Official Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate-and High-risk PAH Patients
NCT Number:	NCT04811092
Document Date:	17-Dec-2024

Protocol A011-13 (HYPERION)

MK-7962-005

PROTOCOL TITLE:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate- and High-risk PAH Patients
SHORT TITLE:	A Phase 3 Study of Sotatercept in Newly Diagnosed Intermediate- and High-risk PAH Patients
REGULATORY AGENCY IDENTIFYING NUMBERS:	IND 136150 EudraCT 2021-000199-12 EU CT 2023-509139-16-00
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:	13 January 2021
PROTOCOL VERSION 2.0:	28 April 2021
PROTOCOL VERSION 3.0:	24 January 2022
PROTOCOL VERSION 4.0:	10 November 2022
PROTOCOL VERSION 5.0:	03 July 2023
PROTOCOL VERSION 6.0:	25 April 2024
PROTOCOL VERSION 7.0:	17 December 2024

See Appendix 8 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 Food and Drug Administration (US 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 are provided in the Investigator Site File.	Details are provided in the Investigator Site File.
Pharmacovigilance	Safety Check Desk	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

EMEA = Europe, the Middle East and Africa; LA = Latin America; RTP=Real-time Transport Protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

This amendment was created primarily to terminate the blinded study so that all eligible participants could receive sotatercept either by transitioning to the extension study (SOTERIA, MK-7962-004) or by commercial access, if available, and to add a secondary endpoint of overall survival.

Changes from protocol version 6.0 (25 April 2024) to protocol version 7.0 (17 December 2024) are detailed below in the order they appear in the protocol. Minor edits are not included. See Appendix 7 for the Protocol Amendment History.

Protocol Location	Description of Change	Brief Rationale
Title page	Added the EU CT number to the section with regulatory agency identifiers.	For regulatory compliance.

Protocol Location	Description of Change	Brief Rationale
Section 1, Study Design	Added a note: "Results of the recently-completed interim analysis of ZENITH (MK-7962-006), demonstrated that sotatercept treatment – compared with placebo – led to a statistically significant and clinically meaningful reduction in the risk of morbidity or mortality events in adults with PAH WHO FC III or IV at high risk of mortality. In conjunction with results from STELLAR (MK-7962-003), these results confirm a lack of clinical equipoise and no longer justify continuing a placebo-controlled trial with sotatercept in PAH. Therefore, the Sponsor has decided to terminate HYPERION (A011-13, MK-7962-005) to permit all eligible participants to receive sotatercept either in the extension study (SOTERIA, MK-7962-004) or via commercial access (where available). The prespecified IA will not be conducted and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP. All eligible participants will complete the EOT visit before enrollment in SOTERIA. or initiation of commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit. Follow-up Telephone Calls and annual Follow-up Visits will not be conducted."	Protection of participants' interest.
Section 1, Efficacy Endpoints	Added overall survival to the Efficacy Endpoints subsection as a secondary endpoint.	To provide a more comprehensive assessment of treatment effects.

Protocol Location	Description of Change	Brief Rationale
Section 1, Sample Size Determination and Power Calculations	Added text to explain the cancellation of the prespecified IA.	Refer to Section 1 rationale (study termination).
Section 1, Statistical Methods	Edited the statement on the alpha level for secondary endpoint testing.	Refer to rationale for Section 1, Efficacy Endpoints
Section 1, Statistical Methods	Added a note to the Statistical Methods subsection stating that the prespecified IA will not be conducted.	Refer to Section 1 rationale (study termination).
Section 1.1, Study Schematic	Added a note stating that the study will be stopped so that all eligible participants can receive sotatercept treatment in the extension study or via commercial access. Clarified the study closeout visits and the analysis plan.	Refer to Section 1 rationale (study termination).
Section 2, Schedules of Events	See Section 1, Study Design	Refer to Section 1 rationale (study termination).
Section 5.3, Secondary Efficacy Endpoints and Rationale	Added overall survival as a secondary endpoint.	Refer to Section 1 rationale (added secondary endpoint).
Section 6.4, Study Design, Stratification, and Treatment Assignment	See Section 1, Study Design	Refer to Section 1 rationale (study termination).
Section 9.2.3, End of Treatment Visit Following a Clinical Worsening Event, 21 ± 7 Days from Last Dose for Early Discontinuation, or Study Completion	See Section 1, Study Schematic	Refer to Section 1 rationale (study termination).

Protocol Location	Description of Change	Brief Rationale
Section 9.4.1, Early Discontinuation of Study Treatment	Added a note stating that the study will be stopped so that all eligible participants can receive sotatercept treatment in the extension study or via commercial access. Clarified the study closeout visits.	Refer to Section 1 rationale (study termination).
Section 11.2, Sample Size Determination	See Section 1, Study Design	Refer to Section 1 rationale (study termination).
Section 11.5.2, Secondary Endpoints	Added overall survival as a secondary endpoint.	Refer to Section 1 rationale (added secondary endpoint).
Section 11.5.2, Secondary Endpoints	Edited the statement on the alpha level for secondary endpoint testing.	Refer to Section 1 rationale (added secondary endpoint).
Section 11.8, Interim Analysis	Added a note stating that the study will be stopped so that all eligible participants can receive sotatercept treatment in the extension study or via commercial access. Clarified the analysis plan.	Refer to Section 1 rationale (study termination).
Section 11.11.1, Estimands for the Time-to-Event Endpoints	Added overall survival to the estimands for time-to-event endpoints.	Refer to Section 1 rationale (added secondary endpoint).
Section 18, Appendix 7, Protocol Amendment History	Deleted the change from amendment version 5 (03 July 2023) in Sections 2 and 13.4 regarding optional informed consent forms (ICFs) and consent to photography.	To correct an error in the summary of changes regarding a change that was never implemented in the study protocol.

EU CT = European Union Clinical Trial registration number; IA = interim analysis; ICF = informed consent form.

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1 PROTOCOL SYNOPSIS

Protocol Title	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate- and High-risk PAH Patients
Short Title	A Phase 3 Study of Sotatercept in Newly Diagnosed Intermediate- and High-risk PAH Patients
Protocol Number	A011-13 (HYPERION) (MK-7962-005)
Study Type	Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study
Rationale	Pulmonary Arterial Hypertension is a progressive, fatal disease that causes marked limitations in physical activity and quality of life, even when treated with approved therapies. This Phase 3 study is supported by data from the PULSAR study (Phase 2, NCT03496207) and the STELLAR study (Phase 3, NCT04576988). In PULSAR, participants taking any approved single or combination therapy for PAH were randomized to receive sotatercept (ACE-011, MK-7962) or placebo for 24 weeks. PULSAR demonstrated a statistically significant improvement in its primary endpoint, pulmonary vascular resistance (PVR). Additionally, improvement was observed in 6-minute walk distance (6MWD), N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, and other endpoints. In STELLAR, participants taking single or combination PAH therapy were randomized to receive sotatercept or placebo for 24 weeks. STELLAR demonstrated a statistically significant and clinically meaningful improvement in its primary endpoint, 6MWD, and achieved statistical significance in 8 of 9 secondary efficacy outcome measures, including improvements in PVR and the World Health Organization (WHO) functional class (FC) [Hoeper, M. M., et al 2023].
Study Objective	The objective of this study is to evaluate the effects of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) on time to clinical worsening (TTCW) in participants who are newly diagnosed with PAH and are at intermediate or high risk of disease progression.

Study Population	Participants diagnosed within 12 months of study screening with symptomatic PAH (WHO Group 1, classified as FC II or III) who present with idiopathic or heritable PAH, PAH associated with connective tissue diseases (CTDs), drug- or toxin-induced PAH, after shunt correction PAH, or PAH presenting at least 1 year following the correction of congenital heart defects. Participants must have either a Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 Risk Score of ≥ 6, or COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above) and be on background PAH therapy, which includes either a double or triple combination of PAH background therapies (per local standard-of-care guidelines).
Number of Participants	Approximately 444 participants will be randomly assigned in a 1:1 ratio to the 2 study treatment groups (222 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 (Time to Event). Each eligible participant will be randomized in a 1:1 ratio to 1 of the following 2 treatment arms during 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, SC every 21 days plus background PAH therapy Each study participant will remain in the DBPC Treatment Period until 1 of the following occurs, whichever comes first (1) they experience an event of clinical worsening, (2) the time when the required number of primary endpoint events are accrued for the final analysis, or (3) the study is stopped early at the interim analysis (IA). A planned IA will occur when approximately 61 participants have experienced a primary endpoint event. Upon experiencing an event of clinical worsening (after sponsor confirmation of completeness of the electronic data capture (EDC) forms related to clinical worsening) or at the time of study unblinding, participants will complete the End of Treatment (EOT) Visit and may be eligible to enroll in SOTERIA. Participants who do not choose to enroll in SOTERIA will undergo a Follow-up Period in this study of 8 weeks that will include both the EOT and the End of Study (EOS) Visits Figure 1. Participants who discontinue the DBPC

	Treatment Period early, without experiencing an event of clinical worsening, will complete the EOT Visit at the time of discontinuation and will be asked to return to complete the EOS Visit, and Follow-up Calls/Visits, provided that consent is not withdrawn. Follow-up Telephone Calls can replace Follow-up Visits if the participant cannot visit the site. These participants who discontinue the DBPC Treatment early, without experiencing an event of clinical worsening, will not be eligible to enroll in SOTERIA. **MK-7962-005-11 Implementation:** Results of the recently-completed interim analysis of ZENITH (MK-7962-006) demonstrated that sotatercept treatment – compared with placebo – led to a statistically significant and clinically meaningful reduction in the risk of morbidity or mortality events in adults with PAH WHO FC III or IV at high risk of mortality. In conjunction with results from STELLAR (MK-7962-003), these results confirm a lack of clinical equipoise and no longer justify continuing a placebo-controlled trial with sotatercept in PAH. Therefore, the Sponsor has decided to terminate HYPERION (A011-13, MK-7962-005) to permit all eligible participants to receive sotatercept either in the extension study (SOTERIA, MK-7962-004) or via commercial access (where available). The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP. All eligible participants will complete the EOT visit before enrollment in SOTERIA or initiation of commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit. Follow-up Telephone Calls and annual Follow-up Visits will not be conducted.
Estimated Duration of the Study	Study duration for a given participant in Study A011-13 (MK-7962 -005) will be up to approximately 47 months, as follows: • Screening Period (up to 4 weeks) • DBPC Treatment Period (until event occurrence, up to approximately 44 months) • Follow-up Period (up to 8 weeks)

Inclusion Criteria	Eligible participants must meet all of the following criteria to be enrolled in the study: 1. Age ≥ 18 years 2. Documented diagnostic right heart catheterization (RHC) within 12 months of screening documenting a minimum PVR of ≥ 4 Wood units and pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of ≤ 15 mmHg, with the diagnosis of WHO PAH Group 1 in any of the following subtypes: • Idiopathic PAH • Heritable PAH • Drug-/toxin-induced PAH • PAH associated with CTD • PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair 3. Symptomatic PAH classified as WHO FC II or III 4. Either REVEAL Lite 2 risk score ≥ 6 or COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above) 5. Diagnosis of PAH within 12 months of screening and on stable doses of a double or triple combination of background PAH therapies and diuretics (if any) for at least 90 days prior to screening. Background PAH therapy and diuretics are further defined in Section 7.2. 6. 6MWD ≥ 150 m repeated twice at screening at least 4 hours apart, but no longer than 1 week apart, and both values are within 15% of each other (calculated from the highest value) 7. Females of childbearing potential (as defined in Appendix 4) must meet the following criteria: • Have 2 negative urine or serum pregnancy tests as verified by the investigator during the Screening Period; • Agree to ongoing pregnancy testing (either urine or serum) 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 – Agreed 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 meet the following criteria: • 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 documented informed consent

Exclusion Criteria	Participants will be excluded from the study if any of the following criteria are met: 1. Diagnosis of pulmonary hypertension (PH) WHO Groups 2, 3, 4, or 5 2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, pulmonary veno occlusive disease and pulmonary capillary hemangiomatosis 3. Hgb at screening above gender-specific upper limit of normal (ULN), per local laboratory test 4. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 180 mmHg or sitting diastolic BP > 110 mmHg during the Screening Visit after a period of rest 5. Baseline systolic BP < 90 mmHg at screening 6. Pregnant or breastfeeding women 7. Any of the following clinical laboratory values at the Screening Visit: • Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (as defined by MDRD equation) • Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels > 3 × ULN (For United Kingdom [UK], refer to the specific requirement in Appendix 6) • Platelet count < 50,000/mm^3 (< 50.0 × 10^9/L) 8. Currently enrolled in or have completed any other investigational product study within 30 days for small molecule drugs or within 5 half-lives for investigational biologics prior to the date of documented informed consent 9. Known allergic reaction to sotatercept (ACE-011), its excipients, or luspatercept 10. History of pneumonectomy 11. Pulmonary function test values of forced vital capacity < 60% predicted within 1 year prior to the Screening Visit 12. Stopped receiving any PH chronic general supportive therapy (e.g., diuretics, oxygen, anticoagulants, and digoxin) within 60 days prior to the Screening Visit 13. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to the Screening Visit or planned initiation during the study (participants who are

	stable in the maintenance phase of a program and who will continue for the duration of the study are eligible) 14. Untreated more than mild obstructive sleep apnea 15. History of known pericardial constriction 16. History of restrictive cardiomyopathy 17. History of atrial septostomy within 180 days prior to the Screening Visit 18. Electrocardiogram (ECG) with Fridericia's corrected QT interval > 500 ms during the Screening Period (For UK and South Korea, refer to the specific requirements in Appendix 6). 19. Personal or family history of long QT syndrome or sudden cardiac death 20. Left ventricular ejection fraction < 50% documented by a historical echocardiograph (ECHO) or cardiac magnetic resonance imaging (MRI) within the last 12 months prior to screening (if there is more than 1 assessment of left ventricular ejection fraction (LVEF), the value from the most recent measurement should be used in assessing eligibility) 21. Coronary artery disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the Screening Visit 22. Cerebrovascular accident within 3 months prior to the Screening Visit 23. Acutely decompensated heart failure within 30 days prior to the Screening Visit, as per investigator assessment 24. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease 25. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, and vasopressin) within 30 days prior to the Screening Visit 26. Active malignancy with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or prostate cancer that is not currently or expected, during the study, to be treated with radiation therapy, chemotherapy, and/or surgical intervention, or hormonal treatment.

Efficacy Endpoints	**Primary Efficacy Endpoints** The primary efficacy endpoint is TTCW, defined as the time from randomization to the first confirmed morbidity event or death. The events that will comprise this endpoint include the following: • All-cause death • Non-planned PAH-related hospitalization of ≥ 24 hours in duration • Atrial septostomy • Lung transplant • Deterioration in performance in exercise testing due to PAH, defined as a decrease in 6MWD from baseline (average of screening) on 2 consecutive tests (which must be at least 4 hours apart) and at least 1 of the following: – Worsening of WHO FC from baseline – Signs/symptoms of increased right heart failure – Addition of a background PAH therapy or change in the background PAH therapy delivery route to parenteral All events will be adjudicated by a blinded, independent committee of clinical experts. **Secondary Efficacy Endpoints** The 10 secondary endpoints are ranked as follows: 1. Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline: • Improvement in 6MWD (increase ≥ 30 meters [m]) • Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L • Improvement in WHO FC or maintenance of WHO FC II 2. Proportion of participants who maintain or achieve a low-risk category of REVEAL Lite 2 risk score at Week 24 versus baseline 3. Proportion of participants who maintain or achieve a low risk score at Week 24 versus baseline using the simplified French Risk score calculator 4. Change from baseline in NT-proBNP levels at Week 24 5. Proportion of participants who improve in WHO FC or maintain WHO FC II at 24 weeks from baseline

	6. Change from baseline in 6MWD at Week 24 7. Overall survival 8. Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) at Week 24 9. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24 10. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24 **Exploratory Endpoints** • Change in dyspnea score (assessed by Borg Dyspnea Scale [Borg CR10 Scale®]) at Week 24 versus baseline • Change from baseline in C-reactive protein (CRP) levels at Week 24 • Change of Cardiovascular Symptoms domain score from baseline in PAH-SYMPACT® at Week 24 • Change from baseline in EuroQol – 5 dimensions scale 5 levels (EQ-5D-5L) index score at Week 24 • Change from baseline in EQ-5D-5L visual analog scale (VAS) at Week 24 • Changes from baseline in ECHO parameters (e.g., RVSP [right ventricular systolic pressure] and TAPSE [tricuspid annular plane systolic excursion]) at Week 24 • Proportion of participants who maintain or achieve a low or intermediate-low-risk based on COMPERA 2.0 four-stratum risk score 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

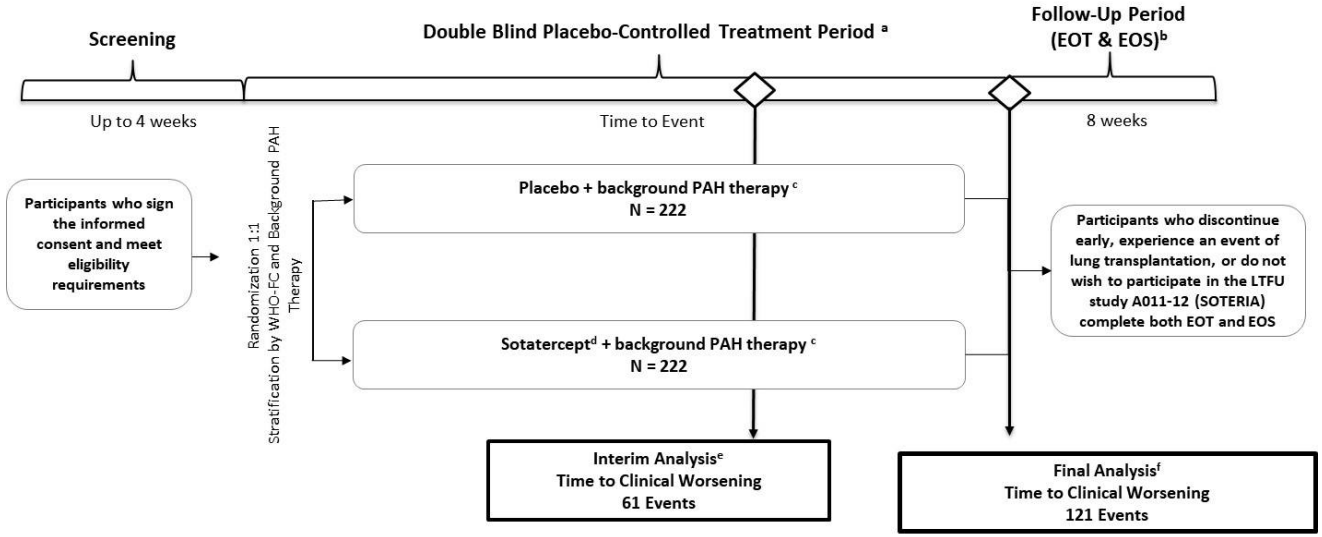
Sample Size Determination and Power Calculations	The sample size determination is based on the primary efficacy endpoint of TTCW using EAST version 6. Given a 1:1 randomization, a 1-sided 0.025 Type I error rate, 90% power, and an assumed true hazard ratio of 0.55, and with a planned IA at approximately 50% of the required number of events with the option to stop the study for futility, approximately 121 events will be required at the final analysis, based on the log-rank test. Approximately 444 participants are planned to be enrolled in this study. With an accrual period of approximately 35 months, assuming an accrual rate of approximately 12.5 participants per month, a dropout rate of approximately 0.4% per month (5% per year), and the placebo event rate of 0.20 per year (cumulative annual survival probability of 0.80), the IA is expected to occur at 30 months. If the study continues after the IA, the final analysis is expected to occur at 44 months. **MK-7962-005-11 Implementation:** The prespecified IA will not be conducted and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP.
Stratified Randomization Factors	Randomization will be stratified by the following: • Baseline WHO FC (Class II or III) • Background PAH therapy (double or triple therapy)
Statistical Methods	**Efficacy Analyses:** All efficacy analyses will be based on the Full Analysis Set (FAS), which is defined as all randomized participants. **Safety Analyses:** All safety analyses are based on the Safety Set, which is defined as all participants who receive at least 1 dose of study treatment. **Analysis of Study Endpoints:** **Efficacy Endpoints** <u>Interim Analysis</u> An IA of TTCW will be performed when approximately 61 events (roughly 50% of required events) have occurred 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 TTCW. 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. **MK-7962-005-11 Implementation:** The prespecified IA will not be conducted and the final analysis will be performed using

	all available participant data at a prespecified data cutoff date. More details will be described in the SAP. Primary Endpoint A stratified log-rank test with randomization factors as strata will be used for the analysis of TTCW. The point estimate of the hazard ratio with 95% CI will be estimated by a Cox regression model stratified by the randomization factors. Secondary Endpoints The aligned rank stratified Wilcoxon test will be used for continuous variables. In this test, the endpoint values are first aligned across the randomization strata using the stratum-level Hodges-Lehmann location shift estimates, and the aligned values are then analyzed using a Wilcoxon rank sum test. The output from this analysis will be used to provide a 2-sided p-value and corresponding Hodges-Lehmann location-shift estimate of the overall treatment difference with 95% CI. The stratified Cochran-Mantel-Haenszel test will be used for dichotomous variables, and the stratified 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 the same alpha level as used for the primary endpoint event proceeding successively in the order of the secondary endpoints listed above after each of the preceding endpoints is tested to be statistically significant. **Safety Endpoints** Safety data will be summarized descriptively by treatment arm.
Safety and Pharmacovigilance	An unblinded, external, independent Data Monitoring Committee (DMC) will monitor participant safety throughout the course of the study. A detailed charter will outline all activities of the DMC (including but not limited to the composition of the DMC, the type of data to be reviewed, the DMC responsibilities, and the frequency of meetings). Internal data review of safety-related data will occur in a blinded manner at a preplanned frequency throughout the study duration.

1.1 Study Schematic

MK-7962-005-11 Implementation: The Sponsor has decided to close the HYPERION study (A011-13, MK-7962-005) so that all eligible participants in HYPERION can receive sotatercept either by extension study (SOTERIA, MK-7962-004) or by commercial access, if available. The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP. All eligible participants will complete the EOT visit before enrollment in SOTERIA or initiating commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit.

Figure 1: Schematic of Study A011-13 (MK-7962-005)



EDC = electronic data capture; EOS = End of Study; EOT = End of Treatment; ; FC = functional class; LTFU = long-term follow-up; PAH = pulmonary arterial hypertension; SC = subcutaneous(ly); WHO = World Health Organization

a Participants will continue in the Double-blind Placebo-controlled Treatment Period until they experience an event of clinical worsening, at which point they will complete the EOT Visit after the sponsor has confirmed completeness of EDC forms related to clinical worsening and will be eligible to enter into SOTERIA.

b Participants who choose to enroll SOTERIA, will not complete the EOS Visit.

c Background PAH therapy refers to approved PAH-specific medications and may consist of a double or triple combination of therapy with endothelin-receptor antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogs or receptor agonists.

e Sotatercept at a starting dose of 0.3 mg/kg SC with a target dose of 0.7 mg/kg SC.

e Interim analysis will occur when 50% of the target events of clinical worsening (approximately 61 events) have been recorded.

f Primary endpoint analysis will be completed after approximately 121 events of clinical worsening are recorded.

2 SCHEDULES 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) Periods and Table 3 for the Follow-up Period.

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

MK-7962-005-11 Implementation: The Sponsor has decided to close the HYPERION study (A011-13, MK-7962-005) so that all eligible participants in HYPERION can receive sotatercept either by extension study (SOTERIA, MK-7962-004) or by commercial access, if available. The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP. All eligible participants will complete the EOT visit before enrollment in SOTERIA or initiation of commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit. Follow-up Telephone Calls and annual Follow-up Visits will not be conducted.

Table 2: Schedule of Events – Screening and Double-blind Placebo-controlled Periods

Study Procedure/ Assessment	Screening Period (up to 4 weeks prior to Visit 1)	DBPC Treatment Period[a, b, c]							
		Visit 1 (Study Day 1)	Visits 2-4 21±3 days	Visit 5 21±3 days	Visits 6-8 21±3 days	Visit 9 (6-month Site 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[f, p, q]
Inclusion/exclusion criteria	X								
Randomization		X							
Medical history review[d]	X								
Physical examination[e]	X	X		X		X		X	
ECG (12-lead)[f]	X					X			
Vital signs including weight[g]	X	X	X	X		X		X	
Pregnancy test (urine or serum)[h]	X	X	X	X	X	X	X	X	
Hematology (CBC)[i]	X		X	X		X		X	
Serum chemistry[j]	X	X		X		X		X	
Urinalysis	X			X		X		X	
6MWT	X (in duplicate)[k]	X	X	X		X		X	

Study Procedure/ Assessment	Screening Period (up to 4 weeks prior to Visit 1)	DBPC Treatment Period[a, b, c]							
		Visit 1 (Study Day 1)	Visits 2-4 21±3 days	Visit 5 21±3 days	Visits 6-8 21±3 days	Visit 9 (6-month Site 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
Borg Dyspnea Scale (pre- and post-6MWT)	X	X	X	X		X		X	Repeat visits 10-13 until the end of the DBPC Treatment Period[f, p, q]
WHO FC assessment[u]	X	X	X	X		X		X	
Clinical worsening assessment[l]		X	X	X		X		X	
Risk score assessment[m]	X								
NT-proBNP, activin A, and CRP sample collection[n]	X	X[o]	X	X		X		X (NT-proBNP and CRP only)	
ADA sample collection[n]	X	X	X	X		X		X	
PK sample collection[n]		X[o]	X	X		X		X	
ECHO[p]	X					X			
Study drug administration[a, b]		X	X	X	X[q]	X	X[q]	X	
AE/SAE review	X	X	X	X	X	X	X	X	

Study Procedure/ Assessment	Screening Period (up to 4 weeks prior to Visit 1)	DBPC Treatment Period[a, b, c]							
		Visit 1 (Study Day 1)	Visits 2-4 21±3 days	Visit 5 21±3 days	Visits 6-8 21±3 days	Visit 9 (6-month Site 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
Concomitant medication review[r]	X	X	X	X	X	X	X	X	Repeat visits 10-13 until the end of the DBPC Treatment Period[f, p, q]
PAH-SYMPACT® and EQ-5D-5L assessments[s]		X		X		X			Repeat Every 6 months after Visit 9 (Visits 17, 25, 33, 41, 49, 57, 65, 73, etc)
RHC[t]	X								

6MWD = 6-minute walk distance; 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; ECHO = echocardiogram; EDC = electronic data capture; eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; EQ-5D-5L = EuroQoL – 5 dimensions scale 5 levels; FC = functional class; FSH = follicle stimulating hormone; HCO3 = bicarbonate; Hgb = hemoglobin; HHC = home health care; LTFU = long-term follow-up; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension-Symptoms and Impact; PCWP = pulmonary capillary wedge pressure; PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; RHC = Right heart catheterization; SAE = serious adverse event; ; WHO = World Health Organization.

[a] All study procedures should be done 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 (Visits 6 until the end of the DBPC Treatment Period, except for Visit 9 and quarterly site visits, for participants who consent and are approved for optional home health administration of study drug).

[c] Participants who experience an event of clinical worsening and have elected to not continue into SOTERIA, will complete both the EOT and the EOS Visits. Participants who discontinue the DBPC Treatment Period early, without experiencing an event of clinical worsening, should complete the EOT Visit at the time of discontinuation and will be asked to return to complete the EOS Visit, and Follow-up Calls/Visits, provided that consent is not withdrawn. These participants who discontinue the DBPC Treatment early, without experiencing an event of clinical worsening, will not be eligible to enroll in the SOTERIA study. Refer to Section 9.4.1 for early discontinuation criteria. Participants who have completed all DBPC Treatment Period visits or who have experienced an event of clinical worsening and will continue into the SOTERIA study will be asked to complete only the EOT Visit after the sponsor has confirmed completeness of EDC forms related to clinical worsening.. Refer to Table 3 for EOT and EOS Visit details.

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

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

[f] Electrocardiogram will be performed at screening and at Visits 9, 17, 33, 49, and 65.

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

[h] Two pregnancy tests are required for female participants of childbearing potential during the Screening Period. A pregnancy test is required prior to study drug administration at all other visits.

[i] Complete blood count includes red blood cells, absolute white blood cells, Hgb, hematocrit, and platelet count. Results provided by local laboratory will be evaluated at the Screening Visit and prior to study drug administration (or up to 3 days prior if available) for Visits 2 to 5, Visit 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 (Section 8.3) during non-quarterly visits, a hematology assessment should be performed up to 3 days prior to the next dose administration, and onsite visits are required (Section 6.5). Hematology results collected per SoE and Section 8.3 should be recorded in the EDC.

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

[k] The 6MWT must be performed twice during the Screening Period, at least 4 hours, but no longer than 1 week, apart.

[l] Clinical worsening assessment including 6MWT should be performed whenever a participant's symptoms and condition suggest possibility of clinical worsening event. Participants may be asked to return to the site in an unscheduled visit to assess clinical worsening.

[m] Simplified French Risk score, REVEAL Lite 2 risk score and COMPERA 2.0 four stratum risk score are used for risk assessment. Sites must use central laboratory NT-proBNP and eGFR results to calculate the REVEAL Lite 2 and COMPERA 2.0 risk score during the Screening Period to ensure that inclusion criterion 4: REVEAL Lite 2 risk score ≥6 or COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above) is met. The sponsor will calculate the risk score for all other visits.

[n] On days when study drug is administered, samples for NT-proBNP, activin A, CRP, PK, and ADA assessments will be collected prior to study drug administration.

[o] On Day 1, samples for NT-proBNP, activin A, and PK assessments will be collected pre-dose and at 1 to 2, 2 to 4, and 4 to 8 hours post-dose. One sample for CRP assessment will be collected prior to study drug administration.

[p] ECHOs will be performed at screening, Visits 9 and 33, and the EOT Visit.

[q] For HHC visits, each home administration of study drug will be accompanied by confirmation of proper storage. Documentation of concomitant medications as well as incidence of any aEs, medication errors, accidental exposure of others, or product complaints will also occur at these visits. See Section 6.5 for additional details regarding HHC visits.

[r] A participant may be discontinued early from the study treatment and be ineligible to participate in SOTERIA if any of the following modifications occur to background PAH therapy, and these modifications are not accompanied by a decrease in 6MWD or another event of clinical worsening: (1) the participant is prescribed a new PAH-specific medication, (2) there is an escalation in the background PAH therapy such as a dose increase, or (3) there is a change in delivery route to parenteral. Refer to Section 9.4.1 for details.

[s] EQ-5D-5L can be completed up to 3 days prior to the study visit.

[t] If historical RHC does not provide all the necessary measurements to confirm a minimum PVR of ≥ 4 Wood units and PCWP or LVEDP of ≤ 15 mmHg, with the diagnosis of WHO PAH Group 1, a RHC can be repeated as a screening procedure. However, the historical RHC will be used for the date of PH Group 1 diagnosis.

[u] As described in Section 6.4, WHO FC will be used to stratify participants at the time of randomization. WHO FC must be evaluated on the day of randomization (Visit 1), prior to study dose administration.

Table 3: Schedule of Events–– Follow-up Period

Study Procedure/Assessment	Follow-up Period[a]			
	EOT Visit **(Following a clinical worsening event, 21 ± 7 days from last dose for early discontinuation, or study completion)**	**EOS Visit** **5 weeks ± 7 days after EOT Visit** **(early discontinuation or no LTFU only)**	**Follow-up Telephone Call** **6 months after EOS Visit and yearly after (early discontinuation only)**	**Follow-up Visit** **Yearly after EOS Visit (early discontinuation only)[j]**
Physical examination[b]	X	X		X
ECG (12-lead)	X			
Vital signs including weight	X	X		X
Pregnancy test (urine or serum)[c]	X	X		
Hematology (CBC)[d]	X	X		X
Serum chemistry[e]	X	X		X
Urinalysis	X	X		
6MWT[f]	X	X		X
Borg Dyspnea Scale (pre- and post-6MWT)	X	X		X
WHO FC assessment	X	X		X
Clinical worsening assessment	X	X		
PAH-SYMPACT® and EQ-5D-5L assessments [i]	X	X		
NT-proBNP and CRP sample collection	X	X		X
ADA sample collection[g]	X	X		

Study Procedure/Assessment	Follow-up Period[a]			
	EOT Visit (Following a clinical worsening event, 21 ± 7 days from last dose for early discontinuation, or study completion)	**EOS Visit 5 weeks ± 7 days after EOT Visit (early discontinuation or no LTFU only)**	**Follow-up Telephone Call 6 months after EOS Visit and yearly after (early discontinuation only)**	**Follow-up Visit Yearly after EOS Visit (early discontinuation only)[j]**
PK sample collection	X			
ECHO[h]	X			
AE/SAE review	X	X	X	X
Concomitant medication review	X	X	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; ECHO = echocardiogram; EDC = electronic data captureEOS = End of Study; EOT = End of Treatment; EQ-5D-5L = EuroQoL–- 5 dimensions scale 5 levels; FC = functional class; FSH = follicle stimulating hormone; HCO_3 = bicarbonate; Hgb = hemoglobin; LTFU = long-term follow-up; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; PAH-SYMPACT® = Pulmonary Arterial Hypertension-Symptoms and Impact; PK = pharmacokinetic(s);; SAE = serious adverse event; ; WHO = World Health Organization

[a] Participants who experience an event of clinical worsening and have elected to not continue into SOTERIA, will complete both the EOT and the EOS Visits. Participants who discontinue the DBPC Treatment Period early, without experiencing an event of clinical worsening, should complete the EOT Visit at the time of discontinuation and will be asked to return to complete the EOS Visit, and Follow-up Calls/Visits, provided that consent is not withdrawn. Follow-up Telephone Calls can replace Follow-up Visits if the participant cannot visit the site. These participants who discontinue the DBPC Treatment early, without experiencing an event of clinical worsening, will not be eligible to enroll in the SOTERIA study. Refer to Section 9.4.1 for early discontinuation criteria. Participants who have completed all DBPC Treatment Period visits or who have experienced an event of clinical worsening and will continue into the SOTERIA study will be asked to complete only the EOT Visit after the sponsor has confirmed completeness of EDC forms related to clinical worsening.

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

[c] Two pregnancy tests are required for female participants of childbearing potential at the Screening Visit and prior to study drug administration at all other visits.

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

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

[f] The 6MWT should be performed whenever a participant's symptoms suggest possibility of functional decline.

[g] 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.

[h] Echocardiograms will be performed at screening, Visits 9 and 33, and the EOT Visit.

[i] EQ-5D-5L can be completed up to 3 days prior to each visit. In case the participant goes through early discontinuation, PAH-SYMPACT® can be completed on site for the visit date.

[j] Follow-up telephone calls can replace Follow-up Visits if the participant cannot visit the site.

3 INTRODUCTION: BACKGROUND AND STUDY RATIONALE

3.1 Background

Pulmonary arterial hypertension (PAH) applies to a group of diseases causing a progressive increase in pulmonary vascular resistance (PVR), resulting in right ventricular dysfunction and ultimately failure as well as premature death [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 endothelin1. 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 (BMP) 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 (TGF)-β family members in the pathogenesis of PAH. Sotatercept acts to block activin ligands and growth and differentiation factors (GDFs), may attenuate BMPs, and improve pulmonary vascular remodeling by restoring balance to Smad signaling [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, M. D., et al 2019], end-stage kidney disease [Coyne, D. W., et al 2019], as an erythropoietic agent [Sherman, M. L., et al 2013], and 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 TGF-β superfamily, such as activins A and B and GDF-8 and -11, to suppress their signaling and restore balance between the opposing growth-promoting activin/GDF and growth-inhibiting BMP pathways [Yung, L., et al 2017] [Yung, L., et al 2018].

Preclinical data suggest that sotatercept (murine analogue, RAP-011) may positively affect vascular remodeling in animal models of PAH. RAP-011 was evaluated in both preventative and therapeutic disease models. Affected animals treated with RAP-011 showed substantial improvements in pulmonary vascular and cardiac hemodynamic measurements that were either comparable or superior to agents approved for treatment of PAH. Importantly, a substantial reduction in the proliferation of pulmonary VSMCs was observed in RAP-011-treated animals as assessed by histologic evaluation in both preventative and therapeutic disease models. Taken together, these data indicate that RAP-011 can attenuate the development and progression of PAH, even when administered to animals with established disease. These preclinical data suggest that sotatercept is a mechanism-targeted nonvasodilator therapy that may positively affect vascular remodeling associated with PAH [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 PULSAR study (Phase 2, NCT03496207), and clinical results from the pivotal Phase 3 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 m). 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 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, DBPC study in

participants with PAH (WHO Group 1 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 4. More detailed information about the known and expected benefits and risks of sotatercept can be found in the IB.

3.3 Study Rationale

Study A011-13 (MK-7962-005) is a Phase 3, randomized, DBPC study to evaluate sotatercept when added to background PAH therapy in newly diagnosed intermediate- or high-risk PAH patients.

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

In the PULSAR study, more than 90% of 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 side effects. The treatment-induced increases in Hgb levels and decrease in platelet count observed in the PULSAR study are consistent with effects of sotatercept in previous clinical studies described in Section 3.1 [Ruckle, J., et al 2009] [Raftopoulos, H., et al 2016] [Abdulkadyrov, K. M., et al 2014] [Komrokji, R., et al 2018] [Cappellini, M. D., et al 2019] [Coyne, D. W., et al 2019] [Sherman, M. L., et al 2013].

This study will assess the effects of sotatercept on time to clinical worsening (TTCW) in newly diagnosed, intermediate- and high-risk PAH patients. The incident patient population (< 12 months from diagnosis) typically begins treatment on double oral combination therapy, and a third therapy may be considered if a patient is not at low-risk at 3 months of follow up.

This study design allows for the interrogation of the effects of sotatercept as an early intervention in the incident population, and also enriches the study population for the primary endpoint. Newly diagnosed patients have a higher likelihood of events of PAH progression, and thus the benefit of adding sotatercept to background PAH therapy on TTCW 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 definitively assess the risk:benefit profile of sotatercept in participants who are newly diagnosed with symptomatic PAH.

4 STUDY OBJECTIVES

The objective of this study is to evaluate the effects of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) on TTCW in participants who are newly diagnosed with PAH and are at intermediate or high risk of PAH disease progression.

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 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

The primary efficacy endpoint is TTCW, defined as the time from randomization to the first confirmed morbidity event or death. Time to clinical worsening can be used to assess disease progression associated with PAH and therefore presents a relevant measurement to participants, clinicians, and regulatory agencies. The majority of clinical trials in PAH have included TTCW as a secondary endpoint. Some of the more recent clinical trials have demonstrated a treatment-related delay in TTCW, and while others have not [Galie, N., et al 2010], recent results suggest that TTCW 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 that will comprise this endpoint include the following:

- All-cause death
- Non-planned PAH-related hospitalization of ≥ 24 hours in duration
- Atrial septostomy
- Lung transplant

- Deterioration in performance in exercise testing due to PAH, defined as a decrease in 6MWD from baseline (average of screening) on 2 consecutive tests (which must be at least 4 hours apart) and at least 1 of the following:
  - Worsening of WHO FC from baseline
  - Signs/symptoms of increased right heart failure
  - Addition of a background PAH therapy or change in the background PAH therapy delivery route to parenteral

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

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

5.3 Secondary Efficacy Endpoints and Rationale

The secondary endpoints will be assessed as ranked below:

1. Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline:
   - Improvement in 6MWD (increase ≥ 30 m)
   - Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L
   - Improvement in WHO FC or maintenance of WHO FC II
2. Proportion of participants who maintain or achieve a low-risk category of Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 Risk Score at Week 24 versus baseline
3. Proportion of participants who maintain or achieve a low-risk score at Week 24 versus baseline using the simplified French Risk score calculator
4. Change from baseline in NT-proBNP levels at Week 24
5. Proportion of participants who improve in WHO FC or maintain WHO FC II at 24 weeks from baseline
6. Change from baseline in 6MWD at Week 24
7. Overall survival
8. Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) at Week 24
9. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24
10. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24

5.3.1 Multicomponent Improvement Endpoint Rationale

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

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

- Assessment of risk in PAH is currently based upon recommendations initially issued by the European Society of Cardiology and European Respiratory Society, with subsequent validation and simplified versions using robust registry data. The variables that have consistently been the most significant prognostic indicators of disease progression and survival are NT-proBNP, 6MWD, and WHO FC.
- Four of the most recent clinical trials in PAH that relied upon morbidity and mortality events as a primary endpoint nevertheless utilized 6MWD and WHO FC in the composite endpoint of "clinical worsening."
- NT-proBNP, as described in Section 5.3.4, has been consistently shown to be an independent predictor of survival in PAH.

5.3.2 REVEAL Lite 2 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 [Benza, R. L., et al 2021] [Benza, R. L., et al 2012] [Benza, R. L., et al 2019] [McLaughlin, V. V., et al 2018] [Galiè, N., et al 2016] [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 can predict both clinical worsening, as well as mortality. The REVEAL Lite 2 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 BP, and 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 ≥ 8 indicate high risk, scores of 6 through 7 indicate intermediate risk, and scores ≤ 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 identified that the REVEAL Lite 2 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 risk score calculator is presented in Appendix 2.

5.3.3 Simplified French Risk Score Calculator Rationale

The simplified French Risk scoring system is based on the 2015 European Society of Cardiology/European Respiratory Society Guidelines for the diagnosis and treatment of PH. In this study, the noninvasive parameters will be used to determine the score. “Low-risk” is defined as attaining or maintaining all 3 low-risk criteria: WHO FC I or II, 6MWD > 440 m, and NT---proBNP < 300 ng/L [Galie, N., et al 2017].

5.3.4 N-Terminal Prohormone B-type Natriuretic Peptide Rationale

NT-proBNP is secreted by cardiomyocytes in response to ventricular stretch and is an established noninvasive marker of ventricular dysfunction in patients with PAH. Plasma NT-proBNP levels correlate with functional capacity, right ventricular function, and echocardiographic and hemodynamic variables, and it has been consistently shown to be an independent predictor of survival in PAH [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].

5.3.5 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 2019].

World Health Organization 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.

5.3.6 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 became limited, particularly in more contemporary trials involving sequential, add-on therapies, in which the change from baseline in 6MWD was smaller than the clinically relevant thresholds of around 30 m [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 remains an important prognostic factor in the risk scores but as absolute thresholds (< 165 m, 165 to 440 m, and > 440 m)

[Galiè, N., et al 2016] instead of changes from baseline. Based on these scores, patients who walk > 440 m have a low (< 5%) risk of mortality in 1 year.

5.3.7 Quality-of-Life Assessments Rationale

Disease-specific 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 PAH-SYMPACT®.

The PAH-SYMPACT® was developed based on interviews with patients with PAH. It is the only PAH-specific instrument developed and validated in accordance with United States Food and Drug Administration (US FDA) guidance on PRO development process therefore providing a validated insight of disease impact in PAH patients.

5.4 Exploratory Endpoints and Rationale

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

- Change in dyspnea score (assessed by Borg Dyspnea Scale [Borg CR10 Scale®]) at Week 24 versus baseline
- Change from baseline in C-reactive protein (CRP) levels at Week 24
- Change of Cardiovascular Symptoms domain score from baseline in PAH-SYMPACT® at Week 24
- Change from baseline in EuroQol–- 5 dimensions scale 5 levels (EQ-5D-5L) index score at Week 24
- Change from baseline in EQ-5D-5L visual analog scale (VAS) at Week 24
- Changes from baseline in ECHO parameters (e.g., RVSP [right ventricular systolic pressure] and TAPSE [tricuspid annular plane systolic excursion]) at Week 24
- Proportion of participants who maintain or achieve a low or intermediate-low-risk based on COMPERA 2.0 four-stratum risk score at Week 24

5.4.1 COMPERA 2.0 Four-Stratum Risk Score Calculator Rationale

The Comparative, Prospective Registry of Newly Initiated Therapies for PH (COMPERA) 2.0 four-stratum risk score is based on WHO FC, 6MWD and NT-proBNP. This 4-stratum model was developed and validated in PAH patients for whom all three 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 nearest integer. Participants will be categorized on the final risk score value: 1, low-risk; 2, intermediate–low-risk; 3, intermediate–high risk, 4, high risk. Sites will be required to calculate the COMPERA 2.0 four-stratum risk score at Screening Visit only
[Hoeper, M. M., et al 2022] [Boucly, A., et al 2022]. The COMPERA 2.0 four-stratum risk score calculator is presented in Appendix 3

5.5 Safety Endpoints

Safety will be evaluated by collecting the following:

- Adverse Events (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, DBPC study to evaluate sotatercept when added to background PAH therapy in newly diagnosed intermediate- and high-risk PAH patients.

Participants enrolled in the study will have a diagnosis within 12 months of study screening of symptomatic PAH (WHO Group 1, classified as FC II or III) and presentation of idiopathic or heritable PAH, PAH associated with connective tissue diseases (CTDs), drug- or toxin- induced PAH, after shunt correction PAH, or PAH presenting at least 1 year following the correction of congenital heart defects.

6.2 Duration of Study

- Each participant will be enrolled in the study for up to approximately 47 months, as follows:
- The Screening Period will be up to 4 weeks in duration.
- The DBPC Treatment Period will be until event occurrence, up to approximately 44 months in duration.
- The Follow-up Period will be up to 8 weeks in duration.

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 $\geq$ 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 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, a starting dose of 0.3 mg/kg was selected and will be administered at Visit 1 and a target dose of 0.7 mg/kg will be administered at Visit 2 and for the remainder of the treatment period. All doses will be administered subcutaneously (SC) every 21 days with appropriate dose modification guidelines (see Section 8.3).

6.4 Study Design, Stratification, and Treatment Assignment

This is a Phase 3, randomized, DBPC, multicenter, parallel group study. Participants who have provided documented informed consent and meet all eligibility criteria will be stratified by the following:

- WHO FC (Class II or III), defined as the evaluation taken at Visit 1 prior to randomization
- Background PAH therapy (double or triple therapy)

Up to approximately 444 participants will be randomly assigned in a 1:1 ratio to receive SC injections of either placebo or sotatercept at a starting dose of 0.3 mg/kg SC at Visit 1. Participants will then be escalated to the target dose level of 0.7 mg/kg SC at Visit 2 and will remain at this target dose level for all subsequent DBPC Treatment Period visits. Randomization is described in Section 6.6.

Dosing will be once every 21 days for a total consecutive period of up approximately 44 months during the DBPC Treatment Period. All participants will remain on background PAH therapy during the study.

The study is divided into a Screening Period (up to 4 weeks), a DBPC Treatment Period (up to approximately 44 months), and a Follow-up Period (up to 8 weeks). During the DBPC Treatment Period, selected study visits may be performed as home health care (HHC) visits as described in Section 6.5.

Each study participant will remain in the DBPC Treatment Period until they experience an event of clinical worsening, and the study will remain blinded until the required number of events of clinical worsening have been recorded. A planned interim analysis (IA; described in Section 11.8) will occur when approximately 61 participants have experienced a primary endpoint event.

When a participant experiences an event of clinical worsening, and the sponsor has confirmed completeness of electronic data capture (EDC) forms related to clinical worsening, they will complete the End of Treatment (EOT) Visit and will be eligible to enroll into the open-label, long-term follow-up (LTFU) study, A011-12 (SOTERIA). A participant who experiences an event of lung transplantation will not be eligible to rollover to SOTERIA.

Participants who experience a worsening event during the DBPC Treatment Period and do not wish to participate in the SOTERIA study will undergo a Follow-up Period of 8 weeks

that will include both the EOT and the End of Study (EOS) Visits, as described in Section 9.2.3 and Section 9.2.4, respectively.

Participants who discontinue the DBPC Treatment Period early, without experiencing an event of clinical worsening, will complete the EOT Visit at the time of discontinuation and will be asked to return to complete the EOS Visit and Follow-up Calls/Visits as described in Section 9.4.1, provided that consent is not withdrawn. These participants will not be eligible to enroll in the SOTERIA study.

After the study is unblinded, participants who are currently on treatment (sotatercept or placebo) in the DBPC Treatment Period may be eligible to participate in the SOTERIA study following completion of the EOT Visit. For these participants, the EOS Visit can be waived.

MK-7962-005-11 Implementation: Results of the recently-completed interim analysis of ZENITH (MK-7962-006) demonstrated that sotatercept treatment – compared with placebo – led to a statistically significant and clinically meaningful reduction in the risk of morbidity or mortality events in adults with PAH WHO FC III or IV at high risk of mortality. In conjunction with results from STELLAR (MK-7962-003), these results confirm a lack of clinical equipoise and no longer justify continuing a placebo-controlled trial with sotatercept in PAH. Therefore, the Sponsor has decided to terminate HYPERION (A011-13, MK-7962-005) to permit all eligible participants to receive sotatercept either in the extension study (SOTERIA, MK-7962-004) or via commercial access (where available).

The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP. All eligible participants will complete the EOT visit before enrollment in SOTERIA or initiation of commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit. Follow-up Telephone Calls and annual Follow-up Visits will not be conducted.

6.5 Home Health Care Visits

Select study visits (Visits 6 until the end of the DBPC Treatment Period, except for 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 who 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 the informed consent and meet all eligibility criteria will be stratified by baseline WHO FC and background PAH therapy and then randomized to receive either placebo plus background PAH therapy or sotatercept plus background PAH therapy. Randomization assignments will be generated through a computerized system, provided through Interactive Response Technology (IRT) (see IRT Manual for details).

In the event of a medical emergency for an individual participant in which knowledge of the study drug is critical to the participant's medical management, the investigator may break the blind for that participant via the IRT (see IRT 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 should 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 in the SOTERIA study. The investigator should not inform the participant of their treatment assignment under any circumstances.

7 STUDY POPULATION

7.1 Rationale for Selected Population

Participants diagnosed within 12 months of study screening with symptomatic PAH (WHO Group 1, classified as FC II or III) who present with idiopathic or heritable PAH, PAH associated with CTD, drug- or toxin-induced PAH, after shunt correction PAH, or PAH presenting at least 1 year following the correction of congenital heart defects will be eligible for this study.

PAH is considered a relatively rare condition, with approximately 80% of PAH patients presenting as WHO FC II to III. Typically, WHO FC I PAH patients are excluded from interventional studies due to the relatively low rate of identification, low prevalence, and mild symptomatology. Similarly, there is a low prevalence of PAH patients with WHO FC IV, and given their severe disease burden, these patients have a limited ability to participate in longer interventional studies.

The selected population was chosen to align with current PAH treatment algorithms and allow for participants to receive standard-of-care therapies, as well as to address 2 distinct goals of the study: 1) to assess the effects of sotatercept as an early intervention, on top of background PAH therapies, in an incident PAH population; and 2) to assess the effects of sotatercept on top of background PAH therapies on TTCW in support of its potential disease-modifying functions.

Current treatment guidelines suggest the initiation of treatment with double oral combination therapy [Galie, N., et al 2019]. If the patient has not achieved low-risk status after 3 to 6 months of treatment, a third therapy may be added. However, in some patients at high risk, triple therapy may be implemented earlier. The inclusion criteria for this study allows patients on triple combination therapy; however, all therapies, whether double or triple combinations, must be stable for 90 days prior to entry into this study.

The study population selection also enriches for the primary endpoint of TTCW. Newly diagnosed patients have a greater likelihood of experiencing events of clinical worsening [McLaughlin, V. V., et al 2018]. The inclusion of only participants at intermediate to high risk on the REVEAL Lite 2 risk assessment instrument and intermediate-low to high risk on the COMPERA 2.0 four stratum risk assessment enriches the study for events, allowing the assessment of sotatercept on TTCW in the population in which a difference is more likely to be evident within the timeframe of the clinical study, and in a population who may benefit the most from the intervention.

7.2 Background PAH Therapy and Diuretics

Background PAH therapy refers to approved PAH-specific medications and may consist of a double or triple combination of therapy with endothelin-receptor antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogs or receptor agonists. Background PAH therapy should be stable at least 90 days prior to screening. Adjustments in parenteral prostacyclin doses by up to 10% are permitted and

should not affect therapy stability determination. As described in Section 9.4.1, a participant may be discontinued early from the study treatment and be ineligible to participate in SOTERIA if any of the following modifications occur to background PAH therapy, and these modifications are not accompanied by a decrease in 6MWD or another event of clinical worsening: (1) the participant is prescribed a new PAH-specific medication, (2) there is an escalation in the background PAH therapy such as a dose increase, or (3) there is a change in the background PAH therapy delivery route to parenteral. During the trial, changes in background PAH therapy, intended as dose reduction, interruption or medication change, should be avoided unless deemed for safety concerns (i.e., background therapy tolerability issues).

Stable diuretic therapy is defined as no addition of a new diuretic and no switching of a preexistent oral diuretic to parenteral administration for at least 90 days; however, dose adjustments (up or down) in preexistent oral diuretics are acceptable.

7.3 Inclusion Criteria

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

1. Age ≥ 18 years
2. Documented diagnostic right heart catheterization (RHC) within 12 months of screening documenting a minimum PVR of ≥ 4 Wood units and pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of ≤ 15 mmHg, with the diagnosis of WHO PAH Group 1 in any of the following subtypes:
    - Idiopathic PAH
    - Heritable PAH
    - Drug/toxin-induced PAH
    - PAH associated with CTD
    - PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
3. Symptomatic PAH classified as WHO FC II or III
4. Either REVEAL Lite 2 risk score ≥ 6 or COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above)
5. Diagnosis of PAH within 12 months of screening and on stable doses of a double or triple combination of background PAH therapies and diuretics (if any) for at least 90 days prior to screening. Background PAH therapy and diuretics are further defined in Section 7.2.
6. 6MWD ≥ 150 m repeated twice at screening at least 4 hours apart, but no longer than 1 week apart, and both values are within 15% of each other (calculated from the highest value)
7. Females of childbearing potential (as defined in Appendix 4) must meet the following criteria:
    - Have 2 negative urine or serum pregnancy tests as verified by the investigator during the Screening Period;

- Agree to ongoing pregnancy testing (either urine or serum) 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:
  - Use highly effective contraception without interruption for at least 28 days prior to starting the investigational product AND
  - Agreed 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 meet the following criteria:
   - 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 documented informed consent

7.4 Exclusion Criteria

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

1. Diagnosis of PH WHO Groups 2, 3, 4, or 5
2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, pulmonary veno occlusive disease and pulmonary capillary hemangiomatosis.
3. Hgb at screening above gender-specific ULN, per local laboratory test
4. Uncontrolled systemic hypertension as evidenced by sitting systolic BP > 180 mmHg or sitting diastolic BP > 110 mmHg during the Screening Visit after a period of rest
5. Baseline systolic BP < 90 mmHg at screening
6. Pregnant or breastfeeding women
7. Any of the following clinical laboratory values at the Screening Visit:
   - eGFR < 30 mL/min/1.73 m^2 (as defined by MDRD equation)
   - Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels > 3 × ULN (For United Kingdom [UK], refer to the specific requirement in Appendix 6)

- Platelet count < 50,000/mm^3 (< 50.0 × 10^9/L)

8. Currently enrolled in or have completed any other investigational product study within 30 days for small-molecule drugs or within 5 half-lives for investigational biologics prior to the date of documented informed consent
9. Known allergic reaction to sotatercept (ACE-011), its excipients, or luspatercept
10. History of pneumonectomy
11. Pulmonary function test values of forced vital capacity < 60% predicted within 1 year prior to the Screening Visit
12. Stopped receiving any PH chronic general supportive therapy (e.g., diuretics, oxygen, anticoagulants, and digoxin) within 60 days prior to the Screening Visit
13. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to the Screening Visit or planned initiation during the study (participants who are stable in the maintenance phase of a program and who will continue for the duration of the study are eligible)
14. Untreated more than mild obstructive sleep apnea
15. History of known pericardial constriction
16. History of restrictive cardiomyopathy
17. History of atrial septostomy within 180 days prior to the Screening Visit
18. Electrocardiogram with Fridericia's corrected QT interval (QTcF) > 500 ms during the Screening Period Appendix 6 (For UK and South Korea, refer to the specific requirement in Appendix 6)
19. Personal or family history of long QT syndrome or sudden cardiac death
20. Left ventricular ejection fraction < 50% documented by a historical ECHO or cardiac MRI within the last 12 months prior to screening (if there is more than one assessment of LVEF, the value from the most recent measurement should be used in assessing eligibility)
21. Coronary artery disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the Screening Visit
22. Cerebrovascular accident within 3 months prior to the Screening Visit
23. Acutely decompensated heart failure within 30 days prior to the Screening Visit, as per investigator assessment
24. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease
25. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, and vasopressin) within 30 days prior to the Screening Visit
26. Active malignancy with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or prostate cancer that is not currently or expected, during the study, to be treated with radiation therapy, chemotherapy, and/or surgical intervention, or hormonal treatment.

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 document the informed consent form (ICF). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and AEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with the approval of the study Medical Monitor. 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 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 medication 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. Refer to the Pharmacy Manual for details.

The study intervention to be used in this study is outlined 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	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

EEA =European Economic Area; EOS=end of study; EOT=end of treatment; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; SC=subcutaneous(y); 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 EEA. 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. 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.

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 Screening 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 increases greater than 4 g/dL above the participants baseline value, the study Medical Monitor should be consulted; if Hgb increases greater than 2 g/dL above gender specific ULN, dose hold should be applied for at least 1 visit, and Medical Monitor should be consulted. Refer to Figure 3 for additional details.

8.3.3 Dose Modifications Due to Low Platelet Count

If platelet count is less than 50,000/mm^3, dose delay is allowed for up to 3 visits. If platelet count remains less than 50,000/mm^3 after 3 consecutive dose delays, then study 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 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.

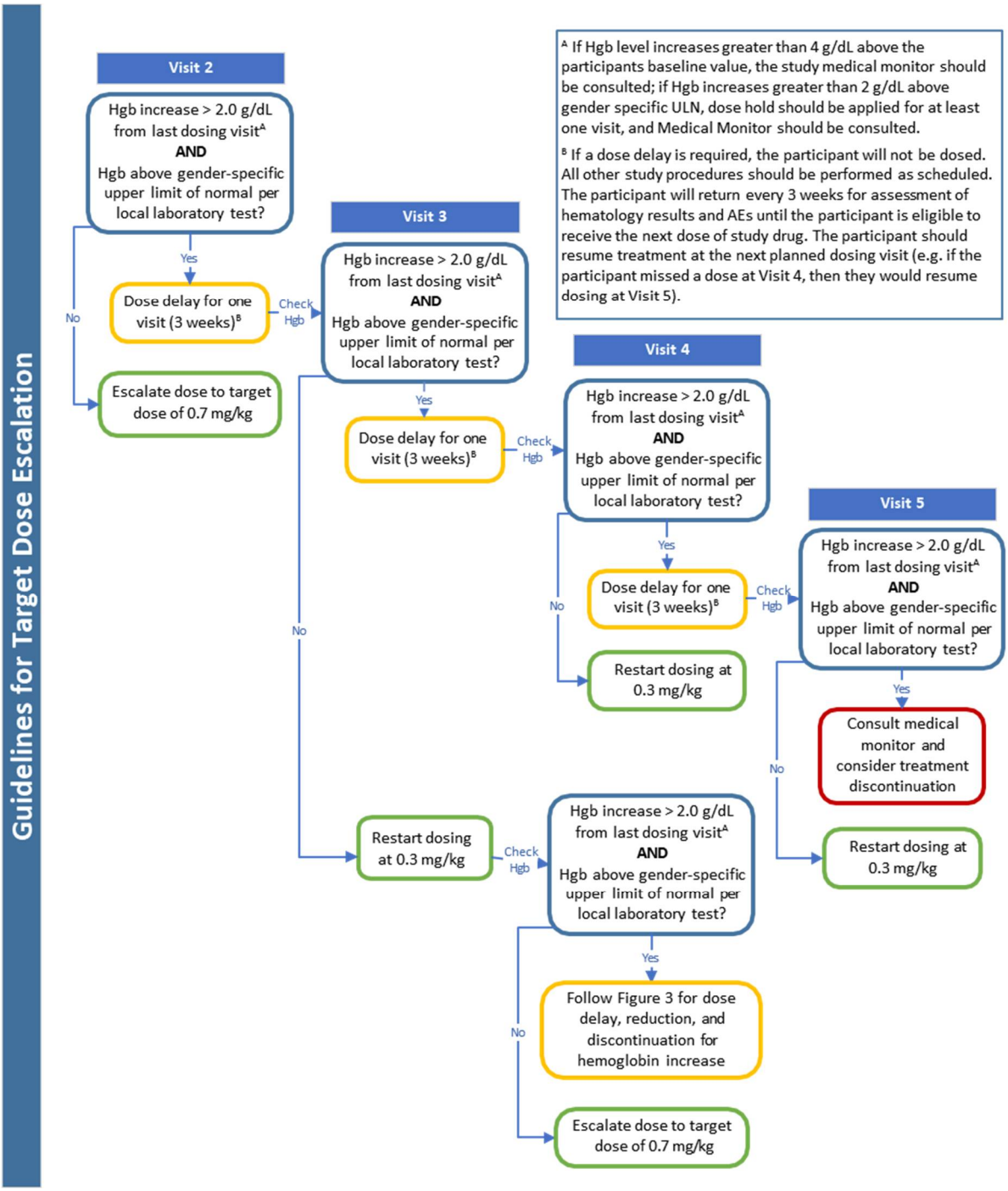
8.3.5 Dose Delays Due to SAEs of Bleeding

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

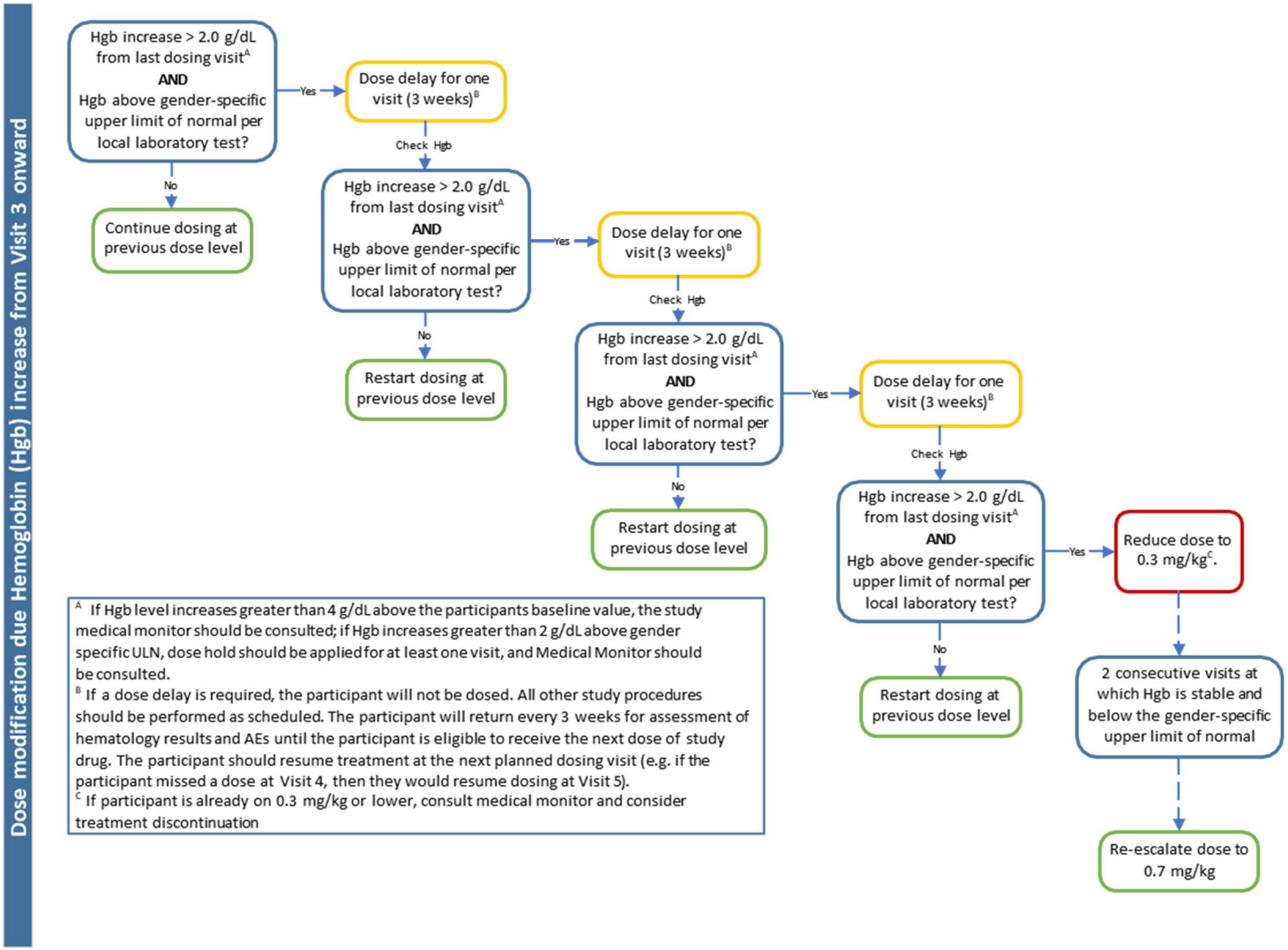
In cases of dose reduction due to an AE not related to study drug, the dose can be re-escalated when the AE is resolved. In cases of dose reduction due to increases in Hgb, the dose will be re-escalated to 0.7 mg/kg after 2 consecutive visits at which Hgb values are stable and equal to or lower than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



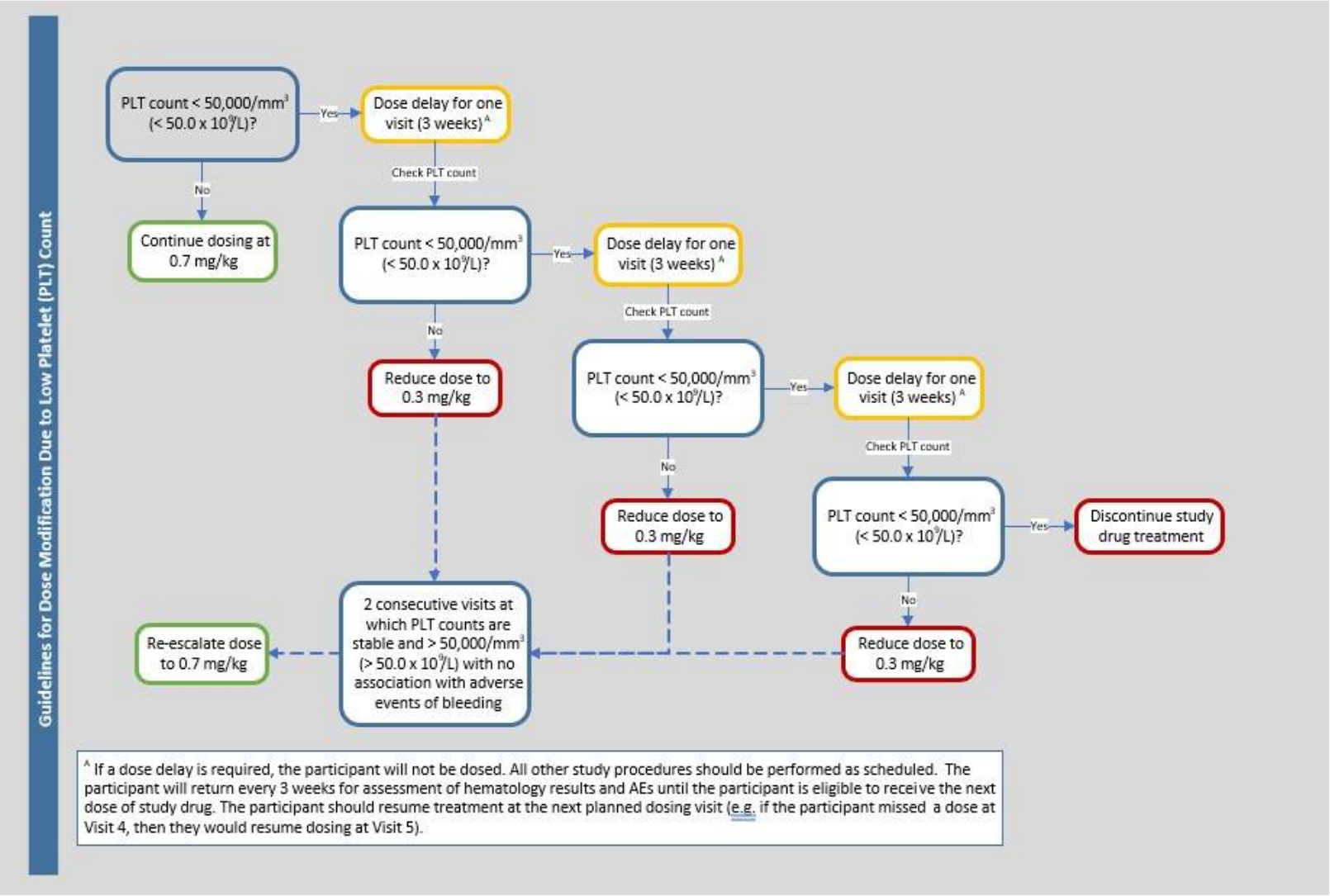
AE = adverse event; Hgb = hemoglobin.

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



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 for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The investigator must return all unused vials of study drug to Acceleron Pharma Inc. at the end of the study, or the study drug may be destroyed at the clinical site after Acceleron Pharma Inc.'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 document an ICF before any study-specific screening tests are conducted. Informed consent must be documented 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. If historical RHC does not provide all the necessary measurements to confirm a minimum PVR of ≥ 4 Wood units and pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of ≤ 15 mmHg, with the diagnosis of WHO PAH Group 1, a RHC can be repeated as a screening procedure. However, the historical RHC will be used for the date of PH group 1 diagnosis.

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

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

Screening procedures include the following:

- Informed consent
- Inclusion/exclusion criteria
- Medical history review
- Physical examination
- 12-lead ECG
- Vital signs including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (complete blood cell [CBC] count)
- Serum chemistry
- Urinalysis (dipstick)
- Six-minute walk test (6MWT)
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Risk score assessment
- NT-proBNP, activin A, and CRP sample collection
- ADA sample collection
- ECHO
- AE/serious adverse event (SAE) review
- Concomitant medication review
- Right heart catheterization (if applicable)

9.2.2 Double-blind, Placebo-controlled Treatment Period (Visits 1 to 9)

Study procedures for Visits 1 to 9 vary dependent on the visit number. All study procedures/assessments should be performed prior to the administration of the study drug 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
- Clinical worsening assessment
- PAH-SYMPACT® and EQ-5D-5L assessments
- NT-proBNP, activin A, and CRP sample collection
  - Samples for NT-proBNP and activin A will be collected pre-dose and at 1 to 2 hours, 2 to 4 hours, and 4 to 8 hours post-dose. One sample for CRP assessment will be collected prior to study drug administration.
- PK sample collection
  - Samples for PK assessments will be collected pre-dose at 1 to 2 hours, 2 to 4 hours, and 4 to 8 hours post-dose.
- ADA sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.2 Visits 2 through 4 (21 ± 3 days)

Visit day windows are relative to the date of the previous dose of study drug: every 21 days (± 3 days). Visits 2 through 4 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
- Clinical worsening assessment
- NT-proBNP, activin A, and CRP sample collection
- ADA sample collection

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

9.2.2.3 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 (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- PAH-SYMPACT® and EQ-5D-5L assessments
- NT-proBNP, activin A, and CRP sample collection
- ADA sample collection
- PK sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.4 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

9.2.2.5 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 (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- PAH-SYMPACT® and EQ-5D-5L assessments
- NT-proBNP, activin A, and CRP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.6 Visits 10 through 12 (21 ± 3 days)

Visits 10 through 12 procedures include the following:

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

9.2.2.7 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 (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK sample collection
- Study drug administration
- AE/SAE review
- Concomitant medication review

9.2.2.8 Visits 14 Onward Until the End of the DBPC Treatment Period (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 at quarterly site visits (Visits 17, 21, 25, etc.) include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-lead ECG (Visits 17, 33, 49, and 65 only)
- Vital signs including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK sample collection
- ECHO at Visit 33
- Study drug administration
- AE/SAE review
- Concomitant medication review

The procedures that occur every 6-months during onsite visits (Visits 17, 25, 33, 41, 49, 57, 65, 73, etc) include the following:

- PAH-SYMPACT® and EQ-5D-5L assessments

9.2.3 End of Treatment Visit Following a Clinical Worsening Event, 21 ± 7 Days from Last Dose for Early Discontinuation, or Study Completion

The EOT Visit should occur 21 days (± 7 days) after the last study drug administration. Participants who discontinue early, without experiencing an event of clinical worsening, should complete the EOT Visit at the time of discontinuation. Participants who experience a clinical worsening event can complete the EOT Visit after the sponsor confirms completeness of EDC forms related to clinical worsening. Discontinuation of study drug administration can occur at any visit during the DBPC Treatment Period. Reasons for early discontinuation are described in Section 9.4.1. The procedures at the EOT Visit include the following:

- Targeted cardiopulmonary and skin physical examinations
- 12-lead ECG
- Vital signs including weight
- Serum or urine pregnancy test (where applicable)
- Hematology (CBC)
- Serum chemistry
- Urinalysis (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- PAH-SYMPACT® and EQ-5D-5L assessments
- NT-proBNP and CRP sample collection
- ADA sample collection
- PK sample collection
- ECHO
- AE/SAE review
- Concomitant medication review

MK-7962-005-11 Implementation: The Sponsor has decided to close the HYPERION study (A011-13, MK-7962-005) so that all eligible participants in HYPERION can receive sotatercept either by extension study (SOTERIA, MK-7962-004) or by commercial access, if available.

The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP. All eligible participants will complete the EOT visit before enrollment in SOTERIA or initiation of commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit. Follow-up Telephone Calls and annual Follow-up Visits will not be conducted.

9.2.4 End of Study Visit (5 Weeks ± 7 Days from End of Treatment Visit)

The EOS Visit will be completed by participants who do not wish to participate in the SOTERIA study and for participants who discontinue treatment early for reasons other than clinical worsening. These participants should also complete their EOT Visit assessments as described in Section 9.2.3 as long as consent is not withdrawn.

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 (dipstick)
- 6MWT
- Borg Dyspnea Scale (pre- and post-6MWT)
- WHO FC assessment
- Clinical worsening assessment
- PAH-SYMPACT® and EQ-5D-5L assessments
- 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: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 as per the SoE. During the Screening Period, the 6MWT should be performed twice at least 4 hours, but no longer than 1 week, apart. The average of the 2 screening 6MWDs should be used for the REVEAL Lite 2.0 calculation.

A standardized 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) [Singh, S. J., et al 2014] 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).

The 6MWD will be calculated and recorded. If the participant discontinues the test prematurely, the time (mm:ss) and distance walked will be recorded. Requirement of acute supportive rescue medication (e.g., oxygen therapy) and any AEs occurring during the 6MWT must be recorded. If a participant is on chronic oxygen therapy, oxygen should be administered at their standard rate, or as directed by the investigator. During the study, the 6MWT should be performed at approximately the same time of day to avoid diurnal variation. The 6MWT should be performed under the same conditions at least between screening and Visit 9, including chronic oxygen therapy and the use of walking aids or the same type of mask (e.g., surgical or N95) 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 5 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 PH

The 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 FC	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.

9.3.5 Clinical Worsening Assessment

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

Clinical worsening must be assessed using the following criteria:

- All-cause death
- Non-planned PAH-related hospitalization of ≥ 24 hours in duration
- Atrial septostomy
- Lung transplant
- Deterioration in performance in exercise testing due to PAH, defined as a decrease in 6MWD from baseline (average of screening) on 2 consecutive tests (which must be at least 4 hours apart) and at least 1 of the following:
  - Worsening of WHO FC from baseline
  - Signs/symptoms of increased right heart failure
  - Addition of a background PAH therapy or change in the background PAH therapy delivery route to parenteral

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

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

9.3.6 Risk Score Assessment

Risk scores will be based on the simplified French Risk score, the REVEAL Lite 2 risk calculator, and the COMPERA 2.0 four-stratum model; these approaches use noninvasive variables to determine risk score for classification into a risk category. The simplified French Risk scoring system uses WHO FC, 6MWD, and NT-proBNP to determine the score. The REVEAL Lite 2 uses renal insufficiency (by eGFR), WHO FC, systolic BP and heart rate, 6MWD, and NT-proBNP to determine the score (Appendix 2) The COMPERA 2.0 is a 4-stratum risk score assessment based on WHO FC, 6MWD and NT-proBNP [Hoeper, M. M., et al 2022] [Boucly, A., et al 2022]. REVEAL Lite 2 and COMPERA 2.0 must be calculated using central laboratory NT-proBNP and eGFR values. Sites will use this score to ensure that inclusion criterion #4: either REVEAL Lite 2 risk score ≥ 6 OR COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above), is met by the participant at enrollment. Sites will only be required to calculate the REVEAL Lite 2 and COMPERA 2.0 risk score during Screening Period. The sponsor will calculate the risk scores for all other study visits pertinent to endpoint assessments. The simplified French Risk will be calculated solely by the sponsor.

9.3.7 Echocardiogram Parameters

Two-dimensional ECHO (2-D ECHO) parameters will include but not limited to RVSP, TAPSE, right ventricular fractional area change (RVFAC), and right ventricular end diastolic

area (RVEDA). An ECHO performed during the Screening Period is used as the baseline for this study. All ECHOs performed after screening can be performed on the day of the study visit or within 1 week prior to study drug administration. The ECHO parameters review process will be performed by a central vendor, according to the study manual.

9.3.8 Patient-reported Outcomes

9.3.8.1 EuroQol – 5 Dimensions Scale 5 Levels Assessment

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

In the evaluation part, the respondents evaluate their overall health status using the EQ-5D-5L VAS.

Participants will complete the EQ-5D-5L questionnaire prior to study drug administration during the study visits, or up to 3 days prior to the study visit as outlined in the SoEs. Refer to the Study Manual for more details.

9.3.8.2 Pulmonary Arterial Hypertension–Symptoms and Impact

The PAH-SYMPACT® questionnaire is a PRO instrument. The PRO was developed based on interviews with patients with PAH following the process outlined in the US FDA’s PRO guidance.

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

Vital signs will be collected before blood collection and study treatment administration and include the following:

- 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.
- Blood pressure (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 N-Terminal Prohormone B-type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a hormone produced by the heart. NT-proBNP is a non-active prohormone that is released from the same molecule that produces BNP. Both BNP and NT-proBNP are released in response to changes in pressure inside the heart. NT-proBNP levels are primarily used to help detect, support diagnosis, and, in some instances, evaluate the severity of heart failure.

Samples for NT-proBNP analysis will be collected as described in the SoEs (Section 2) and will be shipped and analyzed by a central laboratory.

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 TGF-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 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 subjects. 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 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 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 eCRF.

The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically 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.

9.3.16.1 Hematology

Hematology (CBC) laboratory assessments will be collected and analyzed at the local laboratory of the investigative sites and will be measured at every visit as outlined in the SoEs. CBC count includes RBCs, absolute WBCs, Hgb, Hct, and platelet count.

9.3.16.2 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, creatinine, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorus, glucose, magnesium, follicle-stimulating hormone (FSH), bicarbonate (HCO_3), and albumin will be measured. Investigators must review the results to monitor the participant's safety.

9.3.16.3 Urinalysis (Dipstick)

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.

9.3.16.4 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 4 for further information.

9.3.17 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 updated 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 Early Discontinuation of Study Treatment

Early discontinuation of study treatment refers to permanently stopping study drug administration without experiencing an event of clinical worsening (except for death) during the DBPC Treatment Period or before the trial has been unblinded for participants to rollover into the SOTERIA study. Discontinuation of study treatment does not represent withdrawal from the study.

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 has discontinued treatment. 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's unwillingness or inability to comply with the protocol
- (1) Participant is prescribed a new PAH-specific medication, (2) there is an escalation in the background PAH therapy such as a dose increase (3) there is a change in the background PAH therapy delivery route to parenteral, and these medication changes are not accompanied by a decrease in 6MWD or another event of clinical worsening. Note: Adjustments in parenteral prostacyclin doses by up to 10% are permitted and should not affect therapy stability determination.
- An increase in QTcF of > 60 ms that results in QTcF of > 500 ms (or > 550 ms if right bundle branch abnormality is present) during the treatment period
- More than 3 dose delays required per dose adjustment guidelines (Section 8.3)
- Pregnancy

- Women of childbearing potential not using adequate combination of effective contraception methods throughout the study
- Men with a partner of childbearing potential not accepting to use contraceptive methods throughout the study
- Study terminated by the sponsor
- Lost to follow up
- Death

All participants who discontinue the DBPC Treatment early, without experiencing an event of clinical worsening, will complete the assessments scheduled for the EOT Visit at the time of discontinuation and will be asked to return the clinic to complete the remaining EOS and the Follow-up Visits. Following the EOT and EOS Visits, they will receive telephone contacts for vital status 6 months after the EOS Visit and yearly after. They will also have Follow-up Visits for 6MWT and other procedures as defined in Table 3, 1 year after the EOS Visit and yearly after until the study is unblinded, provided that the consent is not withdrawn. Follow-up Telephone Calls can replace Follow-up Visits if the participant cannot visit the site. Participants who discontinue the DBPC Treatment early, without experiencing an event of clinical worsening, will not be eligible to enroll in the SOTERIA study.

MK-7962-005-11 Implementation: The Sponsor has decided to close the HYPERION study (A011-13, MK-7962-005) so that all eligible participants in HYPERION can receive sotatercept either by extension study (SOTERIA, MK-7962-004) or by commercial access, if available. All eligible participants will complete the EOT visit before enrollment in SOTERIA or initiation of commercial product. Participants not enrolling into SOTERIA or initiating commercial product will complete the EOS Visit. Follow-up Telephone Calls and annual Follow-up Visits will not be conducted.

9.4.2 Participant Withdrawal from the Study

A participant must be withdrawn from the study if he/she withdraws 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. The investigator must notify Acceleron Pharma Inc. and the Medical Monitor when a participant has withdrawn from the study. These participants will not be eligible to enroll in the SOTERIA study.

9.4.3 End of Study Definition

The end of the study is defined as when the last participant completes the last visit.

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. Participants who discontinue the study early or decline enrollment into the SOTERIA study will be asked to return to the clinic for the EOS 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). Each attempt at contact must be documented in the participant's study record.
- If the participant continues to be unreachable after the mentioned attempts, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow up, which should be noted on the participant's eCRF.

9.6 Concomitant Medication and Therapy During Study Conduct

During screening and throughout the study, participants may take stable doses of medications for chronic conditions, including for PAH, as outlined in the study inclusion criteria (Section 7.3). As described in Section 9.4.1, a participant may be discontinued early from the study treatment and be ineligible to participate in SOTERIA if any of the following modifications occur to background PAH therapy, and these modifications are not accompanied by a decrease in 6MWD or another event of clinical worsening: (1) the participant is prescribed a new PAH-specific medication (2) there is an escalation in the background PAH therapy such as a dose increase (3) there is a change in delivery route to parenteral. During the trial, changes in background PAH therapy, intended as dose reduction, interruption or medication change, should be avoided unless deemed for safety concerns (i.e., background therapy tolerability issues) 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) guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

10 SAFETY ASSESSMENT, REPORTING, AND MONITORING

10.1 Adverse Events

10.1.1 Definitions of Adverse Event

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

Abnormal laboratory and other abnormal investigational findings (e.g., physical examination 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

Preexisting medical conditions/signs/symptoms present 30 days prior to the initial study drug administration (Visit 1) that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are not to be considered AEs. Anticipated day-to-day fluctuations of preexisting conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

10.2 Serious Adverse Events

10.2.1 Definition of Serious Adverse Events

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

- Results in death
- Life threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon

appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent 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 documenting the ICF or routine clinical procedures that are not the result of an AE are not to be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either "serious" or "nonserious" according to the usual criteria.

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

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

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, 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 preexisting condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

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

Important medical event: An important medical event is an event that may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent 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 T_{max} at steady state can occur relatively early in the first few days after dose.

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

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

10.5 Documenting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. Participants will be evaluated and questioned generally for AEs during the course of the study, starting at the documenting of the informed consent. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences. The investigator must report in detail all adverse signs and symptoms that are either volunteered by participants or observed during or following the course of investigational product administration on the appropriate eCRF page. All clearly related signs, symptoms, and abnormal results from diagnostic procedures should be recorded under 1 diagnosis. All AEs and SAEs reported from the documenting of the ICF to the EOS Visit and Follow-up Visits/Calls (early discontinuation only) 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 form. If the participant was hospitalized, a summary from the investigator should be included as part of the participant medical file. In all instances, the investigator should follow up with participants until the outcome of the SAE is known.

10.6 Reporting Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately, within a maximum 24 hours after becoming aware of the event, inform Acceleron Pharma Inc. via the contract research organization by entry on the eCRF or, if not available, by telephone or email. A study-specific paper SAE Report Form must also be submitted within 24 hours of becoming aware of the event.

All written reports should 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 the completion instructions are provided for the Investigator Site File. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by email. Reporting procedures and timelines for follow-up information are the same as for the initially reported SAE.

Relevant pages from the eCRF 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 eCRF.

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 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 documenting of the ICF up until the EOS Visit. All participants who took at least 1 dose of study drug, whether they completed the Treatment Period or not, should complete the EOS Visit unless they are transitioning into the SOTERIA study, provided that consent is not withdrawn.

All AEs will be followed until return to screening baseline, resolution, or clinical database lock. All SAEs will undergo active follow up until resolved or the event becomes chronic or stable. Follow-up data for SAEs obtained after clinical database lock will be incorporated into the sotatercept safety database.

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

Acceleron Pharma Inc. will send appropriate safety notifications to health authorities in accordance with applicable laws and regulations.

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

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

Acceleron Pharma Inc. will inform the investigator of AEs that are both serious and unexpected and are considered to be related to study drug (suspected and 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 eCRF. 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 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 Adverse Events of Special Interest

The risks are consistent with the list in the current version of the sotatercept IB. The adverse events of special interest (AESIs) are considered important parameters to be monitored in order to assess the overall safety of the PAH population and therefore will be included in safety monitoring in the sotatercept clinical trial.

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 and increases in Hgb 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 Data Monitoring Committee (DMC) will be convened to monitor the safety of the study participants. An independent blinded adjudication committee will adjudicate all clinical worsening events, including death, up to the end of the study to determine whether these events are due to PAH.

10.9.1 Adverse Events of Special Interest

The monitoring of AESIs is detailed in Table 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 a patient with 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, DBPC, multicenter, parallel-group study to evaluate sotatercept when added to background PAH therapy in newly diagnosed, intermediate- and high-risk PAH patients.

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 TTCW (see Section 5.2) using EAST version 6. Assumptions for the desired treatment effect and estimate of variability (TTCW) are based on data from the STELLAR study. 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.

For TTCW, given a 1:1 randomization, a 1-sided 0.025 Type I error rate, 90% power, assumed hazard ratio of 0.55, and with a planned IA at 50% of the required number of events with the option to stop the study for futility, 121 events will be required at the final analysis based on the log-rank test.

Approximately 444 participants are planned to be enrolled in this study. With an accrual period of approximately 35 months, assuming an accrual rate of approximately 12.5 participants per month, a dropout rate of approximately 0.4% per month (5% per year), and placebo event rate of 0.20 per year (cumulative annual survival probability of 0.80), the IA is expected to occur at 30 months. If the study continues after IA, the final analysis is expected to occur at 44 months. Another criterion for conducting the IA is that median participant time on study must be at least 6 months.

MK-7962-005-11 Implementation: The Sponsor has decided to close the HYPERION study (A011-13, MK-7962-005) so that all eligible participants in HYPERION can receive sotatercept either by extension study (SOTERIA, MK-7962-004) or by commercial access, if available. The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP.

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.
- **Pharmacokinetic Population:** All participants who receive at least 1 dose of investigational product and have sufficient PK samples collected and assayed for PK analysis.

11.4 Statistical Methods

The SAP will be developed and finalized before database lock and will describe the populations to be used in the analyses, and additional details of procedures for accounting for missing, unused, and spurious data as needed. The aligned rank stratified Wilcoxon test will be used for continuous variables [Mehrotra, D. V., et al 2010] [Hodges, J. L., Jr. and Lehmann, E. L. 1962]. In this test, the endpoint values are first aligned across the randomization strata using the stratum-level Hodges-Lehmann location shift estimates, and the aligned values are then analyzed using a Wilcoxon rank sum test. The output from this analysis will be used to provide a 2-sided p-value and corresponding Hodges-Lehmann location-shift estimate of the overall treatment difference with 95% CI. The stratified 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. Statistical analyses of efficacy data will be performed on the FAS. Efficacy results will be deemed to be statistically significant after consideration of the approach to control Type I error in Section 11.5.2. Pooling strategy of the randomization strata might be added in the SAP if the data are too sparse across the strata.

11.5 Study Endpoints

11.5.1 Primary Endpoint

The primary endpoint will be analyzed using a stratified log-rank test with randomization stratification 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 did not experience any of the components of the primary endpoint as of the time of the data cutoff will be censored. Participants who withdraw from the study or are lost to follow-up before experiencing any of the components of the primary endpoint will be censored at the last known study contact record. Details on the handling of censored data will be described in the SAP.

11.5.2 Secondary Endpoints

The 10 secondary endpoints are ranked as follows:

1. Multicomponent improvement endpoint measured by the proportion of participants achieving all of the following at Week 24 relative to baseline:
    - Improvement in 6MWD (increase ≥ 30 m)
    - Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L
    - Improvement in WHO FC or maintenance of WHO FC II
2. Proportion of participants who maintain or achieve a low-risk category of REVEAL Lite 2 risk score at Week 24 versus baseline
3. Proportion of participants who maintain or achieve a low-risk score at Week 24 versus baseline using the simplified French Risk score calculator
4. Change from baseline in NT-proBNP levels at Week 24
5. Proportion of participants who improve in WHO FC or maintain WHO FC II at 24 weeks from baseline
6. Change from baseline in 6MWD at Week 24
7. Overall survival
8. Change from baseline in the Physical Impacts domain score of PAH-SYMPACT® at Week 24
9. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24
10. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH SYMPACT® at Week 24

A gatekeeping method will be used to control the Type I error rate in secondary endpoints by testing in the order of the secondary endpoints listed above, after successful testing for the primary endpoint. Secondary endpoint testing will be performed using a the same alpha 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 secondary endpoints will be described in the SAP.

11.5.3 Exploratory Endpoints

Other endpoints of interest are the following:

- Change in dyspnea score (assessed by Borg Dyspnea Scale [Borg CR10 Scale]) at Week 24 versus baseline
- Change from baseline in CRP levels at Week 24
- Change of Cardiovascular Symptoms domain score from baseline in PAH-SYMPACT® at Week 24

- Change from baseline in EQ-5D-5L index score at Week 24
- Change from baseline in EQ-5D-5L VAS at Week 24
- Changes from baseline in ECHO parameters (e.g., RVSP and TAPSE) at Week 24
- Proportion of participants who maintain or achieve a low or intermediate-low COMPERA 2.0 four-stratum risk score at Week 24

No adjustments for multiplicity will be performed. The SAP will provide more details.

11.6 Analysis of Safety

All safety analyses will be performed on the Safety Set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events are defined as an AE that starts after the first administration of study drug up to 8 weeks after the last dose and summarized by worst severity grade, system organ class, and preferred term. Treatment-emergent adverse events leading to death or discontinuation from treatment, TEAEs related to investigational product, and serious TEAEs will be summarized separately.

Clinical laboratory results will be summarized descriptively by treatment arm. Clinically significant laboratory abnormalities will be listed and summarized by treatment arm. Chemistry and hematology laboratory tests will be collected regularly and reviewed periodically. Descriptive statistics (mean, standard deviation, standard error of the mean, median, minimum, 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 Data Analysis Plan.

11.8 Interim Analysis

MK-7962-005-11 Implementation: The Sponsor has decided to close the HYPERION study (A011-13, MK-7962-005) so that all eligible participants in HYPERION can receive sotatercept either by extension study (SOTERIA, MK-7962-004) or by commercial access, if available. The prespecified IA will not be conducted, and the final analysis will be performed using all available participant data at a prespecified data cutoff date, as described in the SAP.

A planned IA of TTCW will be performed when approximately 61 events (roughly 50% of required events) have occurred 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 TTCW. 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. A recommendation from DMC 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. Table 7 shows the boundary properties for the planned IA 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-Shih-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 tables, 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: 61** **Timing: 30 months** **N: 374**	Z	2.963	-0.458
	p (1-sided)[b]	0.0015	0.677
	HR at boundary[c]	0.466	1.126
Final Analysis: **Required events: 121** **Timing: 44 months** **N: 444**	Z	1.969	NA
	p (1-sided)	0.0245	NA
	HR at boundary	0.698	NA

HR = hazard ratio; IA = interim analysis; NA = not applicable.
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] Hazard ratio at boundary is the approximate HR required to reach an efficacy/futility bound.

If the O'Brien-Fleming boundary is crossed for the primary endpoint, TTCW, at the IA, then analyses of secondary endpoints will be performed using a gatekeeping method similar to what is described for secondary endpoints in Section 11.5.2.. The 1-sided Type 1 error rate is strongly controlled at 0.025.

11.9 Subgroup Analysis

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

11.10 Event Adjudication Committee and Data Monitoring Committee

An independent blinded adjudication committee will adjudicate all clinical worsening events, including death, up to the end of the study 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 & 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.

11.11 Estimands

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 Group 1 PAH

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

11.11.1 Estimand for the Time-to-Event Endpoints

Endpoints:

- Primary endpoint: TTCW, defined as the time from randomization to the first confirmed morbidity event or death
- Secondary endpoint: Overall survival, defined as the time from randomization to date of death due to any cause

Intercurrent events:

Changes in treatment: dose reduction, dose delay, or discontinuation from sotatercept or placebo, or changes to background PAH therapy. A treatment policy strategy will be used, such that the actual outcome is of interest regardless of changes in treatment.

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

11.11.2 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:

- 6MWD
- NT-proBNP
- Physical Impacts domain score of PAH-SYMPACT®
- Cardiopulmonary Symptoms domain score of PAH-SYMPACT®
- Cognitive/Emotional Impacts domain score of PAH-SYMPACT®

Intercurrent events:

- Changes in treatment: Same as for the estimand for the primary endpoint.
- 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.

11.11.3 Estimands for Binary Secondary Endpoints

Endpoints: Indicator (yes/no) of meeting each of the following at Week 24:

- The response criteria for multicomponent improvement
- Maintaining or achieving a low REVEAL Lite 2 risk score
- Improvement in WHO FC or maintain WHO FC II at Week 24 compared to baseline
- Maintaining or achieving a low-risk score at Week 24 compared to baseline using the simplified French Risk score calculator

For all endpoints, if death occurs prior to Week 24, it is defined as not having met the criteria.

Intercurrent events:

- Changes in treatment: Same as for the estimand for the primary endpoint
- 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 in proportion of responders between treatment groups.

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

13.2 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - 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 (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.3 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to ensure that the appropriate IRB/IEC has reviewed and approved this protocol prior to initiating the study. The investigator must provide Acceleron Pharma Inc. or Acceleron Pharma Inc.'s representative with current and revised IRB/IEC membership rosters that include the members' occupations and qualifications. Sites

within the US may provide a copy of the US Department of Health and Human Services Assurance Number.

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

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

13.4 Informed Consent

Prior to study entry, the investigator or designee will explain the nature, purpose, benefits, and risks of participation in the study to each participant, participant's legally acceptable representative, or impartial witness. Participants must be informed that their participation is voluntary. Written and 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 (sign and date) the ICF. A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative, and such action must be documented according to local requirements. The process of obtaining consent will be in compliance with all applicable local and country regulations and ICH requirements.

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

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

- All participant data relating to the study will be recorded on an eCRF unless transmitted to Acceleron Pharma Inc. or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Acceleron Pharma Inc. or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification as indicated to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including 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 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 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 eCRFs 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

- 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

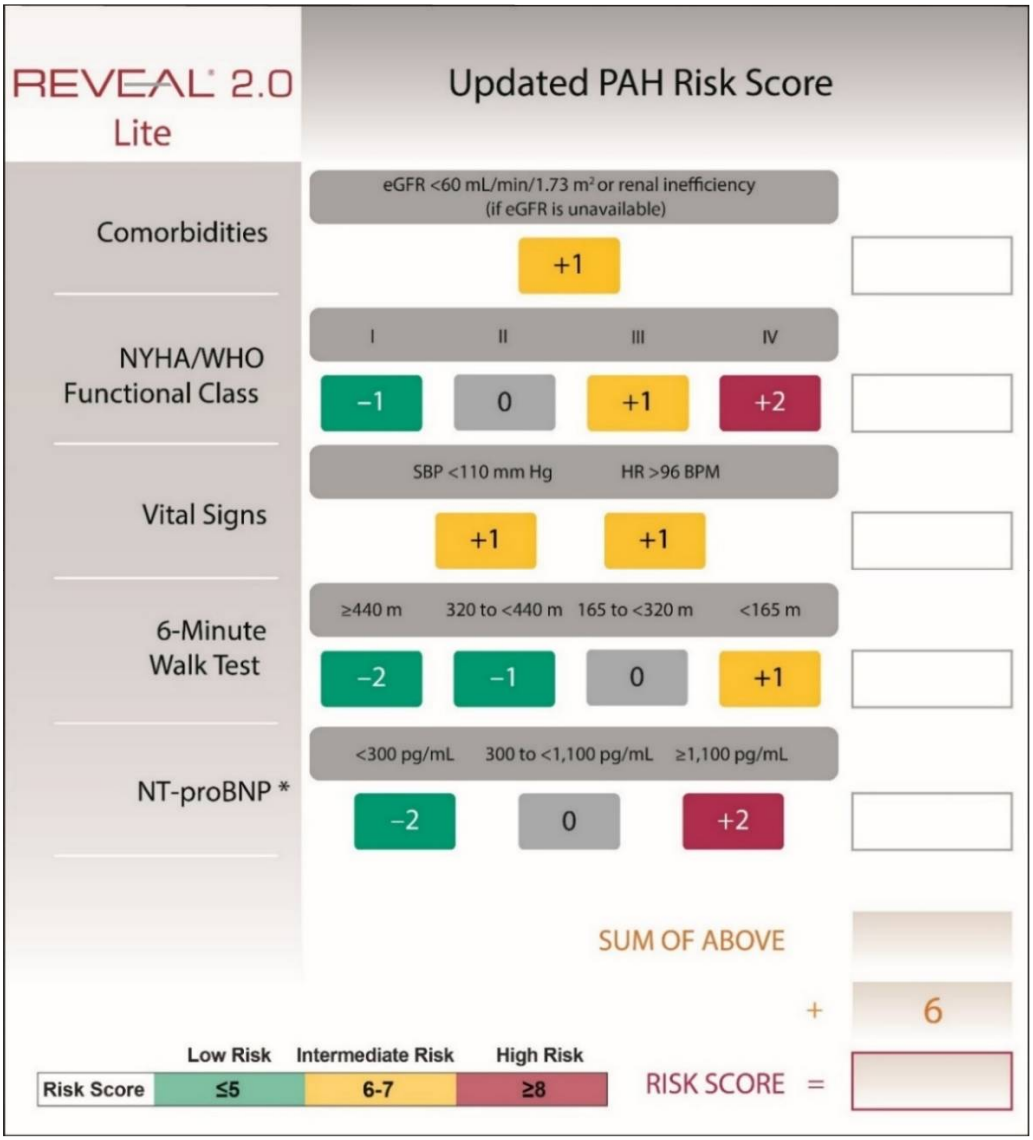
2-D	2 dimensional
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse of Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMP	Bone Morphogenetic Protein
BMPR2	Bone Morphogenetic Protein Type II Receptor
BNP	B-Type Natriuretic Peptide
BP	Blood Pressure
CBC	Complete Blood Cell (Count)
CI	Confidence Interval
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CRP	C-Reactive Protein
CTD	Connective Tissue Diseases
DBPC	Double-blind Placebo-controlled
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
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	United States Food and Drug Administration

FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GDF	Growth and Differentiation Factor
Hct	Hematocrit
Hgb	Hemoglobin
HHC	Home Health Care
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LTFU	Long-Term Follow-Up
LVEDPIA	Left Ventricular end-diastolic Pressure
m	meters
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal Prohormone B-type Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PAH-SYMPACT®	Pulmonary Arterial Hypertension-Symptoms and Impact
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
RHC	Right Heart Catheterization
RVEDA	Right ventricular end diastolic area
RVFAC	Right ventricular fractional area change
RVSP	Right Ventricular Systolic Pressure
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SoE	Schedule of Events
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEAE	Treatment-Emergent Adverse Event
TGF	Transforming Growth Factor
Tmax	Time to Maximum Sotatercept Concentration
TTCW	Time to Clinical Worsening
ULN	Upper Limit of Normal
UK	United Kingdom
US(A)	United States (of America)
VSMC	Vascular Smooth Muscle Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

Appendix 2. REVEAL Lite 2 Updated PAH Risk Score Calculator

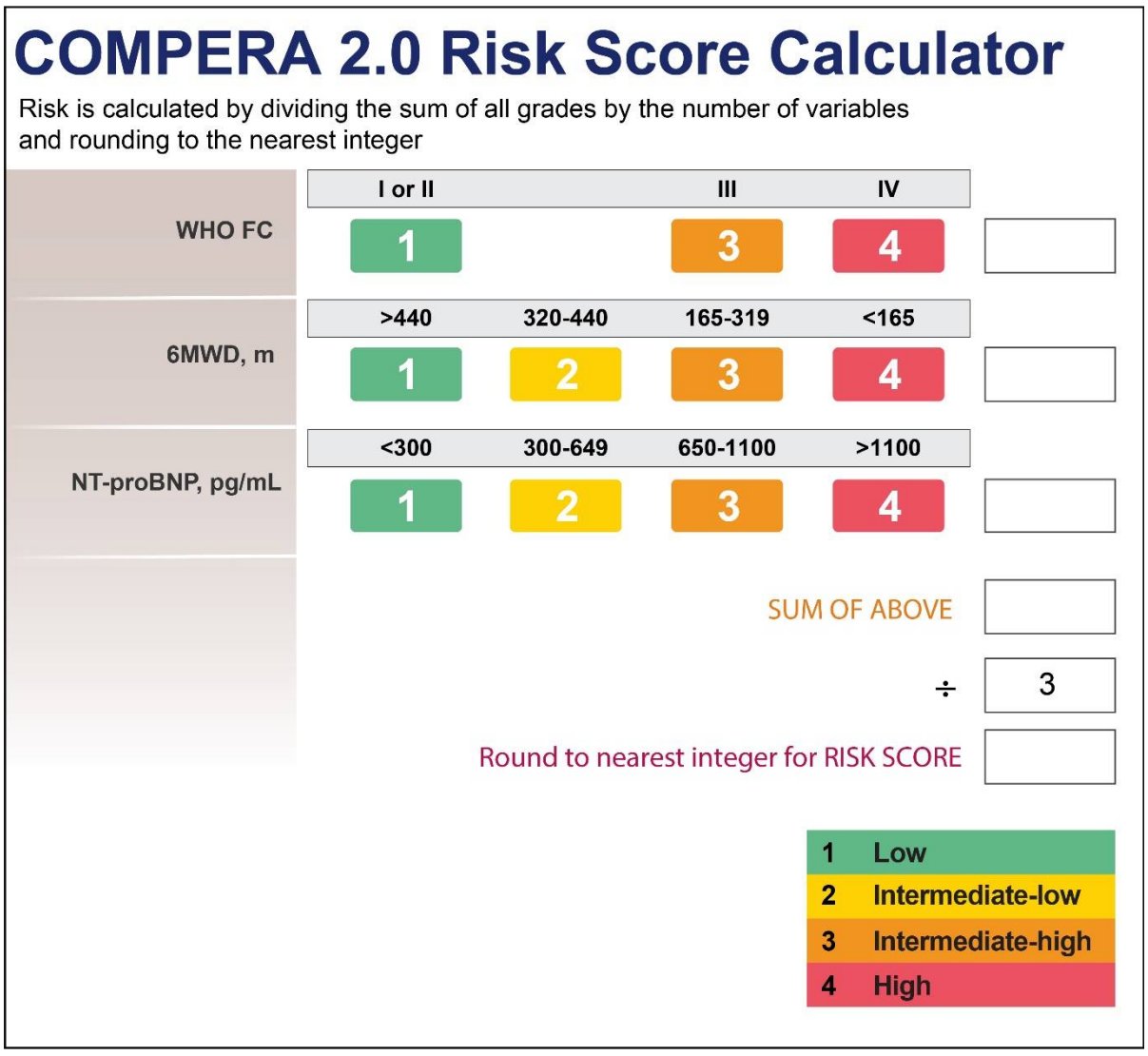
Sites will use this score to ensure that inclusion criterion #4: REVEAL Lite 2 risk score ≥ 6 or COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above), is met by the participant at enrollment. NT-proBNP and eGFR samples should be taken at the initial Screening Visit and should be submitted to the central laboratory for analysis as soon as possible to ensure availability of results prior to randomization. The average of the 2 screening 6MWDs should be used for score calculation as described in Section 9.3.2.[Benza, R. L., et al 2019] [Benza, R. L., et al 2021]



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; SBP = systolic blood pressure.
Adapted from [Benza, R. L., et al 2019] [Benza, R. L., et al 2021]
*Central laboratory NT-proBNP result from initial Screening Visit should be used for score calculation as described in Section 9.3.11

Appendix 3. COMPERA 2.0 Risk Score Calculator

Sites will use this score to ensure that inclusion criterion #4: REVEAL Lite 2 risk score ≥ 6 or COMPERA 2.0 risk score ≥ 2 (intermediate-low-risk or above), is met by the participant at enrollment. NT-proBNP 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. The average of the 2 screening 6MWDs should be used for score calculation as described in Section 9.3.2. [Hoeper, M. M., et al 2022] [Boucly, A., et al 2022].



Appendix 4. 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 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 of < 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 (IUD) Intrauterine hormone-releasing system Bilateral tubal occlusion
Vasectomized Partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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 in the Screening Period.
- 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 and up to 16 weeks (112 days) after last dose of study treatment.
- 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. 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 5. 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 (SpO_2) and follow the manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.
5. Have the participant stand and rate their baseline dyspnea using the Borg Dyspnea Scale.
    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 SpO2 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 6. Country-Specific Information

Changes from the global protocol in bold.

Country-specific Requirements for UK

These changes apply to the following sections:

- Section 7.4, Exclusion Criterion #7: Serum ALT or AST levels > **3× ULN**, or total bilirubin > **1.5× ULN**
- Section 7.4, Exclusion Criterion #18: ECG with QTcF > **450** ms (**or > 500 ms if right bundle branch abnormality is present**) during the Screening Period.

Country-specific Requirements for South Korea

These changes apply to the following sections:

- Section 7.4, Exclusion Criterion #18: ECG with QTcF > **450 ms** (**or > 480** ms if **complete or incomplete right bundle branch block** is present) during the Screening Period.

Country-specific Requirements for the Czech Republic

These changes apply to the following section:

- Synopsis and Section 7.4, Exclusion Criterion #4: Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > **160** mmHg or sitting diastolic BP > **100** mmHg during the Screening Visit after a period of rest

Appendix 7. Protocol Amendment History

Text in this appendix is displayed as it was presented at the time of each protocol amendment.

Protocol Version 2.0 dated 28 April 2021		
Protocol Location	**Description of Change**	**Brief Rationale**
Synopsis	Revised to reflect protocol amendment.	To align with revisions in the body of the protocol.
Section 1.1, Figure 1 Section 7.2	Removed "diuretics" from background PAH therapy.	To clarify that diuretics are not counted as background PAH therapy.
Section 2, Table 2	Remove requirement of risk score assessment at visits after the Screening Visit.	To clarify sites will only be required to calculate the REVEAL Lite 2 and French Risk scores during the screening period.
	Added footnote "r" for PAH-SYMPACT® assessments at screening.	To clarify that this does not need to be completed prior to the Screening Visit.
	Removed footnote "o" for PK sample collection at Visit 1.	To fix a typographical error.
Section 2, Table 3	Removed risk score assessment row and corresponding footnote (previous footnote "g").	To clarify sites will not calculate the risk score at EOT or EOS visit.
Section 6.6	Clarified that individual participants will not be eligible to enroll in Study A011-12 if the blind is broken as a result of a medical emergency.	To clarify study participation when the blind is broken.
Section 7.3	Inclusion Criterion 2 clarified WHO Group 1 PAH	To define the target population better.
Section 7.4	Exclusion Criterion 7 revised to include platelet count < 50,000/mm^3 (< 50.0 × 10^9/L)	To exclude patients with an abnormal platelet count.
	Exclusion Criterion 11 revised to forced vital capacity < 60% predicted within 1 year prior to the Screening Visit	To define test values of forced vital capacity correctly.
	Exclusion Criterion 14 clarified untreated obstructive sleep apnea.	To clarify patients with any untreated obstructive sleep apnea are included.
	Exclusion Criterion 18 revised to QTcF > 450 ms (or > 500 ms if right bundle branch abnormality is present).	To align QT interval value requirements with other sotatercept studies.

Protocol Version 2.0 dated 28 April 2021		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 9.2.2	Remove requirement of risk score assessment at visits after the Screening Visit.	To clarify sites will only be required to calculate the REVEAL Lite 2 and French Risk scores during the screening period.
Section 9.3.2	Added "or same type of mask (e.g., surgical or N95)".	To clarify the types of face coverings that may be used during the 6-minute walk test.
Section 9.3.8.2	Clarified completion of PAH-SYMPACT® questionnaire at the Screening Visit.	To clarify when PAH-SYMPACT® questionnaire should be answered.
Section 9.4.1	Revised "right bundle branch block" to "right bundle branch abnormality".	To clarify the abnormal condition.
Section 10.9	Remove subsections for identified and potential risks. Revised adverse events of special interest.	To align with the current Investigator's Brochure.
Section 11	Added of Section 11.11 and associated subsections to specify estimands for primary and secondary efficacy endpoints.	To specify estimands for primary and secondary efficacy endpoints in accordance with the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials.

EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQoL - 5 dimensions scale 5 levels; ICH = International Council for Harmonisation; PAH = pulmonary arterial hypertension; PK = pharmacokinetic(s); PAH-SYMPACT® = Pulmonary Arterial Hypertension-Symptoms and Impact; QTcF = Fridericia's corrected QT interval; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; WHO = World Health Organization

Protocol Version 3.0 dated 24 January 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 1, Section5.3, Section 5.3.7	Removed EQ-5D-5L in the secondary endpoints.	EQ-5D-5L moved to the exploratory endpoint as it is not specific for PAH
Section 1, Section 2, Section 5.2, Section 7.2, Section 9.3.5, Section 9.4.1, Section 9.6	Removed "including an increase of parenteral prostacyclin of ≥ 10%"	Changes in prostacyclin are not considered sufficient to qualify as a clinical worsening event and discontinuation criterion.
Section 1, Section 5.2	Added "the time from randomization" to TTCW definition.	Revised language to clarify the definition of TTCW
Section 1, Table 2, Section 5.2, Section 7.2, Section 9.3.5, Section 9.4.1, Section9.6,	Replaced "change in the composition of PAH background therapy" to "change in the background PAH therapy delivery route to parenteral"	Revised to clarify the clinical worsening condition and discontinuation criteria
Section 1, Section 5.3	Changed Secondary Endpoints to clarify that the Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts domains of the PAH-SYMPACT® will be evaluated.	Updates to endpoints to have separate statistical analyses of the three domains of PAH-SYMPACT, which are shown to be more relevant to the physical functioning of the PAH patients
Section 1, Section 5.4, Section 11.5.3	Added Cardiovascular Symptoms domain score of the PAH-SYMPACT® to the Exploratory Endpoints. EQ-5D-5L index score and VAS were added to exploratory endpoint.	Rearrangement of the endpoints based on their importance
Section 1, Section 5.4, Section 11.5.3	Added "Changes from baseline in ECHO parameters (e.g., RVEF, PAP) at Week 24" as one of the exploratory endpoints.	ECHO parameters added as an exploratory endpoint to measure heart health and function.
Section 1, Section 1.1, Section 7.2, Section 7.3	Replaced "a double combination" with "a double or triple combination". Removed "A triple combination of therapies, with stable doses for 90 days, may be allowed per local standard-of-care guidelines, but is restricted to 10% of the study population." in inclusion criterion #5. 10% cap of the triple combination therapy was removed.	To allow investigators to appropriately increase therapy to meet their patients' clinical needs over 12 months from PAH diagnosis

Protocol Version 3.0 dated 24 January 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 1, Section 7.3	Revised diagnosis of PAH to within "12" months of screening	To expand the target population for efficient recruitment
Section 1, Section 7.3, Appendix 3	Specified the requirement for contraceptive use in females of childbearing potential. Footnote b was deleted in Appendix 3.	To clarify the contraception guidance. Footnote b in Appendix 3 was deleted as it may mislead the reader that three contraception methods are necessary.
Section1, Section 7.4	Modified exclusion criterion 9 to "Known allergic reactions to sotatercept (ACE-011), <u>its excipients, or luspatercept (Reblozyl®)</u>" <u>Reblozyl® was deleted from the same criterion.</u>	To clarify the criterion and align it with other Phase 3 sotatercept trials <u>Reblozyl® deleted as it is a commercial name that can vary by countries</u>
Section1, Section 7.4	Added "schistosomiasis-associated PAH, pulmonary veno occlusive disease and pulmonary capillary hemangiomatosis" to exclusion criterion #5	Added additional PAH Group 1 subtypes to be excluded from the study.
Section 1, Section 7.4	Revised exclusion criterion 18 from "QTcF > 450 ms" to "QTcF > 500 ms" and deleted the right bundle branch abnormality	To align QTcF internal value requirement with other sotatercept studies
Section 1, Section 5.2	Modified the following inclusion criterion: Serum alanine aminotransferase, ~~or~~ aspartate aminotransferase<u>, or total bilirubin</u> levels > 3 × ULN ~~or total bilirubin > 1.5 × ULN~~	To update information and align the criterion with other sotatercept trials
Section 1, Section 7.4	Added "more than mild" to exclusion criterion #14	To clarify the condition of obstructive sleep apnea
Section 1, Section 11.2	Projected time for reaching 124 events added	Updated projection time in the event that the promising zone is not triggered
Section 1, Section 11.4, Section 11.5.1, Section 11.5.2, Section 11.5.3	Added "for the primary endpoint" and "using a log-rank test" and deleted "overall" in the primary endpoint statistical analysis description. Added "Mixed model for repeated measures (MMRM)" as a statistical method to analyze the data	To provide additional information on the terms and to update the methods used in the sections.
Section 1, Section 11.8	Defined the conditional power range for the promising zone	To increase clarity in statistical analysis

Protocol Version 3.0 dated 24 January 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
Table 2, Table 3, Section 9.2.2, Section 9.2.3, Section 9.2.4	Changed the following in footnote E of Table 2and footnote B of Table 3: "perform targeted cardiopulmonary and skin examinations."	Updated based on new information about the study treatment
Table 2, Table 3, Section 9.3.16.2	Changed "CO_2" in footnote J in Table 2 and footnote E in Table 3 to "HCO_3" and added "albumin" A similar change was made to Section 9.3.16.2, Serum Chemistry	Correction
Section 3.2	Added text regarding the risk of telangiectasia.	Updated information for accuracy
Section 5.3.7 Section 9.3.8.2	Removed the statement "…draft consists of 16 symptom and 25 impact items that…"	Removed statement to correct error.
Section 6.6	Changed "must consult" to "should discuss the issue"	To clarify the procedure of breaking the blind
Section 8.3.4, Section 8.3.5, Section 10.9.1	Added language to describe dose modifications required for adverse events of telangiectasia.	Updated to provide guidance on dose modifications required for newly identified AESI of telangiectasia
Section 9.3.5	Deleted "Need for" in atrial septostomy	Clarification
Section 9.4.1	Modified the following text: "An increase in QTcF of > 60 ms that results in QTcF of > 500 ms (or > 550 ms if right bundle branch abnormality is present) during the treatment period."	To clarify the discontinuation criterion
Section 10.3	Added more information about assessment of AE severity	To clarify the definition of severe AE
Section 10.9.1, Table 5	Updated Table 5 and the surrounding text to indicate that telangiectasia is the only AESI and provide monitoring parameters.	Updated information for programmatic consistency and accuracy
Section 11.11.1	Deleted "If a participant dies, the event occurred by definition following "composite estimand strategy" in intercurrent events.	Correcting the error as death cannot be considered an intercurrent event.

AE = adverse event; AESI = adverse event of special interest; DBPC = double-blind placebo-controlled; EQ-5D-5L = EuroQoL - 5 dimensions scale 5 levels; PAH = pulmonary arterial hypertension; PAH-SYMPACT® = Pulmonary Arterial Hypertension-Symptoms and Impact; QTcF = Fridericia's corrected QT interval; ULN = upper limit of normal; VAS = visual analog scale.

Protocol Version 4.0 dated 22 November 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
All relevant sections	Added the subsidiary status to the company name and changed the address. It is now, "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." Also, indicated that the company will be referred to as Acceleron or Acceleron Pharma Inc. throughout the document.	To simplify and merge the roles of Acceleron Pharma, Inc. with Merck & Co., Inc.
Emergency Contact Information	Details of the Medical Monitor replaced with general statement that details can be found in Investigator Site File. Pharmacovigilance contact information updated.	Medical Monitor information changed to align with Sponsor standard flexible language. Pharmacovigilance contact information updated to reflect the updated process of SAE reporting.
All relevant sections	Added the Merck number for this compound, protocol, and/or amendment number, "MK-7962-005-04."	To acknowledge that ACE-011, sotatercept, and MK-7962 are the same molecule and that '-005' represents the HYPERION protocol.
Section 1, Section 5.4, Section 11.5.3	Removed RVEF and PAP and added RVSP and TAPSE to exploratory endpoints	Replaced with more representative parameters of ECHO measurement.
Section 1, Section 7.3	Changed Inclusion Criterion #5 to, "5. Diagnosis of PAH within 12 months of screening and on stable doses of a double or triple combination of background PAH therapies and diuretics for at least 90 days prior to screening. Background PAH therapy and diuretics are further defined in Section 7.2.	Added diuretic therapy to Inclusion Criterion #5
Section 1, Section 7.4	Changed Exclusion Criterion #1 to, "Diagnosis of ~~PAH~~pulmonary hypertension WHO Groups 2, 3, 4, or 5"	Corrected an error in Exclusion Criterion #1 from the previous amendment.

Protocol Version 4.0 dated 22 November 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 1, Section 7.4	Changed Exclusion Criterion #20 to, "Left ventricular ejection fraction < 50% on historical echocardiogram (ECHO) within 1 year prior to the Screening Visit ~~or pulmonary capillary wedge pressure > 15 mmHg as determined by historical RHC within 12 months prior to the Screening Visit~~."	Changed to remove redundancy with Inclusion Criterion #2.
Section 2, Table 2, Section 9.2.1, Section 9.2.2.7, Section 9.2.2.8, Section 9.3.8.2	Moved the PAH-SYMPACT® and EQ-5D-5L assessments to the bottom row of the table, changed the frequency and added the details on PAH-SYMPACT completion in early discontinuation	To clarify on which visits these particular assessments will be conducted and how PAH-SYMPACT should be completed in early discontinued participants.
Section 2, Table 3	Added 2 new columns entitled "Follow-up Telephone Call 6 months after EOS Visit and yearly after (early discontinuation only)" and "Follow-up Visit Yearly after EOS Visit (early discontinuation only)"	Added to provide information about participant follow-up after early discontinuation.
Section 7.2	Changed heading title to, "Background PAH Therapy and Diuretics" and added, "Adjustments in parenteral prostacyclin doses by up to 10% are permitted and should not affect therapy stability determination" and "Stable diuretic therapy is defined as no addition of a new diuretic and no switching of a preexistent oral diuretic to parenteral administration for at least 90 days; however, dose adjustments (up or down) in preexistent oral diuretics are acceptable."	Added description of stable PAH therapy and diuretic therapy.
Section 9.2.1	Added, "Any screening clinical laboratory values considered abnormal may be repeated once during the Screening Period."	Language updated to allow for repeated screening labs, which aligns with an overall programmatic change.

Protocol Version 4.0 dated 22 November 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 9.4.1	Changed the section title to, "~~Participants~~ Early Discontinuation of Study Treatment," and rearranged this section to only include details of discontinuation of treatment and the follow-up method. A separate section was created for participant withdrawal from the study.	Added to provide details on how to follow up the participants who discontinued prematurely.
Section 9.4.2	Changed the section title from "End of Study Definition" to "Participant Withdrawal from the Study" and added new text to describe the participant's complete withdrawal from the study.	Changed to better clarify follow-up procedures after study withdrawal.
Section 9.4.3	The section titled, "End of Study Definition," moved from Section 9.4.2 to 9.4.3, and the end of study definition was moved to the first sentence in the section.	Changed to accommodate new text and clarify the end of study definition in the first sentence of the section.
Section 10.5, Section 10.6	For all SAEs, a paper SAE form is required. Also added statement in Section 10.6, "A study-specific paper SAE Report Form must also be submitted within 24 hours of becoming aware of the event."	Made SAE reporting procedure consistent throughout the sotatercept trials.
Section 10.7	Changed overdose language to, "Sotatercept dosing is weight-based. ~~Therefore, for the purpose of this trial, an overdose is defined as any dose that has exposures in excess of the monkey no-observed-adverse-event level dose of 1 mg/kg (see current IB), which was also the highest dose tested in the human volunteers study (A011-02) with resolvable AEs.~~ Any dose exceeding that of the study-prescribed dose is considered an overdose (see current IB)."	Changed the language in this section to align with the current IB (version 17).

Protocol Version 4.0 dated 22 November 2022		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 10.9.1, Table 5	The following sentence was added in Table 6 "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."	Provided the additional guideline for AESI related to telangiectasia.
Section 11.11	Changed the language in the key attributes of estimands including the treatment, population, and intercurrent events for primary and secondary endpoints in Estimands section	Changed the language to better align with ICH E9 (R1), the addendum on estimands and sensitivity analysis in clinical trials.

AESI = adverse events of special interest; EOS = end of study; EOT = end of trial; EQ-5D-5L = EuroQoL - 5 dimensions scale 5 levels; IB-Investigator's Brochure; ICH E9 (R1) = International Council on Harmonisation E9(R1) Statistical Principles for Clinical Trials; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PH = pulmonary hypertension; RVEF = right ventricular ejection fraction; RVSP = right ventricular systolic pressure; SAE = serious adverse event; TAPSE = tricuspid annular plane systolic excursion; WHO = World Health Organization

Protocol Version 5.0 dated 03 July 2023		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 1 (Protocol Synopsis), Section 5.4, Section 9.3.6, Section 11.5.3, Appendix 3	Added exploratory endpoint, "Proportion of participants who maintain or achieve a low or intermediate-low COMPERA 2.0 four-stratum risk score at Week 24"	To evaluate the effects of sotatercept using a 4-stratum risk-assessment tool based on refined cut-off levels for WHO-FC, 6MWD, and NT-proBNP
Section 1 (Estimated Duration of the Study), Section 6.2	Changed the maximum duration of the study from "up to a maximum of 56 months" to "up to approximately 47 months and DPBC Period from "up to 53 months" to "up to approximately 44 months."	To reflect the change in study design
Section 1 (Protocol Synopsis), Section 6.4	Updated language to include sponsor monitoring of clinical worsening event prior to rollover to SOTERIA and to clarify that participants with a clinical worsening event of lung transplant will not be eligible to rollover to SOTERIA.	To allow the sponsor to review clinical worsening EDC forms and ensure adherence to protocol prior to rollover to SOTERIA
Section 1 (Protocol Synopsis), Section 5.2, Section 9.3.5	Changed the fifth bullet in this section to read, "Deterioration in performance in exercise testing due to PAH, defined as a decrease in 6MWD from baseline (<u>average of screening</u>) on 2 consecutive tests (which must be at least 4 hours apart) and at least 1 of the following:"	To clarify what a participant's baseline value represents when assessing deterioration in performance in exercise testing
Section 1 (Protocol Synopsis), Section 7.1, Section 7.3	Changed IC #4 to include the COMPERA 2.0 four-stratum score as an alternative risk calculator for entry criteria.	To allow for inclusion of participants in the intermediate-low-risk group from COMPERA 2.0 calculator who might be excluded using the REVEAL Lite 2 calculator
Section 1 (Protocol Synopsis), Section 7.3	Changed IC #5 to state, "Diagnosis of PAH within 12 months of screening and on stable doses of a double or triple combination of background PAH therapies and diuretics <u>(if any)…</u>"	To allow for the possibility that diuretics may or may not be used in a participant's treatment.
Section 1 (Protocol Synopsis), Table 2, Table 3, Section 7.3	Updated language of IC #7 to clarify that 2 pregnancy tests are required during the Screening Period.	To clarify that 2 pregnancy tests are required during the Screening Period

Protocol Version 5.0 dated 03 July 2023		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 1 (Protocol Synopsis), Section 7.4	Indicated which EC (#7 and #18) have country-specific requirements and referenced Appendix 6.	To note the EC with country-specific requirements in order to minimize protocol deviations
Section 1 (Protocol Synopsis), Section 7.4	Changed EC #4 exclusive systolic BP from > 160 to > 180 mmHg and diastolic BP from > 100 to > 110 mmHg.	To be more inclusive of participants with occasional increase in BP at Screening Visit without a history of persistent, uncontrolled hypertension
Section 1 (Protocol Synopsis), Section 7.4	Changed EC #20 LVEF < 50% on historical ECHO within 1 year prior to the Screening Visit to LVEF < 50% documented by a historical ECHO or cardiac MRI within the last 12 months prior to screening (if there is more than 1 assessment of LVEF, the value from the most recent measurement should be used in assessing eligibility)	To clarify that the most recent ECHO or cardiac MRI assessment should be used
Section 1 (Protocol Synopsis), Section 7.4	Changed EC #21 to read, "~~Any current of prior history of symptomatic~~ Coronary artery disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the Screening Visit"	To clarify language describing exclusion of participants with coronary artery disease
Section 1 (Protocol Synopsis), Section 7.4	Added new EC #26 regarding active malignancy	To exclude participants with active malignancy from the trial
Section 1 (Protocol Synopsis), Table 3, Section 9.4.1	Provided option for participants who discontinue early to replace on-site Follow-up Visits with telephone calls in body of protocol and modified footnote "a" in Table 3.	To decrease the number of participants lost to follow-up
Table 2, Section 7.2, Section 9.4.1, Section 9.6	Updated background PAH therapy changes that may lead to discontinuation of study treatment.	To clarify that dose increases which could have confounding effects on efficacy outcomes are not permitted.
Section 1 (Protocol Synopsis), Section 11.2, Section 11.8	Projected enrollment rate was updated.	To align with updates to the enrollment plan.

Protocol Version 5.0 dated 03 July 2023		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 1 (Protocol Synopsis), Section 6.4, Section 11.2, Section 11.8	Changed the following operational characteristics: 1) A smaller maximum sample size (from 662 to 444); 2) A reduced number of required events for the IA (from 93 to 61); 3) A reduced number of required events for the final analysis (from 186 to 121); 4) A revised timeline (from 36 to 30 months for the IA and from 53 months to 44 months for the final analysis); 5) Updated the study design from promising zone to group sequential; Other operational characteristics were updated accordingly.	Updated the study design based on the newly available data showing that group sequential design is more appropriate than promising zone Also updated to incorporate new information from STELLAR, the pivotal Phase 3 study of sotatercept in PAH.
Section 1 (Protocol Synopsis), Section 11.3	Removed Per-Protocol Set (PPS) from the analysis plan.	To align with the methods used in STELLAR.
Section 1 (Protocol Synopsis), Section 11.4	Statistical methods have been updated for the continuous endpoints.	To align with the methods used in STELLAR.
Section 1 (Protocol Synopsis), Section 5.3, Section 11.5.2	Updated secondary endpoint of REVEAL Lite 2 risk score.	To include participants who maintain a low-risk score, which is now possible due to the addition of the COMPERA 2.0 assessment for IC #4.
Figure 1	Changed the number of participants and events.	To reflect the new study design.
Section 2, Section 9.2.2.8	Replaced the “Visits 14-73” header with “Visit 14 Onward Until the End of the DBPC Treatment Period.”	Since this is an event driven study, the exact number of visits per participant cannot be predetermined
Table 2	Added footnote “l” for clinical worsening assessment.	To further clarify when clinical worsening assessment should be performed
Table 2, Table 3	Modified Table 2 footnotes “i” and “j,” and Table 3 footnotes “d” and “e” to indicate when hematology and serum chemistries will be performed at local or central laboratory.	To clarify and prevent sites from using the incorrect laboratory for hematology and chemistry tests

Protocol Version 5.0 dated 03 July 2023		
Protocol Location	**Description of Change**	**Brief Rationale**
Table 2, Appendix 2	Updated REVEAL Lite 2 calculator to remove BNP ranges and to indicate that NT-proBNP must be used for the calculation.	Changed to clarify how the score is calculated
Section 3.2	Added results from STELLAR and emphasized referring to the IB for current information.	Results from STELLAR on time to death or the first occurrence of a clinical worsening event are relevant to HYPERION and support the updated hazard ratio
Section 3.2	Updated risk language.	To align with the approved core risk profile language informed by unblinding of STELLAR
Section 8.2.3	Added Table 4, the Study Interventions Table	Added for consistency with company standards
Section 8.3.1	Changed the third sentence to read, "However, if at Visit 2 Hgb increases by more than 2.0 g/dL from the ~~previous dosing~~ Screening Visit…"	Clarified the visit values to which Hgb levels should be compared with in order to justify a dose modification
Section 8.3.2, Figure 2, Figure 3	Updated dose modification due to Hgb increase of > 4 g/dL and > 2 g/dL above ULN.	Clarified dose modifications for large increases in Hgb from baseline or gradual increases above ULN
Section 9.2.1	Updated study procedure to include RHC at Screening Visit if necessary to have complete measurement records.	To allow RHC procedure to be performed during Screening Visit if diagnostic RHC does not have all the necessary measurements
Section 9.3.8.2	Deleted the completion instructions for the PAH SYMPACT®.	To avoid redundancy with the instructions in the study manual
Section 9.4.1	Added reason "Death" that leads to early discontinuation from the study treatment.	To clarify early discontinuation criteria
Section 10.8	Updated circumstances when pregnancy information will be collected for participants who roll over from HYPERION to SOTERIA.	To avoid duplication in reporting of the same case in both studies
Section 10.9.1	Changed the table reference from "Table 1" to "Table 6" in the first sentence of Section 10.9.1.	To correct a typographical error

Protocol Version 5.0 dated 03 July 2023		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 10.9.1	Changed text to read that hepatic toxicity, leukopenia, and neutropenia are no longer considered as AESIs and that erythrocytosis is an important identified risk and severe thrombocytopenia is an important potential risk.	Updated the risks and AESIs for sotatercept based on results from STELLAR
Appendix 4	Changed contraception guidance to read, “agree to use highly effective forms of birth control for at least 28 days prior to starting the ~~study~~ investigational product.”	To correct discrepancy and align with IC #7
Appendix 8	Added a table to clarify the different program and protocol identifiers between Acceleron and Merck.	To reconcile the different nomenclature between the 2 companies

6MWD = 6 minute walk distance; AESI = adverse event of special interest; BNP= B-type natriuretic peptide; BP = blood pressure; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; DBPC =double blind placebo controlled; EC = Exclusion Criterion; ECHO = echocardiogram; FC = functional class; Hgb=hemoglobin; IB= Investigator Brochure; IC = Inclusion Criterion; ICF = informed consent form; LVEF = left ventricular ejection fraction; NT-proBNP= N-terminal; prohormone B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-SYMPACT® = Pulmonary Arterial Hypertension-Symptoms and Impact; REVEAL = Registry to Evaluate Early and Long term PAH Disease Management; RHC = right heart catheterization; SAE = serious adverse event; ULN = upper limit of normal; WHO = World Health Organization.

Protocol Version 6.0 dated 25 April 2024		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 2 (Table 2)	Changed the fourth sentence in footnote 'i' to read, "However, if there is a dose modification based on Hgb levels and platelet count (Section 8.3) during non-quarterly visits, a hematology assessment should be performed up to 3 days prior to the next dose administration,.."	To align with the language in the previous sentence in this footnote.
Section 2 (Table 2)	Added, "Participants may be asked to return to the site in an unscheduled visit to assess clinical worsening," to footnote 'l.'	To clarify that participants may be asked to return to the site to assess clinical worsening in an unscheduled visit, if necessary.
Section 2 (Table 2)	Added a new footnote 'u' that reads, "As described in Section 6.4, WHO FC will be used to stratify participants at the time of randomization. WHO FC must be evaluated on the day of randomization (Visit 1), prior to study dose administration."	To clarify that the WHO FC used for stratification is calculated on the day of randomization and should be calculated and entered into IRT before the first study dose, which will serve as baseline.
Section 2 (Table 3)	Changed footnote 'g', "~~All~~ Participants ~~participants positive for ADA result at their last study 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 a negative result is obtained, or the result is considered stabilized~~."	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 6.4	Added, "~~Baseline~~ WHO FC (Class II or III), defined as the evaluation taken at Visit 1 prior to randomization"	See rationale for Section 2 (Table 2), footnote 'u'.

Protocol Version 6.0 dated 25 April 2024		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 6.4	Changed, "When a participant experiences an event of clinical worsening, and the sponsor has confirmed completeness of electronic data capture (EDC) forms related to clinical worsening, they will complete the End of Treatment (EOT) Visit and will be eligible to enroll into the open-label, long-term follow-up (LTFU) study, A011-12 (SOTERIA) ~~following Sponsor review of completeness of EDC forms related to the clinical worsening event~~."	To remove redundant language
Section 8.3	Changed first paragraph, "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 followed by dose ~~or~~ 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.
Section 8.3.5	Added a new section heading 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, "Measurements/assessments taken during Screening Period will be recorded as the baseline values for study assessment of endpoints unless described otherwise"	Section 9.2.1 is not intended for defining analysis details.

Protocol Version 6.0 dated 25 April 2024		
Protocol Location	**Description of Change**	**Brief Rationale**
Section 9.3.14	Changed, "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), footnote 'g' rationale
Section 9.3.17	Added a new section to describe the collection of clinical event information (full text not shown)	To add details regarding how clinical events will be collected before an eDMC review or an interim/final analysis
Section 10.5	Changed, "All AEs and SAEs reported from the documenting of the ICF to the EOS Visit and Follow-up Visits/Calls (early discontinuation only) are to be reported and documented on the AE eCRF."	To align AE reporting with the Schedule of Events (Section 2)
Section 10.5, Section 10.6	Changed, "For overdose and cancer (serious and non-serious) and all SAEs, a paper SAE Report Form must be completed with ~~as much information as possible~~ a concise account of the event and submitted within the timeframe described…"	To emphasize overdose and cancer as reportable events
Section 10.7	Added, "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 the end of the third paragraph in this section.	To clarify that overdose needs to be reported using the Serious Adverse Event Reporting Form
Section 10.9.1	Deleted the risk language in this section (full text not shown)	To delete information that is redundant with Section 3.2
Section 11.10	Added a paragraph with a description of how clinical events will be adjudicated (full text not shown).	To add specific details about event adjudication

Protocol Version 6.0 dated 25 April 2024		
Protocol Location	**Description of Change**	**Brief Rationale**
Appendix 6	Added a Czech Republic-specific section which reflects that country's changes in bold, "Synopsis and Section 7.4, Exclusion Criterion #4: Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > **160** mmHg or sitting diastolic BP > **100** mmHg during the Screening Visit after a period of rest"	To address country-specific changes required for the Czech Republic

ADA = antidrug antibody; AE = adverse event; BP = blood pressure; eCRF = electronic case report form; EDC = electronic data capture; eDMC = external data monitoring committee; EOS = end of study; EOT = end of treatment; FC = functional class; IB = Investigator Brochure; ICF = informed consent form; IRT = interactive response technology; LTFU = long-term follow up; mmHg = millimeter of mercury; PAH = pulmonary arterial hypertension; PVG = pharmacovigilance; SAE = serious adverse event; WHO = World Health Organization.

Appendix 8. Protocol Nomenclature Mapping

Acceleron Protocol Description (A011-13)	Date	Merck Number (MK-7962-005)
Original Protocol (v1.0)	13 January 2021	MK-7962-005-00
Global Amendment 01 (v2.0)	28 April 2021	MK-7962-005-01
Global Amendment 01 (v2.0), South Korea	09 August 2021	MK-7962-005-02
Global Amendment 02 (v3.0)	24 January 2022	MK-7962-005-03
Global Amendment 03 (v4.0)	10 November 2022	MK-7962-005-04
Global Amendment 02 (v3.0) Sweden	06 October 2021	MK-7962-005-05
Global Amendment 02 (v3.0) France	17 November 2021	MK-7962-005-06
Global Amendment 02 (v3.0), South Korea	03 March 2022	MK-7962-005-07
Global Amendment 02 (v3.0), United Kingdom	04 April 2022	MK-7962-005-08
Global Amendment 04 (v5.0)	03 July 2023	MK-7962-005-09
Global Amendment 05 (v6.0)	25 April 2024	MK-7962-005-10
Global Amendment 06 (v7.0)	17 December 2024	MK-7962-005-11