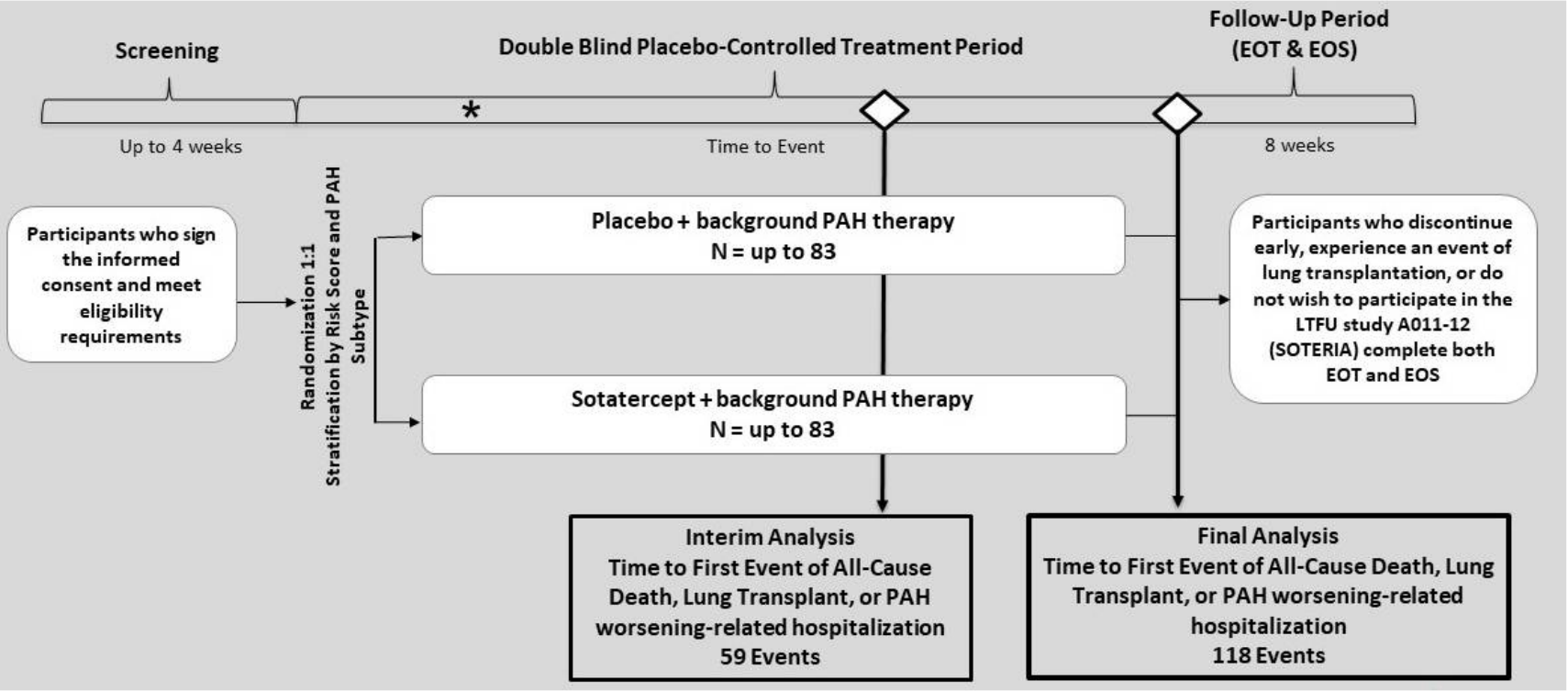
Safety Endpoints	Safety will be evaluated by collecting the following information: • Adverse events (AEs) • Anti-drug antibodies (ADAs) • Laboratory assessments (hematology, serum chemistry, and urinalysis) • Vital signs • Physical examination • 12-lead ECG
Sample Size Determination and Power Calculations	The sample size determination is based on the primary efficacy endpoint of time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours using EAST® version 6.4. In STELLAR, the hazard ratio for time to death or non-fatal clinical worsening in the sotatercept group compared with the placebo group was 0.16 (95% CI: 0.08 to 0.35) [Hoeper, M. M., et al 2023]. Given the differences in the populations and definitions of endpoints between STELLAR and this study, the hazard ratio is assumed to be 0.55 in this study [Hoeper, M. M., et al 2023]. Given a 1:1 randomization, a 1-sided 0.025 Type 1 error rate, 90% power, and with a planned IA at approximately 50% of the required number of events with the option to stop the study for futility, approximately 118 events will be required based on the log-rank test. Given that approximately 166 participants are planned to be enrolled in this study, the accrual period is approximately 26 months, assuming an accrual rate of approximately 6.5 participants per month. In addition, assuming a dropout rate of 0.04% per month (0.5% per year), and the probability of observing an event for placebo is 0.45 for the first year, 0.60 for the second year, and 0.90 for the third year and later, the projected time of the IA will occur around 26 months. If the study continues after the IA, the final analysis will happen around 40 months. Median participant time on study must be at least 6 months in order for analyses following the occurrence of the required number of events.
Stratified Randomization Factors	Randomization will be stratified by: • REVEAL Lite 2.0 risk score (9 to 10 or ≥ 11) at Screening • PAH subtype (CTD-associated or not CTD-associated)

Statistical Methods	**Efficacy Analyses:** All efficacy analyses will be based on the Full Analysis Set (FAS), which is defined as all randomized participants. **Safety Analyses:** All safety analyses will be based on the Safety Set, which is defined as all participants who receive at least 1 dose of study treatment. All participants will be analyzed according to the treatment they are administered. **Analysis of Study Endpoints:** **Efficacy Endpoints** <u>Interim Analysis</u> An IA of the primary efficacy endpoint is planned to occur when approximately 59 participants have experienced a primary endpoint event (roughly 50% of the required number of events) have occurred. A stratified log-rank test with randomization factors as strata will be used for the analysis of the primary efficacy endpoint. The point estimate of the hazard ratio with 95% confidence interval (CI) will be estimated by a Cox regression model stratified by the randomization factors. <u>Primary Endpoint:</u> Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours, will be analyzed using the stratified log-rank test with the randomization factors as strata. The point estimate of the hazard ratio with 95% CI will be estimated by a Cox regression model stratified by the randomization factors. <u>Secondary Endpoints:</u> The aligned rank stratified Wilcoxon test will be used for continuous variables; the Cochran-Mantel-Haenszel test will be used for dichotomous variables, and the log-rank test and Cox regression methods will be used for time-to-event variables. A gatekeeping method will be used to control the Type 1 error rate in secondary endpoints by testing in the order of the secondary endpoints listed below, after successful testing for the primary endpoint. Secondary endpoint testing will be performed using a 1-sided alpha = 0.025 level proceeding successively in the order of the secondary endpoints listed above after each of the preceding endpoints is tested to be statistically significant: • Overall survival • Transplant-free survival • The change in REVEAL Lite 2.0 risk score at 24 weeks from baseline

	• The proportion of participants achieving a low or intermediate (≤ 7) REVEAL Lite 2.0 risk score at 24 weeks • The proportion of participants who experience a mortality event at EOS • The change in NT-proBNP levels at 24 weeks from baseline • The change in mPAP at 24 weeks from baseline • The change in PVR at 24 weeks from baseline • The proportion of participants who improve in WHO FC at the end of the DBPC Treatment Period • The change in 6MWD at 24 weeks from baseline • The change in CO at 24 weeks from baseline • The change in the EQ-5D-5L index score at 24 weeks from baseline Exploratory Endpoints: • The number of PAH-related hospital days during the study will be analyzed using a Poisson regression model. • The change in echocardiogram parameter data describing RV-PA coupling (tricuspid annular plane systolic excursion/ pulmonary arterial systolic pressure) at 24 weeks from baseline will be summarized using descriptive statistics. • The change in biomarker data at 24 weeks from baseline will be summarized using descriptive statistics. • The proportion of participants achieving a low or intermediate-low COMPERA 2.0 4-strata risk score (Section 9.3.6) at 24 weeks will be summarized using descriptive statistics. No adjustments for multiplicity will be performed for statistical analyses of exploratory endpoints. **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. 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 ZENITH



EOT = end of treatment; EOS = end of study; LTFU = long-term follow-up; PAH = pulmonary arterial hypertension.

*Assessments will be collected at the 6-month visit (Visit 9) for secondary endpoint analysis.

2 SCHEDULE OF EVENTS

The schedules of events (SoEs), which provide an overview of the study periods and procedures, are presented in Table 2 for the Screening and Double-blind Placebo-controlled (DBPC) Treatment Periods and Table 3 for the Follow-up Period.

Specific information on visits and assessments during the Screening, DBPC Treatment, and Follow-up Periods are discussed in Section 9.

Table 2 Schedule of Events: Screening and Double-Blind Placebo-Controlled Treatment Periods

Study Procedure/ Assessment[a,b]	**Screening Period (up to 4 weeks prior to Visit 1)**	**Visit 1 (Study Day 1)**	**Visit 2 (21±3 days)**	**Visits 3 and 4 (21±3 days)**	**Visit 5 (21±3 days)**	**Visits 6-8 (21±3 days)**	**Visit 9 (6 month Visit) (21±3 days)**	**Visits 10-12 (21±3 days)**	**Visit 13 (Quarterly Site Visit) (21±3 days)**	**Visits 14-onward until the end of the DBPC Treatment Period (21±3 days)**
Informed consent	X									Repeat Visits 10-13 until the end of the DBPC Treatment Period
Inclusion/exclusion criteria	X									
Randomization		X								
Medical history[c]	X									
Physical examination[d]	X	X			X		X		X	
ECG (12-lead)[e]	X						X			
Vital signs including weight[f]	X	X	X	X	X		X		X	
Pregnancy test (urine or serum)[g]	X	X	X	X	X	X	X	X	X	
Hematology (CBC)[h]	X		X	X	X		X		X	
Serum chemistry[i]	X	X			X		X		X	
Urinalysis	X				X		X		X	
6MWT[j]	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		X	

Study Procedure/ Assessment[a,b]	**Screening Period (up to 4 weeks prior to Visit 1)**	**Visit 1 (Study Day 1)**	**Visit 2 (21±3 days)**	**Visits 3 and 4 (21±3 days)**	**Visit 5 (21±3 days)**	**Visits 6-8 (21±3 days)**	**Visit 9 (6 month Visit) (21±3 days)**	**Visits 10-12 (21±3 days)**	**Visit 13 (Quarterly Site Visit) (21±3 days)**	**Visits 14-onward until the end of the DBPC Treatment Period (21±3 days)**
EQ-5D-5L assessment	X	X			X		X		X	Repeat Visits 10-13 until the end of the DBPC Treatment Period
NT-proBNP and CRP sample collection	X	X	X	X	X		X		X	
REVEAL Lite 2.0 risk score assessment[k]	X									
ADA sample collection	X	X	X	X	X		X		X	
PK and Activin A sample collection[l]		X	X	X	X		X		X	
Right heart catheterization[m]	X						X			
Echocardiogram[n]	X						X			
Study drug administration[a, b, o]		X	X	X	X	X	X	X	X	
AE/SAE review[o]	X	X	X	X	X	X	X	X	X	
Concomitant medication review[o]	X	X	X	X	X	X	X	X	X	

6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell (count); CRP = C-reactive protein; DBPC = double-blind placebo-controlled; ECG = electrocardiogram; EDC = electronic data capture; EOT = end of treatment; EQ-5D-5L = EuroQoL-5 dimensions scale 5 levels; FC = functional class; HCO_3 = bicarbonate; Hct = hematocrit; Hgb = hemoglobin; HHC= home health care; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PK = pharmacokinetic(s); RBC = red blood cell; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; SAE = serious adverse event; WBC = white blood cell; WHO = World Health Organization.

a All study procedures must be performed prior to study drug administration. Dose must be calculated based on the participant's weight on the day of dosing. Dose modification guidelines should be reviewed and implemented prior to dosing (Section 8.3).
b All participants will receive study drug every 21 days (±3 days), either at the study site (Visits 1 to 5, Visit 9, and quarterly site visits for all participants) or at home (Visit 6 onwards, except for Visit 9 and quarterly site visits, for participants who consent and are approved for optional home health administration of study drug).
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 ECG will be performed at Screening and at Visits 9 and EOT. At visits where both ECGs and 6MWT assessments are done, ECGs should be performed prior to 6MWT.
f For dosing visits at which weight is not collected, the most recently collected weight should be utilized for dose calculation.
g Two pregnancy tests are required for female participants of childbearing potential at the Screening Visit. A single pregnancy test is required prior to study drug administration at all other visits.
h Complete blood count includes RBCs, absolute WBCs, Hgb, Hct, and platelet count. Results are evaluated at Screening Visit and prior to study drug administration (or up to 3 days prior if available) for Visits 2 to 5, 9, and quarterly site visits. For HHC visits and non-quarterly site visits starting at Visit 6, hematology results are not required to be evaluated prior to study drug administration. However, if there is a dose modification based on Hgb levels and platelet count (Sections 8.3.2 and 8.3.3) during non-quarterly visits, a hematology assessment should be performed prior to the next dose administration (or up to 3 days prior if available) , and onsite visits are required (Section 6.5). Hematology results collected per SoE and Section 8.3 should be recorded in the EDC.
i Creatinine, BUN, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, follicle-stimulating hormone, albumin, and HCO_3 will be measured.
j The 6MWT should be performed twice during the Screening Period, at least 4 hours, but no longer than 1 week, apart. All 6MWTs performed from Visit 1 onward can be performed at the study visit day or within 10 days prior to study drug administration.
k Sites will receive central laboratory NT-proBNP results from the screening sample only; therefore, sites will only be required to calculate the REVEAL Lite 2.0 risk score during the Screening Period. Sites will use this score to ensure that entry criterion 4: REVEAL Lite 2.0 risk score ≥9, is met by the participant at enrollment. Acceleron will calculate the REVEAL Lite 2.0 risk score for all other study visits (Visits 1 to 5, Visit 9, quarterly site visits, EOT Visit, and EOS Visits).
l Samples for PK and Activin A testing will be collected on Day 1, predose and at 1 to 2, 2 to 4, and 4 to 8 hours postdose. On other visits, samples for PK and Activin A testing will be collected prior to study drug administration.
m Right heart catheterization should be performed last when possible if other assessments are occurring on the same day. All right heart catheterizations performed after Screening may be performed on the day of study visit or within 1 week prior to study drug administration.
n Echocardiograms will be performed at Screening and at Visits 9, 25, and EOT only. All echocardiograms performed after Screening can be performed on the day of the study visit or within 1 week prior to study drug administration. If an echocardiogram has been performed in the past 3 months, it may be exempted at the EOT Visit.
o Documentation of concomitant medications as well as occurrence of any AEs, medication errors, accidental exposure of others, or product complaints will occur at these visits. See Section 6.5 for details regarding HHC visits.

Table 3 Schedule of Events: Follow-up Period

	Follow-up Period[a] (Study Completion or Early Discontinuation)	
Study Procedure/Assessment	**EOT Visit (21 ± 7 days from last dose)**	**EOS Visit (5 weeks ± 7 days after EOT Visit) (early discontinuation, lung transplantation, or not in LTFU only)**
Physical examination[b]	X	X
ECG (12-lead)	X	
Vital signs including weight	X	X
Pregnancy test (urine or serum)	X	X
Hematology (CBC)[c]	X	X
Serum chemistry[d]	X	X
Urinalysis	X	X
6MWT	X	X
Borg Dyspnea Scale (pre- and post-6MWT)	X	X
WHO FC assessment	X	X
EQ-5D-5L assessment	X	X
NT-proBNP and CRP sample collection	X	X
ADA sample collection[e]	X	X
PK and Activin A sample collection	X	
Echocardiogram[f]	X	
AE/SAE review	X	X
Concomitant medication review	X	X

6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood cell (count); CRP = C-reactive protein; DBPC = double-blind placebo-controlled; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; EQ5D-5L = EuroQoL-5 dimensions scale 5 levels; FC = functional class; FSH = follicle-stimulating hormone; HCO_3 = bicarbonate; Hct = hematocrit; Hgb = hemoglobin; LTFU = long-term follow-up; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PK = pharmacokinetic(s); RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell; WHO = World Health Organization.

a Participants who experience an event of lung transplantation, who discontinue early, or who elect not to continue into the LTFU study, A011-12 (SOTERIA), will complete both the EOT and the EOS Visits, provided that consent is not withdrawn. Refer to Section 9.4.1for early discontinuation criteria. Participants who have completed all DBPC Treatment Period visits, or who have experienced an event of PAH worsening-related hospitalization of ≥ 24 hours, and will continue into the LTFU Study, A011-12 (SOTERIA) will be asked to complete the EOT Visit only. The EOT Visit is recommended to occur 21 days (±7 days) after the last study drug administration in the DBPC Treatment Period. The EOS Visit is recommended to occur 5 weeks (± 7 days) after the EOT Visit.

b Perform full physical examination at the Screening Visit only. For all other visits, perform targeted cardiopulmonary and skin examinations.

c CBC includes RBCs, absolute WBCs, Hgb, Hct, and platelet count.

d BUN, creatinine, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, FSH, albumin, and HCO_3 will be measured.

e Participants may be asked to return for additional ADA testing after their last visit if there is any indication of potential immunogenicity-related safety concern.

f Echocardiograms will be performed at Screening Visit, Visits 9, 25, and the EOT Visit. If an echocardiogram has been performed in the past 3 months, it may be exempted at the EOT Visit.

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 (RV) dysfunction, and ultimately failure as well as premature death [Rubin, L. J. 1997] [Simonneau, G., et al 2004]. The pathophysiology of PAH 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 [Schermuly, R. T., et al 2011]. In the absence of treatment, the majority of patients succumb to heart failure within a few years of diagnosis [Vonk-Noordegraaf, A., et al 2013]. 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, and digoxin), current disease-specific treatments for PAH include vasodilator-type agents, such as endothelin-receptor antagonists, phosphodiesterase inhibitors, and prostanoids.

Genetic mutations in the bone-morphogenetic protein type II receptor (BMPR2) are associated with the majority of cases of the familial form of PAH [Morrell, N. W. 2006] [Machado RD, Aldred MA, James V, Harrison RE, Patel B, Schwalbeet EC 2006] and approximately 25% of idiopathic PAH cases. 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-β family members in the pathogenesis of PAH. Sotatercept acts to block activin ligands and growth and differentiation factors (GDFs), may attenuate bone-morphogenetic proteins (BMPs), and improve pulmonary vascular remodeling by restoring balance to Smad signaling [Yung, L., et al 2017].

Sotatercept (ACE-011) 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 [Ruckle, J., et al 2009]. It has previously been tested in chemotherapy-induced anemia [Raftopoulos, H., et al 2016], multiple myeloma [Abdulkadyrov, K. M., et al 2014], bone loss [Ruckle, J., et al 2009], myelodysplastic syndromes [Komrokji, R., et al 2018], β-thalassemia [Cappellini MD, Porter J, Origa R, Forni GL, Voskaridou E, Galactéros F 2019], end-stage kidney disease [Coyne, D. W., et al 2019], as an erythropoietic agent [Sherman, M. L., et al 2013], in pulmonary hypertension (PH), and has been shown to be well tolerated and consistent with its known and potential risks.

Sotatercept binds select ligands in the transforming growth factor-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 [Yung, L., et al 2017] [Yung, L., et al 2018]. Preclinical data suggest that sotatercept (murine analog,

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 [Yung, L., et al 2017]. 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, clinical results from the Phase 2 Study A011-09 (PULSAR; NCT03496207) and clinical results from the Phase 3 pivotal study (STELLAR NCT04576988).

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 in humans, which have been assessed in the PULSAR study, 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) [Badesch, D. B., et al 2020]. PVR was reduced in both sotatercept dose groups versus placebo (least squares mean difference [standard error [Ghofrani, H. A., et al 2013]]) (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 meters (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 to 46.6). Sotatercept also improved N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels. In addition, a greater proportion of participants in the sotatercept treatment groups improved in the World Health Organization (WHO) functional class (FC) compared with placebo.

Results from Study A011-11 (STELLAR), the pivotal Phase 3 study of sotatercept in PAH, further support those from PULSAR. STELLAR was a randomized, double-blind,

placebo-controlled study in participants with PAH (WHO Group 1 pulmonary hypertension [PH]) on stable background PAH therapy. STELLAR demonstrated a statistically significant and clinically meaningful improvement in 6MWD from baseline at 24 weeks. Eight of 9 secondary efficacy outcome measures achieved statistical significance, including the outcome measure of proportion of participants achieving multicomponent improvement (defined as improvement in 6MWD, NT-proBNP level, and either improvement in WHO FC or maintenance of WHO FC II), and the outcome measure of time to death or the first occurrence of a clinical worsening event. For time to death or non-fatal clinical worsening event, and after a median follow-up of 32.7 weeks across the treatment groups, the hazard ratio in the sotatercept group as compared with the placebo group was 0.16 (95% CI: 0.08 to 0.35).

The current important risks for sotatercept in participants with PAH include erythrocytosis, severe thrombocytopenia, and serious bleeding. Erythrocytosis and thrombocytopenia were mostly nonserious, manageable, and tolerable. Participants with serious bleeding events were more likely to be on prostacyclin background therapy and/or anticoagulants, or to have had low platelet counts. Potential risks of embryo-fetal toxicity and impaired fertility are based on nonclinical observations. Details about contraception and collection of pregnancy information can be found in Appendix 3. Details about the known and expected benefits and risks of sotatercept may be found in the current IB.

3.3 Study Rationale

Study A011-14 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate sotatercept versus placebo in participants with PAH WHO FC III or FC IV who are at high risk of mortality.

This Phase 3 study is supported by data from the PULSAR study as described in Section 3.2.

In the PULSAR study, more than 90% of participants 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 participants, including those receiving maximal PAH therapy with double/triple drug combinations and intravenous prostacyclin.

Treatment with sotatercept in addition to background PAH therapies was well tolerated, with thrombocytopenia and increased hemoglobin (Hgb) levels being the most commonly reported drug-related AEs. The treatment-induced increases in Hgb levels and decrease in platelet count observed in the PULSAR study are consistent with the effects of sotatercept in previous clinical studies described in Section 3.1 [Ruckle, J., et al 2009] [Raftopoulos, H., et al 2016] [Abdulkadyrov, K. M., et al 2014] [Komrokji, R., et al 2018] [Cappellini MD, Porter J, Origa R, Forni GL, Voskaridou E, Galactéros F 2019] [Coyne, D. W., et al 2019] [Sherman, M. L., et al 2013].

The current study will assess the effects of sotatercept treatment (plus maximum tolerated background PAH therapy) versus placebo (plus maximum tolerated background PAH therapy) on time to first event of all-cause death, lung transplantation, or PAH worsening-

related hospitalization of ≥ 24 hours, in participants with WHO FC III and FC IV PAH at high risk of mortality. High-risk patients have a higher likelihood of events of PAH progression, and thus the benefit of adding sotatercept to background PAH therapy may be more evident in this patient population.

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 assess the risk-benefit profile of sotatercept in participants with WHO FC III or FC IV who are at high risk of mortality.

4 STUDY OBJECTIVES

The objective of this study is to evaluate the effects of sotatercept treatment (plus maximum tolerated background PAH therapy) versus placebo (plus maximum tolerated background PAH therapy) on time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours, in participants with WHO FC III and FC IV PAH at high risk of mortality.

5 STUDY ENDPOINTS AND RATIONALE

5.1 Endpoints Reported in Previous PAH 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 [Sitbon, O., et al 2020].

However, these endpoints did not consistently correlate with indicators of disease progression, such as PAH-related hospitalization and death. This led to the preference toward morbidity and mortality as primary endpoints, which were used in the following more recent Phase 3 clinical trials for PAH: AC-055-302/SERAPHIN (NCT00660179), AMBITION (NCT01178073), GRIPHON (NCT01106014), and FREEDOM-EV (NCT01560624) [Pulido, T., et al 2013] [Galie, N., et al 2015] [Sitbon, O., et al 2015] [Tapson, V. F., et al 2019]. Despite the limitations of 6MWD and improvement in WHO FC as standalone endpoints, it is noteworthy that all 4 trials referenced include 6MWD and FC in the definition of clinical worsening.

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 [Sitbon, O., et al 2015]. 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

This time-to-event trial will have a composite primary efficacy endpoint of time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours.

All events will be adjudicated by a blinded, independent committee of clinical experts.

Time to PAH 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 time to worsening as a secondary endpoint. Some of the more recent clinical trials have demonstrated a treatment-related delay in time to worsening, and while others have not [Galie, N., et al 2010], recent results suggest that time to worsening shows promise in detecting disease progression [Pulido, T., et al 2013] [Galie, N., et al 2015] [Sitbon, O., et al 2015] [Tapson, V. F., et al 2019].

The events chosen as components in the composite primary efficacy endpoint were included due to their robustness and their relative independence from differences in local practice.

5.3 Secondary Efficacy Endpoints and Rationale

Secondary Efficacy Endpoints

The secondary endpoints are ranked as follows:

1. Overall survival
2. Transplant-free survival
3. Proportion of participants who experienced a mortality event at EOS
4. Change from baseline in Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2.0 risk score at Week 24
5. Proportion of participants achieving a low or intermediate (≤ 7) REVEAL Lite 2.0 risk score at Week 24
6. Change from baseline in NT-proBNP levels at Week 24
7. Change from baseline in mean pulmonary artery pressure (mPAP) at Week 24
8. Change from baseline in PVR at Week 24
9. Proportion of participants who improve in WHO FC at the end of the DBPC Treatment Period
10. Change from baseline in 6MWD at Week 24
11. Change from baseline in cardiac output (CO) at Week 24
12. Change from baseline in EuroQoL-5 dimensions scale 5 levels (EQ-5D-5L) index score at Week 24

5.3.1 N-Terminal Prohormone B-Type Natriuretic Peptide Rationale

N-terminal prohormone B-type Natriuretic Peptide 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, RV function, and echocardiographic and hemodynamic variables, and it has been consistently shown to be an independent predictor of survival in PAH [Tiede, H., et al 2013] [Souza, R., et al 2007] [Souza, R., et al 2005]. 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 [Galie, N., et al 2017] [Chin, K. M., et al 2019].

5.3.2 Six-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 for regulatory approval of epoprostenol [Barst, R. J., et al 1996]. However, the utility of improvement in 6MWD as a primary outcome measure in clinical trials has become limited, particularly in more contemporary trials involving sequential, add-on therapies. In these studies, the change from baseline in 6MWD was smaller than the clinically relevant thresholds of around 30 m [Mathai, S. C., et al 2012], despite the significance achieved by morbidity and mortality outcomes [Pulido, T., et al 2013] [Galie, N., et al 2015] [Sitbon, O., et al 2015]. The 6MWD

is a component of many prognostic risk scores, but is generally included as absolute thresholds (for example, < 165 m, 165 to 440 m, and > 440 m) [Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A 2016] instead of changes from baseline.

5.3.3 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 (PAWP) of ≤ 15 mmHg and a PVR > 3 Wood units (WU) [Tiede, H., et al 2013]. 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 [Benza, R. L., et al 2019].

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 [Tiede, H., et al 2013].

5.3.4 Hemodynamic Parameters Rationale

Three prognostic hemodynamic variables will be assessed by right heart catheterization. The first of these is PVR, the values of which are used in the diagnosis and assessment of the prognosis of PAH. In general, WHO PAH Group 1 describes a group of PH patients characterized hemodynamically by the presence of precapillary PH, which is defined by a PAWP of ≤ 15 mmHg and a PVR> 3 WU [Chin, K. M., et al 2019]. Generally, PVR values < 5 WU are considered to be of good prognostic value. PVR is also a component used in the calculation of the REVEAL risk score [Souza, R., et al 2007]. Earlier trials, including PULSAR, have also used PVR as an endpoint, and decreases in PVR in response to treatment are positively associated with long-term transplant-free survival.

Mean pulmonary arterial pressure (mPAP) is essential to a diagnosis of PAH. Based on the 6th World Symposium on Pulmonary Hypertension, patients are at risk of PAH with an mPAP of 21 to 25 mmHg. Above a pressure of 25 mmHg, a diagnosis of PAH can be made if in conjunction with the above PAWP and PVR criteria.

Cardiac Output is a component of the PVR calculation. Along with right atrial pressure, it is the most important invasive measure to reflect prognosis. As such, it is a component of the REVEAL Risk Calculator. There is a very high risk of morbidity/mortality associated with reduced CO, and values of 4.0 to 8.0 L/min are considered normal.

5.3.5 REVEAL Lite 2.0 Risk Score Rationale

Risk assessment is important for the management of patients with PAH, and achievement of a low mortality risk status is the current goal of PAH treatment [Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A 2016] [Benza, R. L., et al 2019] [Benza, R. L., et al 2021] [Benza, R. L., et al 2012] [McLaughlin, V. V., et al 2018] [Hoeper, M. M., et al 2017]. The REVEAL risk calculator is commonly used to guide treatment decisions in this patient population, and has been validated to discriminate risk at diagnosis and throughout the course

of treatment. The REVEAL 2.0 and the REVEAL Lite 2.0 can predict both clinical worsening as well as mortality. The REVEAL Lite 2.0 is an abridged version of the REVEAL 2.0 that includes only noninvasive variables: renal insufficiency (by estimated glomerular filtration rate [eGFR]), WHO FC, systolic blood pressure (BP), heart rate, 6MWD, and NT-proBNP. Scores are assigned to each of these variables based upon their presentation and contribution to mortality risk, and a total score is obtained. Total scores of ≥ 8 indicate high risk; scores of 6 to 7 indicate intermediate risk, and scores of ≤ 5 indicate low risk. REVEAL 2.0 shows greater risk discrimination (c-index 0.76) than the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension method (c-index 0.62) or the French Pulmonary Hypertension Registry method (c-index 0.64). The development and validation of the REVEAL Lite 2.0 identified that the REVEAL Lite 2.0 risk assessment approximates the REVEAL 2.0 at discriminating low, intermediate, and high risk of mortality in patients in the REVEAL registry (c-index 0.73). The simplicity of this instrument makes it ideal for routine implementation in clinical practice to guide treatment decisions as well as appropriate for use as an endpoint for evaluating the effects of novel treatments on risk of morbidity/mortality. The REVEAL Lite 2.0 risk score calculator is presented in Appendix 2.

5.3.6 World Health Organization Functional Class Rationale

The WHO FC, despite its interobserver variability [Taichman, D. B., et al 2009], remains one of the most powerful predictors of survival not only at diagnosis but also during follow-up [Sitbon, O., et al 2002] [Nickel, N., et al 2012] [Barst, R. J., et al 2013]. 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 [Nickel, N., et al 2012] [Barst, R. J., et al 2013] [Benza, R. L., et al 2010].

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.

5.3.7 Quality of Life Assessments Rationale

Patient-reported outcome (PRO) instruments are essential tools to evaluate disease, treatment, and quality of life. Quality of life for PAH participants in this study will be assessed using the PRO measure EQ-5D-5L index score.

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 captures information directly from the respondent, thereby generating data that conforms to the general requirement of all PRO measures.

5.4 Exploratory Endpoints

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

- Number of PAH-related hospital days during the study
- Change from baseline in RV-pulmonary artery (PA) coupling at Week 24
- Change from baseline in biomarkers; including, but not limited to, serum biomarkers such as C-reactive protein (CRP) and Activin A at Week 24
- Proportion of participants achieving a low or intermediate-low COMPERA 2.0 4-strata risk score (Section 9.3.6) at Week 24

5.5 Safety Endpoints

Safety will be evaluated by collecting the following:

- AEs
- Anti-drug antibodies (ADAs)
- Laboratory assessments (hematology, serum chemistry, and 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, multicenter, parallel-group study to evaluate sotatercept versus placebo in participants with PAH WHO FC III or FC IV who are at high risk of mortality.

The study population includes participants with symptomatic PAH (WHO FC III or FC IV at high risk of mortality) 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 (CHD). Participants must have a REVEAL Lite 2.0 risk score of ≥ 9 and be on maximum tolerated combination background PAH therapy.

6.2 Duration of Study

Each participant will be enrolled in the study for up to approximately 43 months as follows:

- Screening Period (up to 4 weeks)
- DBPC Treatment Period (up to approximately 40 months)
- Follow-up Period (up to 8 weeks)

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 participants 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 as of the preplanned interim data cutoff of 14 January 2020.

Acceleron Pharma Inc.'s interpretation of the PULSAR safety data is that both dose levels are generally safe and well tolerated in participants 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; the 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 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, sotatercept will be administered at a starting dose of 0.3 mg/kg, with a target dose of 0.7 mg/kg, subcutaneously (SC) every 21 days plus background PAH therapy.

6.4 Study Design, Stratification, and Treatment Assignment

The study is divided into a Screening Period (up to 4 weeks), a DBPC Treatment Period (up to approximately 40 months), and a Follow-up Period (up to 8 weeks). Participants who have documented informed consent and meet all eligibility criteria will be stratified by REVEAL Lite 2.0 risk score and PAH subtype and then randomized to receive either placebo plus background PAH therapy or sotatercept plus background PAH therapy, as described in Section 6.6. Up to 166 participants will be randomly assigned in a 1:1 ratio to the 2 study treatment groups (83 participants per arm) to receive SC injections of either placebo or sotatercept every 21 ± 3 days, 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 will remain at this target dose level for all subsequent DBPC Treatment Period visits. All participants will remain on background PAH therapy during the study. Median participant time on study must be at least 6 months in order for analyses following the occurrence of the required number of events.

Study participants who have not experienced an event will remain in the DBPC Treatment Period until the required number of participants have experienced a first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization and the study is unblinded. During the DBPC Treatment Period, selected study visits may be performed as home health care (HHC) visits as described in Section 6.5.

When a participant experiences an event of PAH worsening-related hospitalization of ≥ 24 hours, the investigator must complete the Primary Endpoint Event Assessment electronic case report form (eCRF) page. An independent blinded adjudication committee will then adjudicate the event to determine whether the hospitalization is due to PAH. Upon confirmation, the participant will complete the EOT Visit and may be eligible to enroll into the open-label, long-term follow-up (LTFU) study, A011-12 (SOTERIA).

Rollover after site reporting of an event of PAH worsening-related hospitalization but prior to confirmation from the adjudication committee can be considered and will require consultation and written approval from the Sponsor. Upon written approval from the Sponsor, the participant will complete the EOT Visit and may be eligible to enroll into the open-label, LTFU study, A011-12 (SOTERIA).

Participants who experience an event of PAH worsening-related hospitalization of ≥ 24 hours and who do not wish to participate in the LTFU study A011-12 (SOTERIA) will complete the Follow-up Period including both the EOT and EOS Visits (Figure 1).

Participants who experience an event of lung transplantation will complete the Follow-up Period including both the EOT and EOS Visits (Figure 1).

The end of the DBPC Treatment Period will occur when the required number of participants have experienced a primary endpoint event, either for the interim analysis (IA) or the final analysis. If the Sponsor decides to stop the study early following the IA and Data Monitoring Committee (DMC) recommendation, all participants in the DBPC Treatment Period will be called in for their final visit(s), and the study will be terminated. If the study continues after the IA, the end of the DBPC Treatment Period will occur when the required number of participants have experienced a primary endpoint event for the final analysis.

At the end of the DBPC Treatment Period, participants who are currently on treatment (sotatercept or placebo) may be eligible to enroll into the LTFU study, A011-12 (SOTERIA) following completion of the EOT Visit. For these participants, the EOS Visit will be waived. If the participant does not choose to enroll into SOTERIA, they will complete the Follow-up Period including both the EOT and EOS Visits (Figure 1).

Participants who discontinue the DBPC Treatment Period early, without experiencing a primary endpoint event, will complete the EOT Visit at the time of discontinuation as specified in the SoE (Section 2) and EOS Visit (described in Section 9.2.3.2), provided that consent is not withdrawn. Following the EOT and EOS, or if the participant refuses to attend additional study visits, they will receive quarterly telephone contacts for vital status until the study is unblinded. These participants will not be eligible to enroll into the LTFU study, A011-12 (SOTERIA).

6.5 Home Health Care Visits

Select study visits (Visits 6 onward, except for Visit 9 and quarterly site visits) may be performed at the participant's home by a qualified health care professional if permitted by local and institutional regulations and requested by study participants that meet the criteria for HHC visits.

Starting at Visit 6, participants are eligible for HHC visits if dose modification/delays did not occur in the previous 2 consecutive visits. Guidelines for dose modification are described in Section 8.3.

If a dose modification is required at any time during the DBPC Treatment Period, the next 2 visits must be performed on site. The participant will be eligible for HHC visits again following 2 consecutive on-site visits without dose modification.

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 an HHC visit.

For HHC visits, hematology results are not required to be evaluated prior to study drug administration.

6.6 Randomization and Blinding

Participants who have documented informed consent and who meet all eligibility criteria will be stratified by REVEAL Lite 2.0 risk score and PAH subtype. They will then be randomized to receive either placebo to add to their background PAH therapy, or sotatercept to add to their background PAH therapy. Randomization assignments will be generated through a computerized system provided through Interactive Response Technology (IRT) (see the IRT Manual for details).

In the event of a medical emergency for an individual participant, where 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 the IRT Manual for further instruction). If the nature of the emergency does not permit consultation 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 is recommended to discuss the issue 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 into the LTFU study, A011-12 (SOTERIA). 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 III or IV at high risk of mortality), who present with idiopathic or heritable PAH, PAH associated with CTD, drug- or toxin-induced, post-shunt correction PAH, or PAH presenting at least 1 year following the correction of CHDs, will be eligible for this study. Participants must have a REVEAL Lite 2.0 risk score of ≥ 9 and be on maximum tolerated combination background PAH therapy.

PAH is considered a relatively rare condition, with approximately 80% of PAH patients presenting as WHO FC II to III. There is a low prevalence of PAH patients with WHO FC IV, and given their severe disease burden and their need for maximum PAH therapy, these patients have had a limited ability to participate in interventional studies. The study population selected will be receiving the maximum available standard-of-care therapies, which will provide the opportunity to assess the effects of sotatercept, on top of maximum available approved PAH therapies, on mortality and morbidity in a population with advanced PAH and limited to no opportunity for additional interventions.

This Phase 3 study is supported by data from the Phase 2 Study A011-09 (PULSAR; 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, PVR. Additionally, improvements were observed in 6MWD, NT-proBNP, and other endpoints.

7.2 Background PAH Therapy

Background PAH therapy refers to approved PAH-specific medications. Study participants must be stable on maximum tolerated double or triple combination background PAH therapy (per the investigator's judgment) for at least 30 days prior to the Screening Visit. Adjustments in parenteral prostacyclin doses by up to 10% are permitted and should not affect therapy stability determination.

This background PAH therapy should be combination therapy consisting of at least 2 agents (each from a different class) from a list including: endothelin-receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogs or receptor agonists.

7.3 Inclusion Criteria

Eligible participants must meet all of the following criteria to be enrolled in the study:

1. Age 18 to 75 years, inclusive

2. Documented diagnostic right heart catheterization 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 III or IV
4. REVEAL Lite 2.0 risk score of ≥ 9
5. Right heart catheterization performed during screening (or within 2 weeks prior to screening, if done at the clinical study site) documenting a minimum PVR of ≥ 5 Wood units and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of ≤ 15 mmHg
6. Clinically stable and on stable doses of maximum tolerated (per investigator's judgment) double or triple background PAH therapies for at least 30 days prior to screening
7. Females of childbearing potential must:
   - Have 2 negative urine or serum pregnancy tests as verified by the investigator prior to starting study therapy; must agree to ongoing urine or serum pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug
   - If sexually active with a male partner:
     - Used highly effective contraception without interruption; for at least 28 days prior to starting the investigational product AND
     - Agree to use the same highly effective contraception in combination with a barrier method 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

7.4 Exclusion Criteria

1. Diagnosis of PH WHO Groups 2, 3, 4, or 5
2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus-associated PAH and PAH associated with portal hypertension
3. Diagnosis of pulmonary veno-occlusive diseases or pulmonary capillary hemangiomatosis or overt signs of capillary and/or venous involvement
4. Hemoglobin at screening above gender-specific upper limit of normal (ULN), per local laboratory test
5. Baseline platelet count < 50,000/mm^3 (< 50.0 x 10^9/L) at screening
6. Baseline systolic blood pressure < 85 mmHg at Screening
7. Pregnant or breastfeeding women
8. Serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels > 3.0 × ULN
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 or known allergic reaction to sotatercept, its excipients, or luspatercept
11. History of pneumonectomy
12. This criterion has been removed
13. Untreated more than mild obstructive sleep apnea
14. History of known pericardial constriction
15. History of restrictive or congestive cardiomyopathy
16. Electrocardiogram (ECG) with Fridericia's corrected QT interval (QTcF) > 500 ms during the Screening Period
17. Personal or family history of long QT syndrome or sudden cardiac death
18. Left ventricular ejection fraction < 45% on historical echocardiogram within 1 year prior to the Screening Visit

19. Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) in the past 6 months prior to the Screening Visit
20. Cerebrovascular accident within 3 months prior to the Screening Visit
21. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease
22. Currently on dialysis or anticipated need for dialysis within the next 12 months

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 provide documented informed consent. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, 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. Rescreening must occur at least 1 week after the initial screening attempt. 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 linked to the human immunoglobulin G1 Fc domain. Sotatercept is the generic name assigned to ActRIIA-IgG1Fc. The laboratory code is ACE-011. The Chemical Abstracts Service Registry number for sotatercept is 1001080-50-7; the United States (US) Adopted Name and the International Nonproprietary Name 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 6.6.

PAH background therapy will not be provided as study treatment during the study. To be enrolled in the study, participants must be on stable PAH background therapy according to local practice. 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 for reconstituting the lyophilized sotatercept or its matching placebo. Each kit also contains ancillary components as follows:

- A swabable 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 1 of the following 2 treatment arms:

- Arm 1: Placebo administered 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

Prior to administration, the lyophilized sotatercept drug product (60 mg/vial) or matching placebo will be reconstituted with 1.3 mL of sterile water for injection. Reconstituted sotatercept yields a 50 mg/mL solution of sotatercept. Study intervention details are in Table 4.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Placebo (Arm 1)	Placebo Comparator	Placebo	Placebo	Injection, Powder, Lyophilized, For Solution	0 mg	0 mg Q3W	SC	V1 to EOT/EOS	Placebo	IMP	Central
Sotatercept (Arm 2)	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 mg/kg Q3W	SC	V1	Test Product	IMP	Central
Sotatercept (Arm 2)	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.7 mg/kg Q3W	SC	V2 to EOT/EOS	Test Product	IMP	Central

EOS=end of study; EOT=end of treatment; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; SC=subcutaneous; TBD=to-be-determined; V=Visit.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area. A. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
Sotatercept dose reductions (from 0.7 to 0.3 mg/kg) due to a safety event are described in Section 8.3.2, 8.3.3 and 8.3.4. Sotatercept dose re-escalation may occur according to Section 8.3.6.

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. Guidance for dose modifications and dose delays are summarized in Figure 3 and Figure 4. For safety reasons other than those listed in Figure 3 and Figure 4, dose delays followed by dose reductions can be implemented at any time per the investigator's assessment.

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, except for Visit 1.

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 or Section 8.3.3 are met. However, if at Visit 2 Hgb increases by more than 2.0 g/dL from the previous dosing visit 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 the previous dosing visit 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 the previous dosing visit 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 2 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 DBPC 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 increase more than 4 g/dL above the participant's baseline value, the study Medical Monitor should be consulted, and treatment discontinuation should be considered; if Hgb increases greater than 2g/dL and above the gender-specific ULN, dose hold should be applied for at least 1 visit, and the Medical Monitor should be consulted. Refer to Figure 3 for additional details.

8.3.3 Dose Modifications Due to Low Platelet Count

From Visit 3 onwards, 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 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 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 1 visit if the participant was receiving 0.7 mg/kg study drug, or for 3 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.

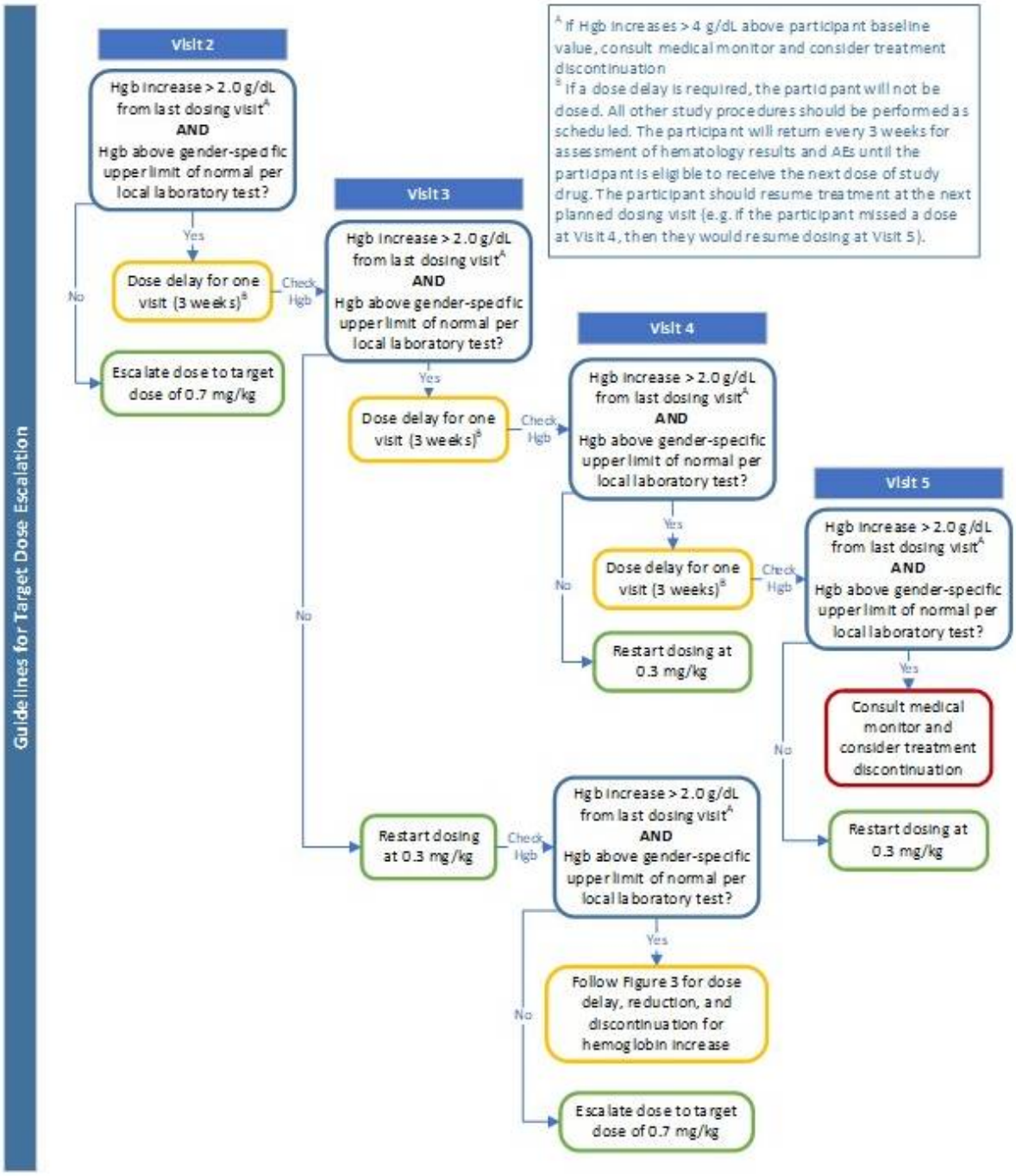
8.3.5 Dose Delays Due to SAEs of Bleeding

In cases of serious active bleeding, the dose of study intervention should be delayed until the event resolves. If more than one dose delay due to a serious bleeding event occurs, then the Medical Monitor should be consulted.

8.3.6 Dose Re-escalation Following Dose Reduction

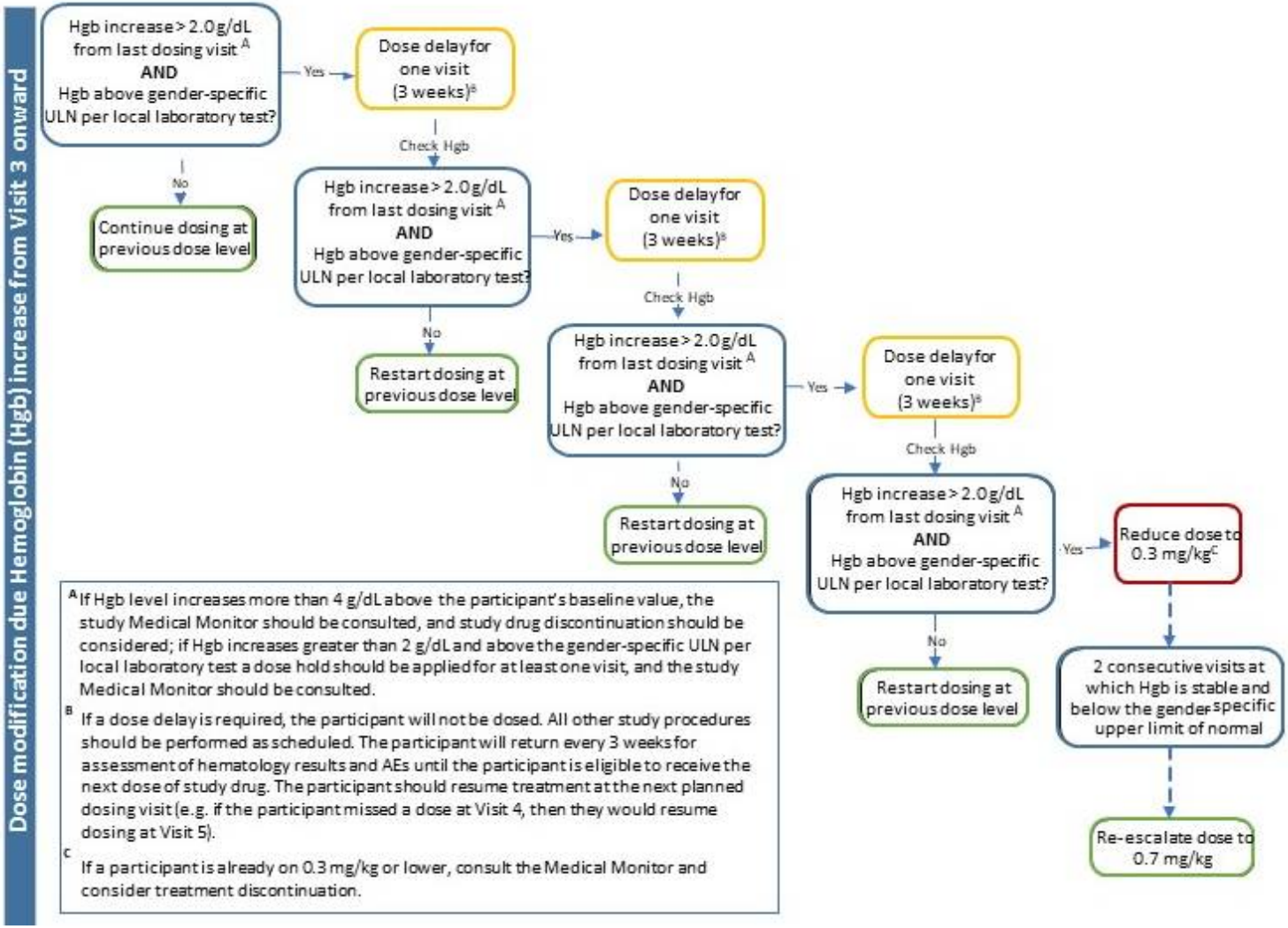
In cases of dose reduction due to an AE not related to study drug, the dose can be re-escalated when the AE is resolved. In cases of dose reduction due to increases in Hgb, the dose will be re-escalated to 0.7 mg/kg after 2 consecutive visits at which Hgb values are stable and equal to or lower than the ULN (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 (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)



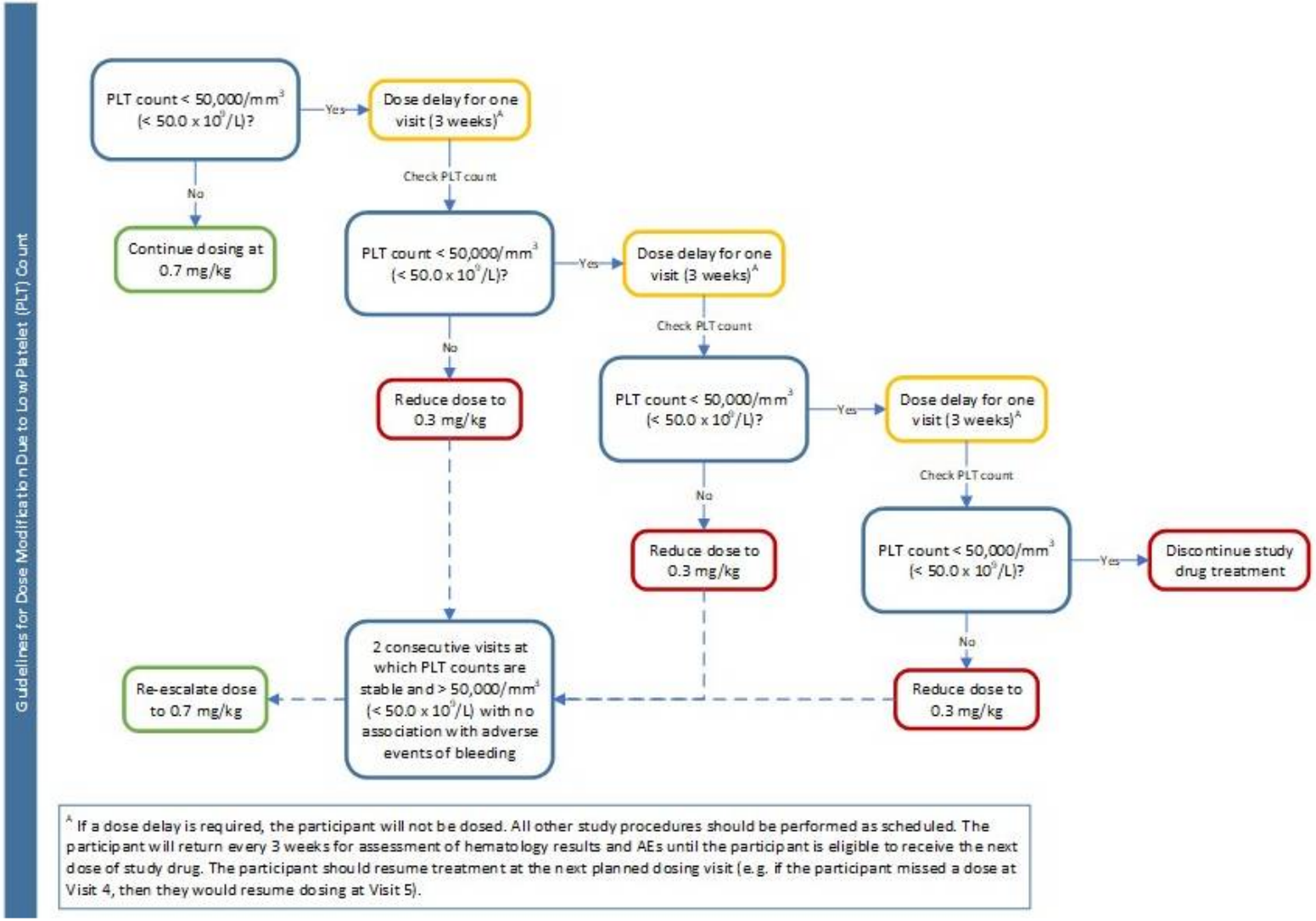
AE = adverse event; Hgb = hemoglobin.

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



AE = adverse event; Hgb = hemoglobin.

Figure 4 Guidelines for Dose Modification Due to Low Platelet Count From Visit 3 Onward



AE = adverse event; PLT = platelet.

8.3.7 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 to allow for drug accountability to be completed by the monitor. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed. 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.'s approval. Either method must be documented on the drug accountability log.

The study will meet all applicable regulatory requirements for study drug accountability.

9 STUDY CONDUCT

9.1 General Instructions

- Study procedures and their timing are summarized in the SoEs (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 SoEs, 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 provide documented 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 (Table 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 right heart catheterization, when possible (right heart catheterization should be performed last and after all other Screening procedures are done, when possible, as described below and in the SoE).

Screening procedures may be performed and completed over the course of several days for the Screening Visit, as long as all Screening procedures are completed within the 4 weeks (28 days) immediately preceding Visit 1.

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

Screening procedures include the following:

- Informed consent
- Inclusion/exclusion criteria
- Medical history review
- Physical examination
- 12-lead ECG
- Vital signs, including weight
- Two serum or urine pregnancy tests (where applicable)
- Hematology (complete blood cell [CBC] count)
- Serum chemistry
- Urinalysis
- Six-Minute Walk Test (6MWT)
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- REVEAL Lite 2.0 risk score assessment
- ADA sample collection
- Right heart catheterization
- Echocardiogram
- AE/serious adverse event (SAE) review
- Concomitant medication review

9.2.2 Double-blind, Placebo-controlled Treatment Period (Until Event Occurrence)

Study procedures for Visits 1 to 9 vary dependent on the visit number and must be completed per the SoEs (Table 2). All study procedures/assessments must be performed prior to the administration of the study drug unless otherwise noted.

9.2.2.1 Visit 1

Visit 1 procedures include the following:

- Randomization
- Targeted cardiopulmonary and skin physical examinations

- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Serum chemistry
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection; samples will be collected predose and at 1 to 2 hours, 2 to 4 hours, and 4 to 8 hours postdose
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.2 Visit 2 (21 ± 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 the following:

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

9.2.2.3 Visits 3 and 4 (21 ± 3 days)

Visit day windows are relative to the date of the previous dose of study drug: every 21 days (± 3 days). Visit 3 and 4 procedures include the following:

- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- WHO FC assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.4 Visit 5 (21 ± 3 days)

Visit 5 procedures include the following:

- Targeted cardiopulmonary and skin physical examinations
- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection
- Study drug administration
- AE/SAE review

- Concomitant medication review

9.2.2.5 Visits 6 Through 8 (21 ± 3 days)

Visits 6 through 8 may be performed as HHC visits for eligible participants; refer to Section 6.5 for details.

Visits 6 through 8 procedures include the following:

- Serum or urine pregnancy test (where applicable)
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.6 Visit 9 (21 ± 3 days)

The procedures at Visit 9 (6-month site visit) include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-lead ECG
- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection
- Right heart catheterization
- Echocardiogram
- Study drug administration
- AE/SAE review

- Concomitant medication review

9.2.2.7 Visits 10 Through 12 (21 ± 3 days)

Visits 10 through 12 (HHC eligible) procedures include the following:

- Serum or urine pregnancy test (where applicable)
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.8 Visit 13 (21± 3 days)

The procedures at Visit 13 include the following:

- Targeted cardiopulmonary and skin physical examinations
- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.9 Visits 14 Onward (21 ± 3 days)

Visits 14 onward, except for quarterly site visits, may be performed as HHC visits for eligible participants.

The procedures for non-quarterly visits (Visits 14, 15, 16, 18, 19, 20, etc.) include the following:

- Serum or urine pregnancy test (where applicable)
- Study drug administration
- AE/SAE review
- Concomitant medication review

The procedures for quarterly site visits (Visits 17, 21, 25, etc.) include the following:

- Targeted cardiopulmonary and skin physical examinations
- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection
- Echocardiogram (Visit 25 only)
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.3 Follow-up Period (up to 8 Weeks)

9.2.3.1 End of Treatment Visit (21 ± 7 Days from Last Dose)

The EOT Visit is recommended to occur 21 days (±7 days) after the last study drug administration in the DBPC Treatment Period. The procedures at the EOT Visit include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-lead ECG
- Vital signs, including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK and Activin A sample collection
- Echocardiogram (if an echocardiogram has been performed in the past 3 months, it may be exempted at the EOT Visit)
- AE/SAE review
- Concomitant medication review

9.2.3.2 End of Study Visit (5 Weeks ± 7 Days After EOT Visit)

Participants who discontinue early, experience an event of lung transplantation, or do not wish to participate in the LTFU study, A011-12 (SOTERIA), will complete both the EOT and the EOS Visits. The EOS Visit is recommended to occur 5 weeks (± 7 days) after the EOT Visit. Reasons for early discontinuation are described in Section 9.4.1.

The procedures for the EOS Visit include the following:

- Targeted cardiopulmonary and skin physical examinations
- Vital signs, including weight

- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- EQ-5D-5L assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- AE/SAE review
- Concomitant medication review

9.3 Description of Study Procedures

9.3.1 12-Lead Electrocardiogram

A single 12-lead ECG will be obtained at study visits as outlined in the SoEs and will be transferred to a central laboratory for reading and interpretations. Parameters obtained will be heart rate, QRS, and QT interval (QTcF).

- Clinically significant abnormal findings will be reported as AEs.
- At visits where both ECGs and 6MWT assessments are done ECGs should be performed prior to 6MWT.

9.3.2 Six-Minute Walk Test

The 6MWD will be measured by the 6MWT during the Screening period and at multiple timepoints (See Table 2). During the Screening Period, the 6MWT should be performed twice, unless deemed inappropriate by the investigator based on the participant's disease state, at least 4 hours, but no longer than 1 week, apart. The average of the two 6MWDs should be used for the REVEAL Lite 2.0 calculation (Appendix 2).

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 [Singh, S. J., et al 2014] [American Thoracic Society 2002]. 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).

If the participant discontinues the test prematurely, the time (mm:ss) and distance walked will be recorded. Requirement of acute supportive rescue medication (e.g., oxygen therapy) and any AEs occurring during the 6MWT 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 the Screening Visit and Visit 9, including chronic oxygen therapy and the 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 4 for additional details.

9.3.3 Borg Dyspnea Scale

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

9.3.4 World Health Organization Functional Class Assessment for Pulmonary Hypertension

The modified NYHA/WHO classification of functional status is used to provide information about how affected an individual is by their disease [Stuart, R. 1998]. The 4 FCs that are used to rate how ill a PAH participant is are detailed in Table 5.

Table 5 NYHA/WHO FC Assessment for PAH

NYHA/WHO Functional 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.

FC = functional class; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; WHO = World Health Organization;

Note: NYHA/WHO functional class is modified after NYHA functional assessment.

9.3.5 REVEAL Lite 2.0 Risk Score

REVEAL Lite 2.0 [Benza, R. L., et al 2019] [Benza, R. L., et al 2021] risk score assessment uses noninvasive variables to determine the risk score for classification into a risk category. REVEAL Lite 2.0 will be calculated using central laboratory NT-proBNP, central laboratory eGFR, WHO FC, systolic BP, heart rate, and 6MWD (Appendix 2). Sites will use this score to ensure that entry criterion 4: REVEAL Lite 2.0 risk score ≥ 9, is met by the participant at enrollment. Sites will only be required to calculate the REVEAL Lite 2.0 risk score at Screening. The Sponsor will calculate the REVEAL Lite 2.0 risk score for all other study visits (Visits 1 to 5, Visit 9, quarterly site visits, EOT Visit, and EOS Visits). Importantly, the Screening NT-proBNP and eGFR samples should be taken at the initial Screening Visit and should be submitted to the central laboratory for analysis as soon as possible to ensure availability of results prior to randomization.

9.3.6 COMPERA 2.0 Four-Strata Risk Score

The Comparative, Prospective Registry of Newly Initiated Therapies for PH (COMPERA) 2.0 4-strata risk score is based on WHO FC, 6MWD and NT-proBNP. This 4-strata model was developed and validated in PAH patients for whom all 3 variables are available. Based on the cut-off levels proposed in the 2022 ESC/ERS guidelines [Humbert, M., et al 2022], each variable is graded from 1 to 4, where 1 defines low risk, 2 intermediate-low risk, 3 intermediate-high risk and 4 high risk. The final risk score value is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer. Participants will be categorized as low, intermediate–low, intermediate–high, or high risk depending on the final risk score value. Sites will not be required to calculate the COMPERA 2.0 4-strata risk score. The Sponsor will calculate the 4-strata risk score risk score at Screening and Visit 9 [Hoeper, M. M., et al 2022] [Boucly, A., et al 2022].

9.3.7 Echocardiogram Parameters

Two-dimensional echocardiogram parameters will include but not be limited to: tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), RV fractional area change, and RV end diastolic area. An echocardiogram performed during the Screening Period is used as the baseline for this study. Right ventricular-pulmonary artery coupling will be assessed by evaluating the relationship between TAPSE and PASP (TAPSE/PASP). Right ventricular-pulmonary artery coupling is a noninvasive measure of end systolic arterial elastance and is a reflection of RV diastolic stiffness. Prognosis declines with a value < 0.31 mm/mmHg.

All echocardiograms performed after Screening can be performed on the day of the study visit or within 1 week prior to study drug administration. The echocardiogram parameters review process will be performed by a central vendor, according to the Study Manual.

9.3.8 Patient-reported Outcomes

9.3.8.1 EuroQoL - 5 Dimensions Scale 5 Levels Assessment

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

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

In the description part, health status is measured in terms of 5 dimensions: 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 the "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 analog scale.

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

9.3.9 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 visits that occur after Screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.10 Vital Signs

Vitals signs will be collected before blood collection and study treatment administration and include the following (refer to the Study Manual for more details):

- Temperature, pulse rate, respiratory rate, BP, and weight will be assessed at study visits as outlined in the SoEs. Weight will be measured in indoor clothing but

without shoes. Dose will be calculated based on the participant's most recently recorded weight.

- BP and pulse measurements will be assessed while seated after a period of rest in a quiet setting with no distractions (e.g., television and 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).

9.3.11 NT-proB-type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a hormone produced by the heart. NT-proBNP is a nonactive 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 SoEs and will be shipped and analyzed by a central laboratory. The Screening NT-proBNP sample should be taken at the initial Screening Visit and should be submitted to the central laboratory for analysis as soon as possible to ensure availability of results prior to randomization.

9.3.12 Activin A Assessments

Genetic mutations in the BMPR2 are associated with the majority of the familial form of PAH and approximately 25% of idiopathic PAH. Specifically, the impairment of the BMPR2-associated signal pathway appears to lead to the uncontrolled proliferation of pulmonary VSMCs, the principal cause of PAH. These data strongly suggest a key role of transforming growth factor-β family members in the pathogenesis of PAH. Sotatercept acts to block activin ligands and GDFs, may attenuate BMPs, and improve pulmonary vascular remodeling by restoring balance to Smad signaling. The assessment of ligand-trapping activity of sotatercept is therefore important and can provide better understanding in its role in disease modification.

Activin A is a ligand that is bound by sotatercept. Serum Activin A levels correlate with sotatercept ligand-trapping activity. Samples for analysis of Activin A will be collected as described in the SoEs and will be shipped and analyzed by a central laboratory.

9.3.13 C-Reactive Protein

C-reactive protein is a non-specific marker of inflammation and tissue damage and is a well-accepted indicator of cardiovascular risk [Quarck, R., et al 2009] [Labarrere, C. A. 2004] [Elstein, D., et al 2005]. Elevated CRP predicts risk of recurrent ischemia and death in patients with atherosclerosis and is associated with systemic inflammation in patients with chronic obstructive pulmonary disease. Circulating CRP is increased in PAH patients as compared to control patients. In a small study analyzing data from 57 participants with PAH, a potential role of CRP levels in predicting response to therapy and in survival was identified.

In this study, the participants who exhibited CRP levels that were decreased to under the ULN following treatment initiation had significantly better survival, a decrease in New York Heart Association FC, and an increase in cardiac index.

Samples for CRP analysis will be collected as described in the SoEs and will be shipped and analyzed by a central laboratory.

9.3.14 Anti-Drug Antibody Assessments

Anti-drug antibody samples will be collected as outlined in the SoEs and will be analyzed by a central laboratory. Participants may be asked to return for additional ADA testing after their last visit if there is any indication of potential immunogenicity-related safety concern.

9.3.15 Pharmacokinetics Measurements

Serum samples will be collected for measurement of serum concentrations of sotatercept as specified in the SoEs. 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 Acceleron Pharma Inc. The actual date and time (24-hour clock time) of each sample collection 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.

9.3.16 Right Heart Catheterization Assessment

Right heart catheterization assessments will be performed as outlined in the right heart catheterization 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 CO. Left ventricular end-diastolic pressure may be substituted for mean PCWP if mean PCWP is not reliable. The following hemodynamic parameters will be assessed when the participant is in a stable hemodynamic rest state (as demonstrated by 3 consecutive CO measurements within 10% of each other) while the participant is breathing ambient air or oxygen:

- Right atrial pressure, mPAP, mean PCWP, systolic pulmonary artery pressure (PAP), diastolic PAP, SvO_2, and heart rate
- Cardiac output measured in triplicate by the thermodilution technique or by the Fick method (the same method must be used for all right heart catheterization assessments for each participant)

PVR will be calculated and populated in the eCRF. RV pressure data from the right heart catheterization 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, right heart catheterization at the Screening Period should be performed last and after all Screening tests for eligibility are done, when possible. All right heart catheterizations 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, right heart catheterization should be performed last, when possible.

9.3.17 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 case report form (CRF). These steps should be completed by the investigator prior to study drug administration from Visit 1 onwards.

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

9.3.17.1 Hematology

Hematology (CBC) laboratory assessments will be collected and analyzed locally at the investigative sites and will be measured at every visit as outlined in the SoEs. Complete blood cell count includes red blood cells (RBCs), absolute white blood cells (WBCs), Hgb, hematocrit (Hct), and platelet count.

9.3.17.2 Serum Chemistry

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 SoEs and should be drawn prior to dosing. Blood urea nitrogen (BUN), creatinine, total bilirubin, direct bilirubin, AST,

ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, follicle-stimulating hormone (FSH), albumin, and HCO_3 will be measured. Investigators must review the results to monitor the participant's safety.

9.3.17.3 Urinalysis

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

9.3.17.4 Pregnancy Testing

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

9.3.18 Clinical Event Information

To ensure current and complete clinical event information is available at the time of database locks, updated information may be requested during the study by the Sponsor. For example, occurrence of clinical events including efficacy, safety, hospitalizations, lung transplantation, and death may be requested before but not limited to, an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their clinical information.

If a participant withdraws consent or is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations, unless the participant has specifically withdrawn consent for collection of vital status data.

9.4 Discontinuation and Withdrawal Criteria

9.4.1 Participant Early Discontinuation

Early discontinuation of study treatment refers to permanently stopping study drug administration without experiencing lung transplantation or PAH worsening-related hospitalization of $\geq$ 24 hours during the DBPC Treatment Period, or before the trial has been unblinded for participants to rollover into the LTFU Study, A011-12 (SOTERIA).

The reason for early discontinuation from treatment must be recorded in the corresponding participant's eCRF. The investigator must notify Acceleron Pharma Inc. and the Medical Monitor when a participant discontinues treatment or withdraws from the study. Reasons that may lead to discontinuation from the study treatment include the following:

- AE If a participant discontinues due to a drug-related 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
- An increase in QTcF of > 60 ms that results in QTcF > 500 ms (or > 550 ms if a 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 sponsor
- Lost to follow-up
- Death

All participants who discontinue study treatment early, without experiencing a primary endpoint event, should complete the EOT Visit at the time of discontinuation as specified in the SoE (Section 2) and EOS Visit (described in Section 9.2.3.2), provided that consent is not withdrawn. Following the EOT and EOS Visits, or if the participant refuses to attend additional study visits, they will receive quarterly telephone contacts for vital status until the study is unblinded. These participants will not be eligible to enroll into the LTFU study, A011-12 (SOTERIA).

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.

A participant who experiences an event of PAH worsening-related hospitalization of ≥ 24 hours is considered to have completed the study if they completed the EOT Visit and enroll into the LTFU study, A011-12 (SOTERIA), or if they decline enrollment into SOTERIA and completed the Follow-up Period including both the EOT and EOS Visits.

A participant who experiences an event of lung transplantation is considered to have completed the study if they completed the Follow-up Period including both the EOT and EOS Visits.

Participants who discontinue the study early, who experience an event of lung transplantation, and who decline enrollment into the LTFU study, A011-12 (SOTERIA) will be asked to return to the clinic for the EOS Visit. The end of the study is defined as when the last participant completes the last visit.

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.

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, 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, including for PAH, as outlined in the study inclusion criteria (Section 7.3). There are no restrictions on concomitant medications in this study. If there is an immediate clinical need during the study to prescribe a new medication or a new dosage of an existing medication for either a new or worsening pre-existing condition, concurrent therapy may be administered at the discretion of the investigator. The investigator may consult the Medical Monitor regarding what constitutes a stable dose or a chronic condition. After documenting the ICF, information regarding concomitant medications will be collected in the eCRF.

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. reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion.

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. 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) regulations.
- 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 and 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

Pre-existing 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 pre-existing 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 1 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 providing documented 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, and 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 pre-existing condition unrelated to the studied indication
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above

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 1 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; incapacitating; potentially 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 maximum sotatercept concentration (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 Tmax 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 when documented informed consent is provided. 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 one diagnosis. All AEs and SAEs reported after documented informed consent is provided to the EOS Visit are to be reported and documented on the AE eCRF. Any AE related to a protocol procedure should be marked as such on the eCRF.

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic

procedures will be recorded on the AE eCRF. Any clinically relevant changes in laboratory assessments or other clinical findings as described 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 overdose and cancer (serious and non-serious) and all SAEs, a paper SAE Report Form must be completed with a concise account of the event 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 paper SAE Report 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 of 24 hours after becoming aware of the event, inform Acceleron Pharma Inc. via the contract research organization by entry on the eCRF or, if not available, by telephone or email. An initial study-specific paper SAE Report Form must also be submitted within 24 hours of becoming aware of the event.

All written reports must be transmitted using the study-specific paper SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, email addresses, and telephone numbers for SAE reporting are located on the paper SAE Report Form and in the completion instructions provided for the Investigator Site File. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by 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 and concomitant therapy). In all cases, the information provided in the paper 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 or Medical Monitor, or an Acceleron Pharma Inc. pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

For overdose and cancer (serious and non-serious) and all SAEs, a paper SAE Report Form must be completed with a concise account of the event and submitted within the timeframe described in this section.

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 paper SAE Report 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, A011-12 (SOTERIA), 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 submit 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 guidance, 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. Any dose exceeding that of the study-prescribed dose is considered an overdose (see current IB).

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. Additionally, the Serious Adverse Event Reporting Form must be submitted within the same timeframe. This form is to be submitted to the PPD PVG at the email address found at the bottom of the form.

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 current 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 treatment, unless the participant is enrolled in the SOTERIA study. If the participant is enrolled in SOTERIA after completion of this study, pregnancy will be reported and followed up in SOTERIA. 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, and 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

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 will be included in safety monitoring in the sotatercept clinical trial. For further information, consult the current 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 Event of Special Interest

Monitoring of the AESI is detailed in Table 6.

Based on review of safety data from the PULSAR and STELLAR studies, and the adequacy of routine safety monitoring described above, hepatic toxicity, leukopenia, and neutropenia are no longer considered as AESIs and will be followed by routine medical monitoring and signal detection activities.

Table 6 Monitoring of Adverse Events of Special Interest

Description	Monitoring Parameters
Telangiectasia	Any investigator who reports an AE of telangiectasia (spider veins, spider naevi) must complete a customized page in the eCRF. Investigators are strongly encouraged to have the participant evaluated by a dermatologist, or other appropriate specialist, and to consider photo-documentation of the affected skin.

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 evaluate sotatercept when added to maximum tolerated background PAH therapy in participants with PAH WHO FC III or IV at high risk of mortality.

Planned statistical analyses to be conducted are outlined in the sections that follow. Additional details 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

The sample size determination is based on the primary efficacy endpoint of time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours using EAST® version 6.4. In STELLAR, the hazard ratio in the sotatercept group compared with the placebo group was 0.16 (95% CI: 0.08 to 0.35) [Hoeper, M. M., et al 2023]. Given the differences in the populations and definitions of endpoints between STELLAR and this study, the hazard ratio is assumed to be 0.55 in this study. Assuming a hazard ratio of 0.55, a 1:1 randomization, a 1-sided 0.025 Type 1 error rate, 90% power, and with a planned IA at approximately 50% of the required number of events with the option to stop the study for futility, approximately 118 events will be required based on the log-rank test.

Given that approximately 166 participants are planned to be enrolled in this study, the accrual period is approximately 26 months, assuming an accrual rate of approximately 6.5 participants per month. In addition, assuming a dropout rate of 0.04% per month (0.5% per year), and the probability of observing an event for placebo is 0.45 for the first year, 0.60 for the second year, and 0.90 for the third year and later, the projected time of the IA will occur around 26 months. If the study continues after IA, the final analysis will happen around 40 months. Another criterion for conducting the IA is that median participant time on study must be at least 6 months in order for analyses following the occurrence of the required number of events.

11.3 Populations for Analysis

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

- **Full Analysis Set (FAS):** All randomized participants. 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 are administered.

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, the aligned rank stratified Wilcoxon test [Mehrotra, D. V., et al 2010] [Hodges, J. L., Jr. and Lehmann, E. L. 1962] will be used for continuous variables; Cochran-Mantel-Haenszel test will be used for dichotomous variables; the stratified log-rank test by the randomization factor and Cox regression methods will be used for time-to-event variables. For the primary endpoint, efficacy results are deemed to be statistically significant after consideration of controlling the overall 1-sided Type 1 error to be at 0.025. For the secondary endpoints, statistical tests performed will use 1-sided tests at the 0.025 significance level. Statistical analyses of efficacy data will be performed on the FAS. Pooling strategy of the randomization strata might be added in the SAP if the data is too sparse across the strata.

11.5 Study Endpoints

11.5.1 Primary Endpoint

Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥ 24 hours, will be analyzed using a stratified log-rank test with randomization factors as strata.

The point estimate of the hazard ratio with 95% CI will be estimated by a Cox regression model stratified by the randomization factors.

11.5.1.1 Handling of Censored Data

Participants who do did not experience any of the components of the primary endpoint at the time of the data cutoff will be censored. Participants who withdraw from the study or lost to follow-up before experiencing any of the components of the primary endpoint will be censored at the last known study contact record. Additional details on the handling of censored data will be described in the SAP.

11.5.2 Secondary Endpoints

The secondary endpoints are ranked and analyzed as follows:

1. Overall survival will be analyzed using the stratified log-rank test with randomization factors as strata. Supportive analyses will include the inverse probability of censoring weights (IPCW) [Robins, J. M. and Finkelstein, D. M. 2000] and 2-stage, rank preserving structural failure time (RPSFT) methods [Robins JM, Tsiatis AA. 1991].

2. Transplant-free survival will be primarily analyzed using the stratified log-rank test with randomization factors as strata. Supportive analyses will include the IPCW and 2-stage, RPSFT methods [Robins JM, Tsiatis AA. 1991].
3. Proportion of participants who experience a mortality event at EOS will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization factors.
4. Change in REVEAL Lite 2.0 risk score at 24 weeks from baseline will be analyzed using an aligned rank stratified Wilcoxon test with the randomization factors as strata.
5. Proportion of participants achieving a low or intermediate (≤7) REVEAL Lite 2.0 risk score at 24 weeks will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization factors.
6. Change in NT-proBNP levels at 24 weeks from baseline will be analyzed using the aligned rank stratified Wilcoxon test with the randomization factors as strata.
7. Change in mPAP at 24 weeks from baseline will be analyzed using the aligned rank stratified Wilcoxon test with the randomization factors as strata.
8. Change in PVR at 24 weeks from baseline will be analyzed using the aligned rank stratified Wilcoxon test with the randomization factors as strata.
9. Proportion of participants who improve in WHO FC at the end of the DBPC Treatment Period will be analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization factors.
10. Change in 6MWD at 24 weeks from baseline will be analyzed using the aligned rank stratified Wilcoxon test with the randomization factors as strata.
11. Change in CO at 24 weeks from baseline will be analyzed using the aligned rank stratified Wilcoxon test with the randomization factors as strata.
12. Change in EQ-5D-5L index score at 24 weeks from baseline will be analyzed using the aligned rank stratified Wilcoxon test with the randomization factors as strata.

A gatekeeping method will be used to control the Type 1 error rate in secondary endpoints by testing in the order of the secondary endpoints listed above, after successful testing for the primary endpoint at IA or final analysis. Secondary endpoint testing will be performed using a 1-sided alpha = 0.025 level proceeding successively in the order of the secondary endpoints listed above 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:

- The number of PAH-related hospital days during the study will be analyzed using a Poisson regression model.
- The change in echocardiogram parameter data describing RV-PA coupling (TAPSE/PASP) at 24 weeks from baseline

- The change in biomarker data at 24 weeks from baseline
- Proportion of participants achieving a low or intermediate-low COMPERA 2.0 4-strata risk score (Section 9.3.6) at 24 weeks

All exploratory endpoints will be summarized using descriptive statistics. No adjustments for multiplicity will be performed for statistical analyses of exploratory endpoints.

11.5.4 Estimands

The estimands of this study were constructed in accordance with ICH E9 (R1).

The Treatment and Population attributes of all estimands in this study are as follows:

Treatment: Sotatercept or placebo on top of background PAH therapy.

Population: Adults with PAH WHO FC III or FC IV.

The Endpoint, Intercurrent Events, and Population-level Summary attributes for each estimand are provided below.

11.5.4.1 Estimand for Time-to-Event Endpoints

Endpoints:

- Primary endpoint: Time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours.
- Secondary endpoints:
  - Overall survival, defined as the time to date of death due to any cause
  - Transplant-free survival, defined as the time to the first lung transplantation or death from any cause

Intercurrent events: Changes in treatment (dose reduction, dose delay, discontinuation from sotatercept or placebo, or changes to background PAH therapy); a treatment policy strategy will be used. Thus, the endpoint is of interest regardless of changes in treatment.

Population-level summary: Hazard ratio (sotatercept relative to placebo)

11.5.4.2 Estimand for Continuous Secondary Endpoints

Endpoints: Change from baseline at Week 24 in each of the following, with death prior to Week 24 represented quantitatively by any fixed worst-rank change from baseline to reflect the worst clinical outcome:

- REVEAL Lite 2.0 risk score
- NT-proBNP

- mPAP
- PVR
- 6MWD
- CO
- EQ-5D-5L index score

Intercurrent events:

- Changes in treatment: Same as for the estimand for the time-to-event endpoints.
- Death: A composite strategy will be implemented, in which the occurrence of death is incorporated into the definition of the endpoint.

Population-level summary: The midpoint of the distribution of the variable/endpoint noted above, compared between treatment conditions using a difference (sotatercept minus placebo) in midpoints; this between-treatment difference is referred to in statistical terms as the location-shift parameter.

11.5.4.3 Estimand for Binary Secondary Endpoints

Endpoints: Indicator (yes/no) of meeting each of the following:

- Achievement of a low or intermediate [≤ 7] REVEAL Lite 2.0 risk score at Week 24, where death prior to Week 24 is defined as not having met the criteria
- Mortality event
- Improvement in WHO FC, where death prior to the end of the DBPC Treatment Period is defined as not having met the criteria

Intercurrent events:

- Changes in treatment: Same as for the estimand for the time-to-event endpoints
- Death (applicable to only the first and third binary endpoints): A composite strategy will be used, such that anyone who dies prior to Week 24 without having had the endpoint is considered to be a failure.

Population-level summary: The difference (sotatercept minus placebo) in proportions of patients achieving responses.

11.6 Analysis of Safety

All safety analyses will be performed on the Safety Set. All participants will be analyzed according to the treatment they are administered.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE 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 (TEAEs) leading to death or discontinuation from treatment, TEAEs related to investigational product, and serious TEAEs will be summarized separately.

Clinical laboratory results will be summarized descriptively by treatment 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, standard deviation, standard error of the mean, median, minimum, and maximum) 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 arm.

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, maximum plasma concentration, 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 and PK/PD Data Analysis Plan.

11.8 Interim Analysis

An IA of the primary efficacy endpoint is planned to occur when approximately 59 participants have experienced a primary endpoint event (roughly 50% of the required number of events) and the median participant follow-up time is at least 6 months. A stratified log-rank test with randomization factors as strata will be used for the analysis of the primary efficacy endpoint. The point estimate of the hazard ratio with 95% CI will be estimated by a Cox regression model stratified by the randomization factors.

The IA will be performed by an unblinded independent statistics provider and will be presented to the DMC where a recommendation will be communicated to the Executive

Oversight Committee (EOC), which is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study. Table 7 shows the boundary properties for the planned interim and final analysis of the primary endpoint. The efficacy boundary is derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds [Lan, K. K. G. and DeMets, D. L. 1983] and the futility boundary is derived using a gamma family spending function approximating Hwang-Shi-Decani bounds [Hwang, I. K., et al 1990] with gamma = -7. If the actual number of events at the IA and final analysis differ from those specified in the table, the bounds will be adjusted using this spending function evaluated at the observed information fraction (fraction of observed over expected final events) at each analysis.

Table 7 Efficacy and Futility Boundaries and Properties for the Primary Endpoint

Analysis	Value	Efficacy	Futility
IA: 50% [a] information fraction Required events: 59 Timing: 26 months N: 166	Z	2.963	-0.458
	p (1-sided)[b]	0.0015	0.677
	HR at boundary[c]	0.461	1.127
Final Analysis: Required events: 118 Timing: 40 months N: 166	Z	1.969	NA
	p (1-sided)	0.0245	NA
	HR at boundary	0.695	NA

HR = hazard ratio; IA = interim analysis. The number of events and timings are estimated.
a Percentage of total planned events at the IA.
b p (1-sided) is the nominal α for group sequential testing.
c The HR at boundary is the approximate HR required to reach an efficacy/futility bound.

If the efficacy boundary is crossed for the primary endpoint at the IA, then analyses of secondary endpoints will be performed using a gatekeeping method as described for secondary endpoints in Section 11.5.2. The 1-sided Type 1 error rate for the evaluation of secondary endpoints should be 0.025.

11.9 Subgroup Analysis

Analyses of the primary endpoint will be conducted on the following subgroups provided the sample size in the subgroup category is at least 16:

- Baseline REVEAL Lite 2.0 risk score (9 to 10 or ≥ 11) at Screening Visit
- PAH subtype (CTD-associated or not CTD-associated)
- Baseline WHO FC (III or IV)

Additional subgroups may be considered and will be listed in the SAP.

11.10 Event Adjudication Committee and Data Monitoring Committee

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. The adjudication of potential events will be based on available source documentation, including but not limited to anonymized individual clinical study data, office visit notes, hospital records, laboratory analysis, discharge/death summaries, procedural reports and imaging, and/or death certificates. All personnel involved in the adjudication process will remain blinded to study drug allocation throughout the study. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents. The adjudication guidance and clinical endpoint definitions are described in detail in the adjudication committee charter.

An external, independent DMC will review unblinded safety data 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.

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. or the IRB/IEC 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 sponsored by Acceleron Pharma Inc.

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 participants. Compliance with these standards provides assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles in the Declaration of Helsinki, and that the clinical study data are credible. All applicable country and local regulations will also be observed.

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. Documented 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 documented by all participants. The authorized person obtaining the informed consent must also document 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 documenting 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 documented 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 documenting 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 documented 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 (CSRs) 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 Acceleron Pharma Inc.'s confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

It is understood by the investigator that the information developed from this clinical study will be used by 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 practices, Acceleron Pharma Inc. will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMP	Bone morphogenetic protein
BMPR2	Bone morphogenetic protein type II receptor
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CHD	Congenital heart defects
CI	Confidence interval
CO	Cardiac output
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CTD	Connective tissue diseases
DBPC	Double-blind placebo-controlled
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee
eGFR	Estimated glomerular filtration rate
EOC	Executive Oversight Committee
EOS	End of Study

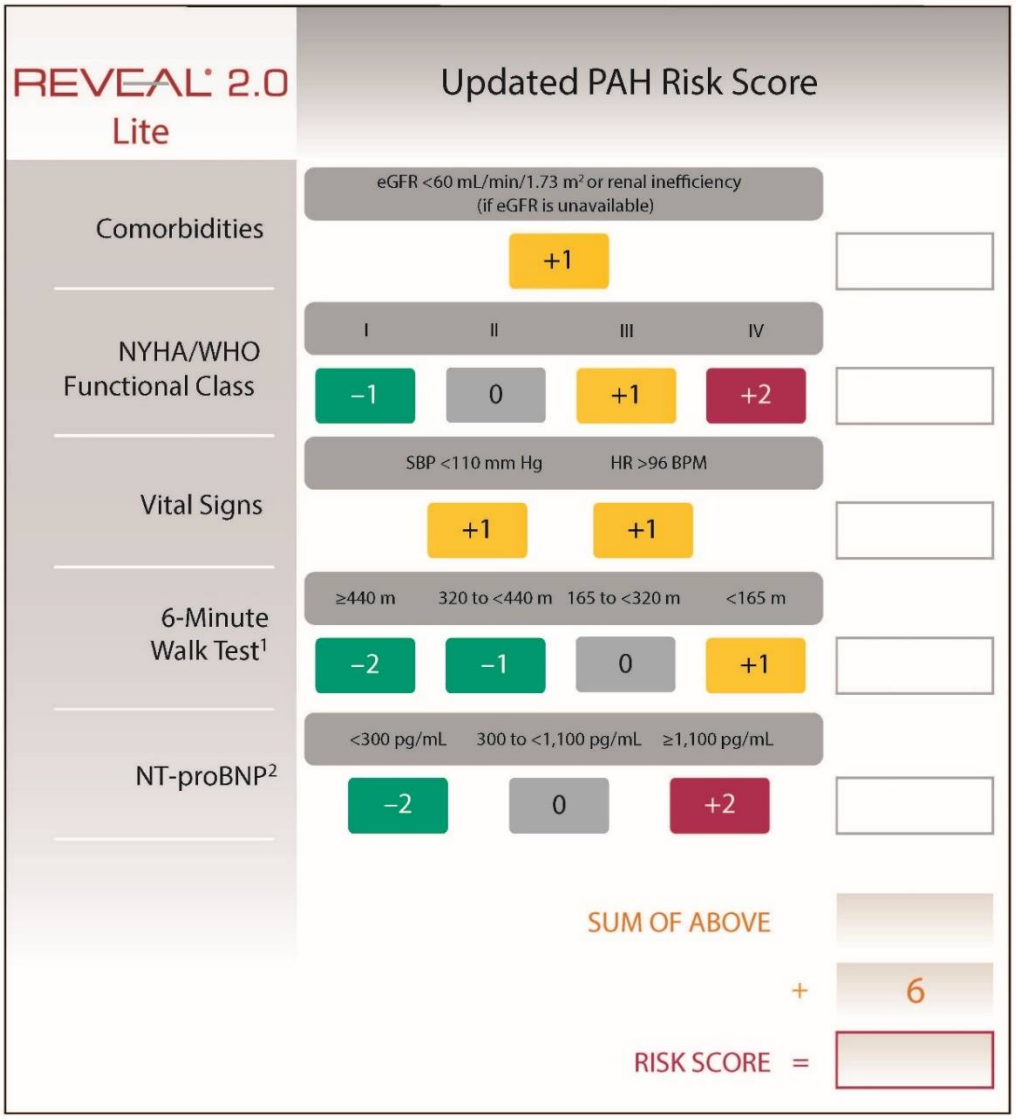
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5 dimensions scale 5 levels
E-R	Exposure-response
FAS	Full analysis set
FC	Functional class
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDF	Growth and differentiation factor
HCO_3	Bicarbonate
Hct	Hematocrit
Hgb	Hemoglobin
HHC	Home health care
HRT	Hormone replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPCW	Inverse probability of censoring weights
IRB	Institutional Review Board
IRT	Interactive Response Technology
LTFU	Long-term follow-up
LVEDP	Left ventricular end-diastolic pressure
m	meters
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary artery pressure
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure

PASP	Pulmonary artery systolic pressure
PAWP	Pulmonary artery wedge pressure
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PVR	Pulmonary vascular resistance
QTcF	Fridericia's corrected QT interval
RBC	Red blood cell
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
RPSFT	Rank preserving structural failure time
RV	Right ventricular
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SoE	Schedule of Events
SpO_2	Oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
SvO_2	Mixed venous saturation of oxygen
TAPSE	Tricuspid annular plane systolic excursion
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum sotatercept concentration
ULN	Upper limit of normal
US	United States
VSMC	Vascular smooth muscle cell
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WU	Wood units

Appendix 2 REVEAL Lite 2.0 Updated PAH Risk Score Calculator

Sites will use this score to ensure that entry criterion 4: REVEAL Lite 2.0 risk score ≥9, is met by the participant at enrollment. The Sponsor will calculate the REVEAL Lite 2.0 risk score for all other study visits (Visits 1 to 5, Visit 9, quarterly site visits, EOT Visit, and EOS Visits).

Importantly, the Screening NT-proBNP and eGFR samples taken at the initial Screening Visit should be submitted to the central laboratory for analysis as soon as possible to ensure availability of results prior to randomization.



BPM = beats per minute; eGFR = estimated glomerular filtration rate; HR = heart rate; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; SBP = systolic blood pressure; WHO = World Health Organization.

[1]The average of the 2 Screening 6MWDs should be used for score calculation as described in Section 9.3.2.

[2]Central laboratory NT-proBNP result from Screening Visit should be used for score calculation as described in Section 9.3.11. Sources:[Benza, R. L., et al 2019] [Benza, R. L., et al 2021]

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 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 partner who is pregnant, breastfeeding, or of childbearing potential 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 16 weeks (112 days) after the last dose of study treatment. 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.

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 8. Females who are exclusively in same-sex relationships are exempt for contraception guidelines.

Female participants of childbearing potential must agree to use highly effective forms of birth control for at least 28 days prior to starting the investigational product and agree to use the same highly effective contraception in combination with a barrier method while participating in the study, and for at least 16 weeks (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 16 weeks (112 days) after the last dose of study treatment.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a]
Failure rate < 1% per year when used consistently and correctly
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • 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 • Intrauterine device • 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.

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.

Pregnancy Testing

- A WOCBP 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 as described in Section 10.8.
- After obtaining the necessary documented informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Acceleron Pharma Inc. 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 Acceleron Pharma Inc. 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 as described in Section 10.8. Information will be recorded on the appropriate form and submitted to Acceleron Pharma Inc. 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 Acceleron Pharma Inc. 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 Acceleron Pharma Inc. 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.

Appendix 4 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 BP, and make sure that clothing and shoes are appropriate. Record in the source documents.
4. Measure and record baseline heart rate and oxygen saturation (SpO2) 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 Scale 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 Scale 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 5 Protocol Nomenclature Mapping

Acceleron Protocol Description (A011-14)	Date	Merck REDS Number (MK-7962-006)
Original Protocol (v1.0)	08 April 2021	MK-7962-006-00
Global Amendment 01 (v2.0)	16 June 2022	MK-7962-006-01
Original Protocol (France)	16 December 2021	MK-7962-006-02
Original Protocol (United Kingdom)	22 October 2021	MK-7962-006-03
Original Protocol (United Kingdom)	03 November 2021	MK-7962-006-04
Global Amendment 02 (v3.0)	10 April 2023	MK-7962-006-05
Global Amendment 02 (v3.0)	29 June 2023	MK-7962-006-06
Global Amendment 03 (v4.0)	23 April 2024	MK-7962-006-07