Official Protocol Title:	A Phase 2, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Effects of Sotatercept versus Placebo for the Treatment of Combined Postcapillary and Precapillary Pulmonary Hypertension (Cpc-PH) due to Heart Failure with Preserved Ejection Fraction (HFpEF)
NCT Number:	NCT04945460
Document Date:	19-Sep-2025

Protocol A011-16 (CADENCE)

PROTOCOL TITLE:	A Phase 2, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Effects of Sotatercept versus Placebo for the Treatment of Combined Postcapillary and Precapillary Pulmonary Hypertension (Cpc-PH) due to Heart Failure with Preserved Ejection Fraction (HFpEF)
SHORT TITLE:	A Phase 2 Study of Sotatercept for Cpc-PH Treatment
REGULATORY AGENCY IDENTIFYING NUMBERS:	IND 154471 EudraCT 2021-003020-32 EU CT 2023-509141-12-00
SPONSOR:	Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA 126 East Lincoln Ave. P.O. Box 2000 Rahway, NJ 07065
PROTOCOL AMENDMENT 07 (MK-7962-007-09) DATE:	19 September 2025

See Appendix 5 for nomenclature mapping

Confidentiality Statement

This confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Acceleron Pharma Inc, a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (henceforth referred to as the Sponsor).

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., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (henceforth referred to as 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 (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	Acceleron Safety Reporting Hotline	EMEA/Asia Tel #: +44 122 337 4240 EMEA/Asia Fax #: +44 122 337 4102 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 protocol amendment was created to address strategy and add an objective and hypothesis for analysis of the key secondary endpoint. Changes from Version 7.0 to Version 8.0 are detailed below.

Protocol Location	Description of Change	Brief Rationale
Synopsis, Section 11.4.5	Added the key secondary endpoint to the multiplicity strategy and specified the approach to testing multiple endpoints as well as doses.	To ensure appropriate analysis of the key secondary endpoint.
Section 4	Added change from baseline in 6MWD at Week 24 as an objective with an associated hypothesis.	To permit inference on the key secondary efficacy endpoint.
Section 6.4	Noted that limited Sponsor personnel will have access to unblinded results.	To clarify that not all Sponsor personnel will remain blind for the duration of the study.
Section 11.2	Added a power calculation for the key secondary endpoint.	To support the addition of the hypothesis for this endpoint.
Section 11.4.1.1	*P*-values for hypothesis tests for efficacy endpoints will be 1-sided.	To harmonize the document to describe all testing in terms of 1-sided alpha=0.025 rather than 2-sided alpha=0.05.
Section 11.4.1.2	Reordered the description of the analysis of TTCW.	To clarify that the *p*-value will not be used to perform inference.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To improve clarity and readability.

6MWD = 6-minute walk distance; TTCW = time to clinical worsening..

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1 PROTOCOL SYNOPSIS

Protocol Title	A Phase 2, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Effects of Sotatercept versus Placebo for the Treatment of Combined Postcapillary and Precapillary Pulmonary Hypertension (Cpc-PH) due to Heart Failure with Preserved Ejection Fraction (HFpEF)
Short Title	A Phase 2 Study of Sotatercept for Cpc-PH due to HFpEF
Protocol Number	A011-16 (MK-7962-007)
Study Type	Phase 2, double-blind, randomized, placebo-controlled, interventional
Rationale	World Health Organization (WHO) Group 2 Pulmonary Hypertension (PH) is associated with left heart disease and represents a high unmet need disease state with 3 primary etiologies: heart failure (HF) with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF), and valvular heart disease. Each etiology group can be further differentiated by hemodynamic characteristics, such as isolated postcapillary PH (Ipc-PH) and combined postcapillary and precapillary PH (Cpc-PH). Sotatercept is a recombinant, homodimeric fusion protein consisting of the extracellular domain (ECD) of human activin receptor type IIA (ActRIIA) linked to the fragment crystallizable (Fc) domain of human immunoglobulin G1. Sotatercept acts as a ligand trap for members of the transforming growth factor (TGF)-β superfamily, including activin [Yung, L. M., et al 2020]. In the context of Group 2 PH, members of the TGF-β superfamily of signaling molecules have also been associated with the pathogenesis associated with left heart disease. Preclinical data generated in animal models support the potential benefit of sotatercept in this patient population. The PULSAR study (Phase 2, NCT03496207) in patients with pulmonary arterial hypertension (PAH; WHO Group 1 PH) has demonstrated statistically significant reductions in pulmonary vascular resistance (PVR) following 6 months of treatment with sotatercept compared with placebo as well as substantial improvement from baseline in 6-minute walk distance (6MWD) in sotatercept-treated participants compared to the placebo group. In addition, a statistically significant greater reduction in plasma N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, a marker of cardiac stress, was observed in the sotatercept treatment groups compared with placebo, and a greater proportion

	of participants in the sotatercept treatment groups improved in functional class (FC) compared with placebo participants. The shared presence of precapillary PH in PAH and Cpc-PH suggests a pathophysiological overlap between the 2 diseases, including increased PVR, right heart dysfunction, and increased mortality [Hoeper, M. M., et al 2017] [Gerges, M., et al 2015]. Genetic studies have also suggested that the Cpc-PH subgroup of WHO Group 2 participants more closely resemble WHO Group 1 (PAH) participants [Assad, T. R., et al 2016]. Given these pathophysiological overlaps, the Sponsor hypothesizes that the efficacy of sotatercept observed in PAH might also be observed in WHO Group 2 subset of participants with Cpc-PH due to HFpEF. Therefore, this study is designed to determine as proof-of-concept, the effect of sotatercept versus placebo on pulmonary vascular resistance and safety in adults with Cpc-PH due to HFpEF.
Study Objectives	**Efficacy:** This study is designed to evaluate the efficacy, measured by change from baseline in PVR (primary endpoint) and 6MWD (key secondary endpoint) of sotatercept versus placebo in adults with Cpc-PH due to HFpEF. **Safety:** The safety and tolerability of sotatercept versus placebo in adults with Cpc-PH due to HFpEF will be assessed by the secondary endpoints listed below.
Study Population	Adults (age 18 to 85) with Cpc-PH due to HFpEF of New York Heart Association (NYHA) FC II or III
Number of Participants	Approximately 150 participants will be randomly assigned in a 1:1:1 ratio to each of the 3 treatment groups (50 per group).
Study Design	This Phase 2, double-blind, randomized, placebo-controlled study will evaluate the efficacy and safety of sotatercept versus placebo in adults with Cpc-PH due to HFpEF. Study participation for each participant includes a 28-Day Screening Period, a 24-week, double-blind, placebo-controlled Treatment Period, an up to 18-month Extension Period, and an up to 8-week Follow-up Period. Eligible participants will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment groups during the Treatment Period: • Treatment Group 1: Placebo delivered subcutaneously (SC) every 3 weeks (Q3W) for 24 weeks • Treatment Group 2: Sotatercept SC at a dose level of 0.3 mg/kg Q3W for 24 weeks • Treatment Group 3: Sotatercept SC at a starting dose level of 0.3 mg/kg for 3 dosing visits (Q3W), then escalating to

	0.7 mg/kg SC on the fourth dosing visit and Q3W for the remainder of the 24-week Treatment Period Chronic medication for HF (including Sodium-Glucose Cotransporter-2 [SGLT2] inhibitors and sacubitril/valsartan) or for any underlying condition will need to be administered at a stable dose for ≥30 days prior to Visit 1. Diuretics and/or anticoagulants are excepted from this rule but should not be newly started or stopped within 30 days of Visit 1, and a prescribed dose change should not occur within 7 days of Visit 1. Anticoagulation may be suspended for right heart catheterization (RHC) if necessary. Therapies specific for PAH are not allowed within 30 days prior to Visit 1. A planned interim analysis (IA) (described in the Statistical Methods section below) will occur when approximately 75 participants across the 3 treatment groups have completed 24 weeks on the study or discontinued study treatment before 24 weeks. Participants who remain on study treatment at the completion of the placebo-controlled Treatment Period may continue in the 18-month Extension Period as follows: • Placebo participants will be re-randomized in a 1:1 ratio to 1 of the 2 sotatercept treatment groups utilized in the placebo-controlled Treatment Period, that is, to receive either of the following: - Placebo-crossed Treatment Group 1: Sotatercept SC at a dose level of 0.3 mg/kg Q3W for approximately 18 months in Extension Period - Placebo-crossed Treatment Group 2: Sotatercept SC at a starting dose of 0.3 mg/kg for 3 dosing visits (Q3W), then escalating to 0.7 mg/kg at the next dosing visit and Q3W for the remainder of the Extension Period • Participants who were treated with sotatercept in the placebo-controlled Treatment Period will continue on their current dose SC Q3W in the Extension Period. As of CADENCE Amendment MK-7962-007-06, the 18-month Extension Period is being removed from CADENCE and being placed in the extension study MK-7962-023 (HARMONIZE). Participants who have completed at least the 24-week placebo-controlled treatment period (through Visit 9) and the end of treatment (EOT) Visit, and who have not discontinued study treatment early, may be eligible to participate in the extension study, HARMONIZE.

Inclusion Criteria	Participants must meet the following criteria to be enrolled in this proof-of-concept study: 1. Age 18 to 85 years 2. Clinical diagnosis of HFpEF: - Left ventricular ejection fraction (LVEF) ≥ 50%, with no history of LVEF below 45% in more than 2 consecutive measurements under stable conditions 3. Demonstrated Cpc-PH by all of the following: - Baseline RHC performed within 28 days of randomization documenting a minimum PVR of ≥ 320 dyn•sec/cm^5 (4 wood units) (see Section 9.2.1 for historic RHC requirements) - Mean pulmonary arterial pressure (mPAP) of > 20 mm Hg - Pulmonary capillary wedge pressure (PCWP) > 15 mm Hg but < 30 mm Hg 4. NYHA FC of II or III 5. Six-Minute Walk Distance ≥ 100 m repeated twice during Screening and both values within 15% of each other, calculated from the highest value (see Section 9.3.2 for details) 6. Chronic medication for HF or for any underlying condition, administered at a stable (per investigator) dose for ≥ 30 days prior to Visit 1. Diuretics and/or anticoagulants are excepted from this rule but should not be newly started or stopped within 30 days of Visit 1, and a prescribed dose change should not occur within 7 days of Visit 1. Anticoagulation may be suspended for RHC if necessary. 7. Women of childbearing potential (defined in Appendix 2) must: - Have 2 negative urine or serum pregnancy tests as verified by the investigator during the Screening Period; must agree to ongoing pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug - If sexually active with a male partner: ◦ Use highly effective contraception without interruption for at least 28 days prior to starting the investigational product, AND ◦ Agree to use the same highly effective contraception in combination with a barrier method during the study (including dose interruptions), and for 16 weeks (112 days) after discontinuation of study treatment - Refrain from breastfeeding a child or donating blood, eggs, or ovum for the duration of the study and for at least 16 weeks (112 days) after the last dose of study drug

	See Appendix 2 for additional contraceptive information. 8. Male participants must: - Agree to use a condom, defined as a male latex condom or non-latex condom NOT made out of natural (animal) membrane (e.g., polyurethane), during sexual contact with a pregnant female or a woman of childbearing potential (WOCBP) 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 (see Appendix 2 for additional contraceptive information) - Refrain from donating blood or sperm for the duration of the study and for 16 weeks (112 days) after the last dose of study drug 9. Ability to adhere to the study visit schedule and understand and comply with all protocol requirements 10. Agreement to not participate in any other trials of investigational drugs/devices while enrolled in the A011-16 study 11. Ability to understand and provide documented informed consent for participation
Exclusion Criteria	Participants will be excluded from the study if any of the following criteria are met: 1. A diagnosis of PH in WHO Group 1, WHO Group 3, WHO Group 4, or WHO Group 5 2. Clinically significant and active lung disease: - Chronic obstructive pulmonary disease with post-bronchodilator forced expiratory volume in the first second (FEV1) < 60% predicted - Restrictive lung disease with total lung capacity < 70% predicted - More than mild interstitial lung disease (ILD), with FVC < 70% or FEV1 < 60% predicted (still appropriate if absence of more than mild ILD, fibrosis, or COPD on computed tomography [CT] imaging) 3. Cardiovascular comorbidities, which include any of the following: - History of more than mild mitral or aortic stenosis, corrected mitral or aortic stenosis by a surgical or transcatheter method within 12 months from Visit 1. (Participants with corrected valvular disease may only be allowed after the Medical Monitor's review).

	- Ongoing more than mild mitral or aortic regurgitation, corrected mitral or aortic regurgitation by a surgical or transcatheter method within 12 months from Visit 1. (Participants with corrected valvular disease may only be allowed after the Medical Monitor's review.) NOTE: If an imaging report reads "mild-to-moderate mitral regurgitation," the participant may still be enrolled if, in the opinion of the investigator, the mitral regurgitation is no more than mild. - More than one valve replacement or repair (mechanical or biomechanical) or anticipation of any valve replacement or repair - Severe tricuspid regurgitation due to primary valvular disease (e.g., from endocarditis, carcinoid, or mechanical destruction) - Occurrence of myocardial infarction, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention within 180 days of Visit 1 - History of serious life-threatening or hemodynamically significant arrhythmia - History of or anticipated heart transplant or ventricular assist device implantation - History of implantable cardioverter defibrillator placement or anticipated implantation of pacemaker, pacemaker implantation within 30 days of Screening - History of known pericardial constriction, hypertrophic cardiomyopathy, sarcoidosis, or amyloid cardiomyopathy - Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 110 mm Hg during Screening after a period of rest - Systemic hypotension as evidenced by sitting systolic blood pressure < 90 mm Hg or sitting diastolic blood pressure < 50 mm Hg during Screening - Resting heart rate of < 45 bpm or > 115 bpm (including atrial fibrillation) - Stroke within 90 days of Visit 1 - Acutely decompensated HF that required hospitalization within 30 days of Visit 1

	- Electrocardiogram (ECG) during Screening Period with Fridericia's corrected QT interval (QTcF) > 470 msec for males or > 480 msec for females, or > 500 msec if a ventricular conduction defect (right bundle branch block; left bundle branch block; or interventricular conduction delay) is present - Personal or family history of Brugada syndrome, sudden cardiac arrest or unexplained sudden cardiac death or arrest - Personal or family history of long QT syndrome unless the subject's ECG shows a normal QTc - Arrhythmogenic right ventricular dysplasia (ARVD) unless the subject has a recent cardiac MRI that shows no evidence of this diagnosis 4. Hospitalization for any worsening of medical conditions or any significant surgery per investigator within 30 days of Visit 1 5. Received any approved PAH-specific therapies (i.e., endothelin receptor antagonists, prostacyclin analogs, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators) within 30 days of Visit 1. The use of an oral phosphodiesterase-5 inhibitor, if only indicated for erectile dysfunction, is permitted, if not administered within 48 hours of a study visit or procedure. 6. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin, or levosimendan) within 30 days of Visit 1 7. Received erythropoietin within 6 months of Visit 1 8. Known history of chronic liver disease, including untreated hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication), with severe hepatic impairment and/or cirrhosis (e.g., hepatic encephalopathy) 9. Prior exposure to sotatercept or luspatercept 10. 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 consent 11. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days of Visit 1 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)

	12. Any of the following clinical laboratory values prior to Visit 1 as specified: - Hemoglobin (Hgb) above the gender-specific upper limit of normal (ULN) per local laboratory test within 28 days of Visit 1 or < 10 g/dL per local laboratory within 28 days of Visit 1 - Serum alanine aminotransferase or aspartate aminotransferase levels > 3× ULN or total bilirubin > 3× ULN within 28 days of Visit 1 - Estimated glomerular filtration rate < 30 ml/min/1.73 m^2 (4-variable Modification of Diet in Renal Disease equation) within 28 days of Visit 1 or required renal replacement therapy within 90 days of Visit 1 - Glycated hemoglobin (HbA1c) > 10% within 28 days of Visit 1 - Platelet count < 75,000/mm^3 within 28 days of Visit 1 13. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in the investigational product 14. Major surgery within 60 days of Visit 1. Participants must have completely recovered from any previous surgery prior to Visit 1 15. Prior organ transplantation (e.g., heart, lung, liver, kidney), bone marrow transplantation, or life expectancy of < 12 months 16. Pregnancy or breastfeeding in females 17. Active malignancy, with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in situ, or ≤ 2 squamous cell carcinomas of the skin 18. History of clinically significant (as determined by the investigator) endocrine, hematologic, hepatic, (auto)immune, infectious (requiring chronic antibiotics), metabolic, urologic, pulmonary, neurologic, neuromuscular, dermatologic, psychiatric, renal, and/or another disease that may limit participation in the study 19. Body mass index ≥ 50 kg/m^2 20. More than mild obstructive sleep apnea (treated or untreated) 21. Any non-cardiopulmonary condition or acute/chronic impairment(s) (other than dyspnea) that limits the ability to perform 6-minute walk test (6MWT)

Efficacy Endpoints	**Primary Efficacy Endpoint** • Change from baseline in PVR at Week 24 **Key Secondary Efficacy Endpoint** • Change from baseline in 6MWD at Week 24 **Other Secondary Endpoints** • Time to first clinical worsening event (TTCW) assessed at Week 24, defined as the number of weeks from first dose date to any of the following: - Hospitalization due to a cardiopulmonary indication (a non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or HF) - Administration of intravenous diuretics or SC furosemide - Death (all causes) - Decrease in 6MWD by ≥ 15% from baseline • Change from baseline in hemodynamic and echocardiography (ECHO) parameters, including but not limited to mPAP, PCWP, tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RVFAC), LVEF, IVRT, ratio of mitral inflow velocity I to mitral annular velocity'(e') (E/e' ratio), ratio of the peak velocity flow of the E wave in early diastole to peak velocity flow of the A wave in late diastole (E/A ratio), and myocardial contraction fraction (MCF) as the ratio of stroke volume to myocardial volume derived from echocardiographic linear dimensions at Week 24 • Change from baseline in NT-proBNP at Week 24 • Change from baseline in NYHA FC at Week 24 **Exploratory Endpoints** • Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) scores at Week 24 • Change from baseline in disease-related biomarkers (ST2 and Activin A) at Week 24 • Change from baseline in dyspnea score (assessed by Borg CR10 scale®) at Week 24 • Identification of molecular biomarkers (e.g., transcriptomics, metabolomics, and/or proteomics) that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of sotatercept and other treatments

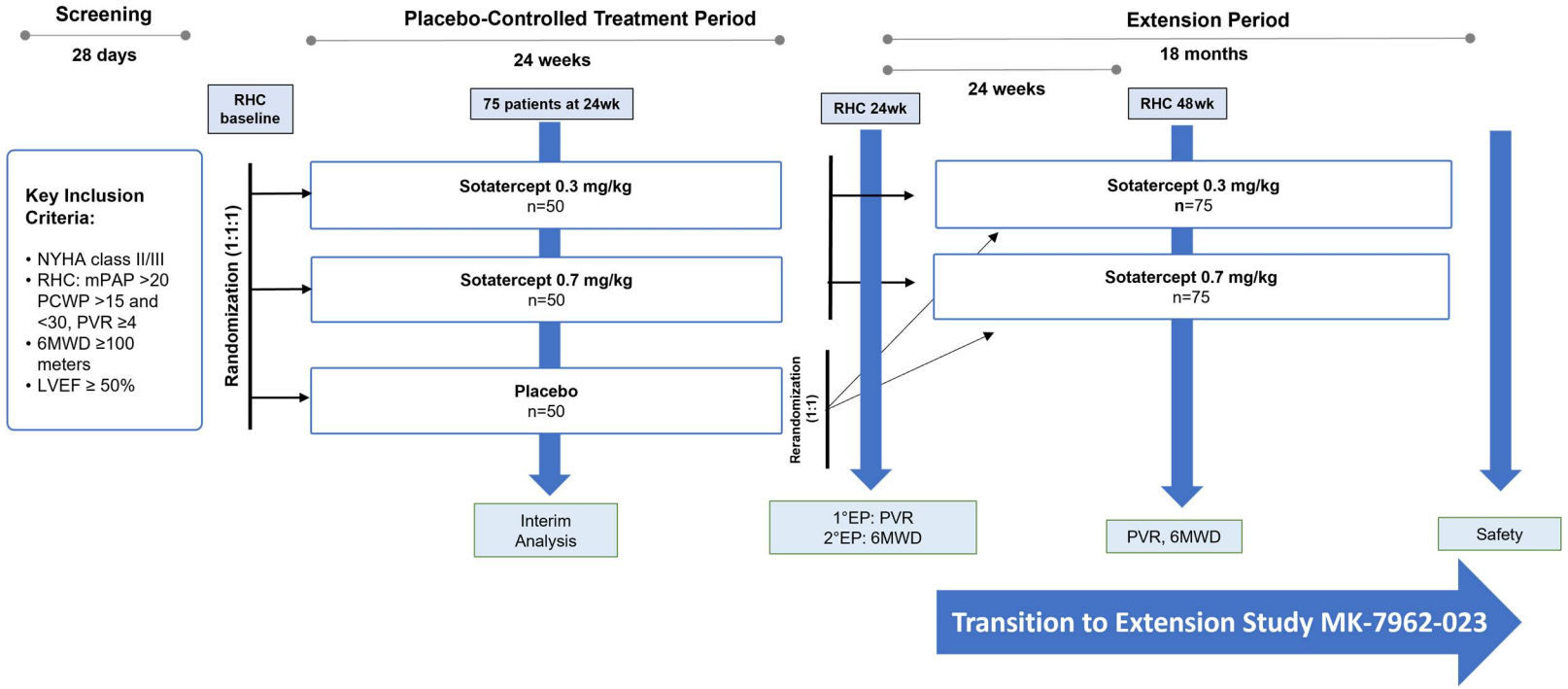
	• Composite endpoint including the following: - All-cause mortality, - Frequency of HF hospitalizations by Week 24, - Change from baseline to Week 24 in 6MWD (meters), and - Change from baseline to Week 24 in NT-proBNP (ng/L)
Safety Endpoints	**Placebo-controlled Treatment Period** • Adverse events (AEs) • Discontinuation of study treatment due to AEs
Pharmacokinetic Endpoints	**Placebo-controlled Treatment Period** • Population pharmacokinetic (PK) parameters of sotatercept and exposure-response relationships in participants with Cpc-PH due to HFpEF.
Sample Size Determination and Power Calculations	Power and sample size are based on the mean change from baseline in PVR at Week 24. Assuming that the true mean decrease from baseline in PVR at Week 24 is approximately 92 dyn•sec/cm^5 for each sotatercept dose versus 0 for placebo and assuming a common standard deviation (SD) of 154, a sample size of 45 per group provides 80% power to demonstrate superiority for each of the sotatercept treatment comparisons using a one-sided alpha=0.025. Through 24 weeks post-randomization, drop-out is expected to be approximately 10% in each treatment group. To account for the assumed drop-out rate, this study will randomize 150 participants in a 1:1:1 ratio into sotatercept 0.3 mg/kg arm, sotatercept 0.7 mg/kg arm, and placebo arm, respectively.
Randomization Stratification Factors	NYHA FC II or NYHA FC III

Statistical Methods	Populations for statistical analyses include the following: **Full Analysis Set (FAS):** All randomized participants. All participants will be analyzed according to the treatment group to which the participant is randomized. **Safety Population:** All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment received. **Interim Analysis** An IA is planned when approximately 75 participants across the 3 treatment groups have completed 24 weeks of treatment in the placebo-controlled Treatment Period or discontinued study treatment before 24 weeks. All randomized participants will be included. The purpose of the IA is to allow an early stop for futility. The futility criterion is that if the Hodges-Lehmann location-shift for the treatment difference (sotatercept minus placebo) in change from baseline in PVR at Week 24 is greater than 0 dyn•sec/cm^5 for both sotatercept dose levels, consideration may be given to stop the study. The estimate will be based on the Aligned Rank Stratified Wilcoxon (ARSW) test. **Analysis of Study Endpoints:** **Efficacy Endpoints** The change from baseline in PVR and in 6MWD at 24 weeks will each be analyzed using the ARSW test [Hodges, J. L., Jr. and Lehmann, E. L. 1962] [Mehrotra, D. V., et al 2010] stratified by the randomization stratification factor. Details are provided in Sections 11.4.1.1 and 11.4.1.2. Multiplicity For the primary endpoint and key secondary endpoint, there are 2 treatment group comparisons that may be tested to address the corresponding hypothesis. Testing will be done using a 1-sided alpha=0.025 level in a sequential manner, in descending order of endpoint priority (primary followed by key secondary), in descending order of sotatercept dose group within each endpoint, stopping at the point statistical significance is not achieved. Details are provided in Section 11.4.5. **Safety Endpoints** Point estimates and 2-sided 95% confidence intervals (CIs) between treatment groups in the percentages of participants will be provided for selected AE summaries that occur in at least 4 participants in any treatment group. CIs for differences between treatment groups will be provided using the Miettinen and Nurminen method [Miettinen, O. S. 1985].

Safety and Pharmacovigilance	An independent, external Data Monitoring Committee (eDMC) will monitor participant safety throughout the study. Internal review of safety-related data will occur at a preplanned frequency throughout the study duration.

1.1 Study Schematic

Figure 1 Schematic of Study Periods for Study A011-16



6MWD = 6-minute walk distance; EP = endpoint; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary arterial pressure; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SC = subcutaneous; Vx = Study Visit (V1 is Visit 1); wk = week.
Note: As of CADENCE Amendment MK-7962-007-06, the 18-month Extension Period is being removed from CADENCE and being placed in the extension study, MK-7962-023 (HARMONIZE). Participants who have completed at least the 24-week placebo-controlled Treatment Period (through V9) and the EOT Visit, and who have not discontinued study treatment early, may be eligible to participate in HARMONIZE.
Participants randomized to receive 0.7 mg/kg sotatercept (Treatment Group 3 and Placebo-Crossed Treatment Group 2) will be administered sotatercept SC at a starting dose level of 0.3 mg/kg for the initial 3 dosing visits (Q3W), then escalated to 0.7 mg/kg SC Q3W for the remainder of the study.

2 SCHEDULE OF EVENTS

The Schedule of Events (SoE), which provides an overview of the study periods and procedures for participants, is presented in [Table 2] and [Table 3]. Specific information on visits and assessments is in Section 9.

Table 2 Schedule of Events: Placebo-controlled Treatment Period

	Screening Period (Up to 28 Days Before Visit 1)	Placebo-controlled Treatment Period (24 Weeks)[a]											24-Week Assess-ments
		Visit 1	Visit 1a	Visit 2	Visit 2a	Visit 3	Visit 4	Visit 4a	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[b,u]
		Study Day 1 (Week 0)	6 to 10 Days from Visit 1	Week 3	6 to 10 Days from Visit 2	Week 6	Week 9	6 to 10 Days from Visit 4	Week 12	Week 15	Week 18	Week 21	Week 24
Informed consent	X												
Optional informed consent forms[s]	X----------X												
Inclusion/exclusion criteria	X												
Medical history review[c]	X												
Physical examination[d]	X												
Targeted physical examination[d] (cardiopulmonary and skin)		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X								X				X
Vital signs including weight[f]	X	X		X		X	X		X	X	X	X	X
Pregnancy test (urine or serum)[g]	X	X		X		X	X		X	X	X	X	X
Hematology (complete blood count)[h]	X	X		X		X	X		X	X	X	X	X
Serum chemistry/FSH[i]	X	X		X		X	X		X	X	X	X	X
HbA1c	X								X				X
Urinalysis (dipstick)	X	X		X		X	X		X	X	X	X	X
Right heart catheterization[j]	X												X
6MWT[k]	X	X								X			X
Borg Dyspnea Scale (pre- and post-6MWT)	X	X								X			X
NYHA FC assessment[t]	X	X		X		X	X		X	X	X	X	X

	Screening Period (Up to 28 Days Before Visit 1)	Placebo-controlled Treatment Period (24 Weeks)[a]										24-Week Assess-ments
		Visit 1	Visit 1a	Visit 2	Visit 2a	Visit 3	Visit 4	Visit 4a	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[b,u]
		Study Day 1 (Week 0)	6 to 10 Days from Visit 1	Week 3	6 to 10 Days from Visit 2	Week 6	Week 9	6 to 10 Days from Visit 4	Week 12	Week 15	Week 18	Week 21	Week 24
Clinical Worsening assessment[k]				X		X	X		X	X	X	X	X
QoL assessments[l]	X	X		X			X			X		X	X
PD blood biomarkers[m]		X	X	X		X	X	X				X	X
ADA sample collection[n]		X		X		X	X					X	X
Pre-dose (or no dose) PK sample collection[o]		X		X		X	X					X	X
Post-dose PK sample collection[p]		X	X		X			X					
Randomization		X											
ECHO[q]	X	X							X				X
Study drug administration[r]		X		X		X	X		X	X	X	X	
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X

6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; Cpc-PH = combined postcapillary and precapillary pulmonary hypertension; E/A ratio = ratio of the peak velocity flow of the E wave in early diastole to peak velocity flow of the A wave in late diastole; ECG = electrocardiogram; E/e' ratio = ratio of mitral inflow velocity I to mitral annular velocity'(e'); ECHO = echocardiogram; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; EOS = End of Study; EOT = End of Treatment; FC = functional class; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HCO3 = bicarbonate; Hgb = hemoglobin; IRT = Interactive Response Technology; IVRT = isovolumetric relaxation time; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MCF = myocardial contraction fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; PD = pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; QoL = quality of life; RHC = right heart catheterization; RVFAC = right ventricular fractional area change; SAE = serious adverse event; ST2 = suppressor of tumorigenicity 2; TAPSE = tricuspid annular plane systolic excursion; WOCBP = women of childbearing potential.
See [Table 3] for Extension Period and early termination procedures.

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

then they would resume dosing at Visit 6). Participants discontinuing study treatment prior to Visit 9 are asked to complete the EOT and EOS (see [Table 3]) visits in that order.

b Visit 9 procedures are to occur prior to Visit 9a procedures (see [Table 3]) on the same Day, except for RHC, 6MWT, Borg Dyspnea Scale, and ECHO, which may be performed earlier per the protocol.

c Medical history review includes confirmation of disease history associated with Cpc-PH.

d As described in Section 9.3.8, a full physical examination should be completed during the Screening Period; a targeted physical (cardiopulmonary and skin) examination should be completed at all other visits.

e At visits where both ECGs and 6MWT assessments are done, ECGs should be performed prior to 6MWT.

f Height measurement will be required at the Screening vital signs collection.

g Two negative urine or serum pregnancy tests are required for WOCBP during the Screening Period. One negative urine or serum pregnancy test is required prior to study treatment administration for all dosing visits (see Appendix 2 for pregnancy follow-up).

h Complete blood count includes red blood cells, absolute white blood cells, Hgb, hematocrit, and platelet count. Results are evaluated prior to study treatment administration. Hematology testing will be performed on the day of the visit or up to 3 days prior (if available). Refer to Section 8.3 for dose modification guidelines based on findings from the hematology panel.

i Blood urea, creatinine, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, HCO3, albumin, and FSH will be measured.

j Three RHCs should be performed during the course of this study: 1 in the Screening Period, 1 in the placebo-controlled Treatment Period, and 1 in the Extension Period. Right heart catheterization in the Screening Period should be performed after all Screening clinical laboratory tests are done for eligibility if possible. The RHCs in the placebo-controlled Treatment Period must occur within 28 days of randomization and within 14 days prior to or at Visit 9. For participants discontinuing the study before Visit 9 (Week 24), an RHC should be performed. If other assessments are occurring on the same Day, RHC should be performed last when possible. The use of a historic RHC for Screening is discouraged. An exception may be granted for a historic RHC done within 14 days from the start of the Screening Period, following the review and approval of the Medical Monitor.

k The 6MWT is to be performed twice during the Screening Period at least 4 hours (but no longer than 1 week) apart. The baseline value for 6MWD is the average of the 2 values collected during Screening. If Screening 6MWT is done within 10 days prior to or at Visit 1, an additional 6MWT does not need to be conducted at Visit 1. All 6MWTs performed from Visit 1 onward can be performed at the study visit Day or within 10 days prior to study treatment administration. If the 6MWT is performed on the day of the study visit, it must be performed before study treatment administration. The 6MWT may also be done twice based on criteria outlined for clinical worsening (Section 9.3.5). Clinical worsening assessment, including the 6MWT/Borg Dyspnea Scale measurement, should be performed whenever a participant's symptoms and condition suggest the possibility of a clinical worsening event. NOTE: Document a single clinical worsening event when consecutive doses of IV diuretics are administered within 24 hours during a hospitalization or when multiple doses are given at a single visit. If more than 24 hours pass between IV diuretic doses/SC furosemide administration, document an additional clinical worsening event.

l The QoL assessments include KCCQ, EQ-5D-5L, PGI-S, and PGI-C. The QoL assessments are to be completed before performing other study assessments if possible (6MWT, blood draws, AE discussions, and RHC). The PGI-C assessment should not be conducted at Screening or Visit 1 (see Section 9.3.7.1 for details).

m On days when study treatment is administered, samples for biomarker assessments (such as NT-proBNP, Activin A, ST2, etc.) will be collected prior to study treatment administration.

n On days when study treatment is administered, samples for ADA assessment will be collected prior to study treatment administration. 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.

o Samples for PK assessments will be collected predose. Ad hoc PK samples may also be collected as needed any time a serious AE occurs or as determined by the investigator.

p Postdose samples for PK assessments will be collected at 1 to 4 hours on the Day of dosing. At Visit 1a, a PK sample will be collected as a second post-dose sample for the dose administered at Visit 1. At Visit 2a and Visit 4a, a PK sample will be collected as a post-dose sample for the dose administered at Visit 2 and Visit 4, respectively.

q ECHO parameters include but are not limited to TAPSE, RVFAC, LVEF, MCF, IVRT, E'/e' ratio, and E/A ratio. During the Screening Period, either a new or historical ECHO will be used for Screening. If an ECHO is performed during the Screening Period, these values may be used as the baseline for this study, and an additional ECHO is

not required at Visit 1. If a historical ECHO is evaluated during the Screening Period, the participant must receive an ECHO at Visit 1, which will serve as the baseline for the study for these participants (provided that it is consistent with the historical ECHO). All ECHOs after Visit 1 may be performed within 7 days prior to or at the study visit.

r All study procedures must be done prior to study treatment administration. Dose must be calculated based on the participant's weight on the Day of dosing. If the participant has rapid weight change caused by fluid retention between visits (e.g., a weight gain of more than 1 kg within a 24-hour period), the Medical Monitor can be consulted for calculating the dose. Dose modification guidelines based on Hgb levels, platelet counts, and related AEs must be reviewed and implemented prior to dosing (Section 8.3).

s Optional ICFs should be collected when appropriate.

t As described in Section 6.3, NYHA FC must be calculated on the day of randomization (Visit 1) and entered into IRT as it will be used to stratify participants at time of randomization.

u Participants who complete Visit 9, and who have not discontinued study treatment early, will complete the EOT Visit (may be completed on the same day as Visit 9) and may be eligible to transfer per treatment schedule to HARMONIZE. Transfer into HARMONIZE may occur on the same day as the EOT Visit in CADENCE. The participant should enter HARMONIZE at the next scheduled study treatment visit after EOT for CADENCE. If entry at the next scheduled study treatment visit is not feasible, please consult the Sponsor.

Table 3 Schedule of Events: Extension Period and Follow-Up Period

	Extension Period (18 Months)[a, s]										Follow-up Period		
	Visit 9a	**Visit 9b**	**Visit 10**	**Visit 10a**	**Visit 11**	**Visit 12**	**Visit 12a**	**Visits, 14-16, 18-20, 22-24, 26-28, 30-32**	**Visits 13, 17, 21, 25, 29, 33**	**Visit 34**	**EOT[p]** **3 Weeks Post Last Dose of Study Treatment or at the Time of Early Discontinuation**	**EOS[p]** **5 Weeks Post EOT- (8 Weeks Post Last Dose of Study Treatment)**	**Quarterly Follow-up Telephone calls[r]**
	Week 24[b]	**6 to 10 Days from Visit 9a**	**Week 27**	**6 to 10 Days from Visit 10**	**Week 30**	**Week 33**	**6 to 10 Days from Visit 12**	**Weeks 39, 42, 45, 51, 54, 57, 63, 66, 69, 75, 78, 81, 87, 90, 93**	**Weeks 36, 48, 60, 72, 84, 96**	**Week 99**			
Targeted physical examination[c]		X	X	X	X	X	X	X	X	X	X	X	
Optional informed consent forms[q]	X----------X												
12-lead ECG[d]										X	X		
Vital signs including weight			X	X	X	X	X	X	X	X	X		
Pregnancy test (urine or serum)[e]			X		X	X		X	X	X	X	X	
Hematology (complete blood count)[f]			X		X	X		X	X	X	X		
Serum chemistry/FSH[g]			X		X	X		X	X	X	X		
HbA1c									X				
Urinalysis (dipstick)			X	X	X	X	X	X	X	X	X		

	Extension Period (18 Months)[a, s]										Follow-up Period		
	Visit 9a	**Visit 9b**	**Visit 10**	**Visit 10a**	**Visit 11**	**Visit 12**	**Visit 12a**	**Visits, 14-16, 18-20, 22-24, 26-28, 30-32**	**Visits 13, 17, 21, 25, 29, 33**	**Visit 34**	**EOT[p]** **3 Weeks Post Last Dose of Study Treatment or at the Time of Early Discontinuation**	**EOS[p]** **5 Weeks Post EOT- (8 Weeks Post Last Dose of Study Treatment)**	**Quarterly Follow-up Telephone calls[r]**
	Week 24[b]	**6 to 10 Days from Visit 9a**	**Week 27**	**6 to 10 Days from Visit 10**	**Week 30**	**Week 33**	**6 to 10 Days from Visit 12**	**Weeks 39, 42, 45, 51, 54, 57, 63, 66, 69, 75, 78, 81, 87, 90, 93**	**Weeks 36, 48, 60, 72, 84, 96**	**Week 99**			
Right heart catheterization[h]									Visit 17 (Week 48) only		X – only for participants who discontinue study treatment early. See footnote 'h' for details		
6MWT[i]									X		X	X	
Borg Dyspnea Scale (pre- and post-6MWT)									X		X	X	
NYHA FC assessment			X		X	X		X	X	X	X	X	
Clinical Worsening assessment[i]			X		X	X		X	X	X	X	X	
QoL assessments[j]			X						X	X	X		
PD blood biomarkers[k]			X		X	X		X	X	X	X	X	
ADA sample collection[l]			X						X	X	X	X	
Pre-dose (or no dose) PK sample collection[m]		X	X	X	X	X	X	X	X	X	X	X	

	Extension Period (18 Months)[a, s]										Follow-up Period		
	Visit 9a	**Visit 9b**	**Visit 10**	**Visit 10a**	**Visit 11**	**Visit 12**	**Visit 12a**	**Visits, 14-16, 18-20, 22-24, 26-28, 30-32**	**Visits 13, 17, 21, 25, 29, 33**	**Visit 34**	**EOT[p] 3 Weeks Post Last Dose of Study Treatment or at the Time of Early Discontinuation**	**EOS[p] 5 Weeks Post EOT- (8 Weeks Post Last Dose of Study Treatment)**	**Quarterly Follow-up Telephone calls[r]**
	Week 24[b]	**6 to 10 Days from Visit 9a**	**Week 27**	**6 to 10 Days from Visit 10**	**Week 30**	**Week 33**	**6 to 10 Days from Visit 12**	**Weeks 39, 42, 45, 51, 54, 57, 63, 66, 69, 75, 78, 81, 87, 90, 93**	**Weeks 36, 48, 60, 72, 84, 96**	**Week 99**			
Randomization	X												
ECHO[n]			X						X		X		
Study treatment administration[o]	X		X		X	X		X	X	X			
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X

6MWT = 6-minute walk test; ADA = antidrug antibody; AE = adverse event; E/A ratio = ratio of the peak velocity flow of the E wave in early diastole to peak velocity flow of the A wave in late diastole; ECG = electrocardiogram; E/e' ratio = ratio of mitral inflow velocity (E) to mitral annular velocity (e'); EOS = End of Study; EOT = End of Treatment; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; FC = functional class; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HCO_3 = bicarbonate; Hgb = hemoglobin; IVRT = isovolumetric relaxation time; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MCF = myocardial contraction fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; PD = pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; QoL = quality of life; RHC = right heart catheterization; RVFAC = right ventricular fractional area change; SAE = serious adverse event; ST2 = suppressor of tumorigenicity 2; TAPSE = tricuspid annular plane systolic excursion; WOCBP = women of childbearing potential. See [Table 2] for placebo-controlled Treatment Period.

a Each dosing visit will be 3 weeks (21 days±3 days) from the previous dosing visit, unless a dose delay is required. The EOT Visit will be 3 weeks ±7 days after the last dose of study treatment (or at the time of early discontinuation) and the EOS Visit will be 5 weeks ±7 days after the EOT Visit. If a dose delay is required per the dose modification guidelines (Section 8.3), the participant will not be dosed and the participant will return every 3 weeks for assessment of hematology results and AEs until the participant is eligible to receive the next dose of study treatment. The participant should resume treatment at the next planned dosing visit (e.g., if the participant missed a dose at Visit 11, then they would resume dosing at Visit 12). Participants discontinuing study treatment are asked to complete the EOT and EOS visits.

b Visit 9 (Week 24) procedures (see [Table 2]) are to occur prior to Visit 9a (Week 24) procedures on the same Day, except for RHC, 6MWT, Borg Dyspnea Scale, and echocardiogram, which may be performed earlier per the protocol.

c Targeted physical (cardiopulmonary and skin) examination only (see Section 9.3.8).

d At visits where both ECGs and 6MWT assessments are done, ECGs should be performed prior to 6MWT.

e Two negative urine or serum pregnancy tests are required for WOCBP during the Screening Period. One negative urine or serum pregnancy test is required prior to study treatment administration at all dosing visits, at EOT, and at EOS (see Appendix 2 for pregnancy follow-up). The pregnancy test performed on Visit 9 will be considered sufficient for dosing on Visit 9a.

f Complete blood count includes red blood cells, absolute white blood cells, Hgb, hematocrit, and platelet count. Results are evaluated prior to study treatment administration. Hematology testing will be performed on the Day of the visit or up to 3 days prior (if available). Refer to Section 8.3 for dose modification guidelines based on findings from the hematology panel.

g Blood urea, creatinine, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, HCO3, albumin, and FSH will be measured.

h Three RHCs should be performed during the course of this study: 1 in the Screening Period, 1 in the placebo-controlled Treatment Period and 1 in the Extension Period at Visit 17 (Week 48). If the participant discontinues the study treatment in the Extension Period after Visit 9 (Week 24) and prior to or at Visit 17 (Week 48), the final RHC should be offered prior to the EOS Visit. If other assessments are occurring on the same Day, RHC should be performed last when possible.

i The 6MWT may be done twice based on criteria outlined for clinical worsening (Section 9.3.5). The baseline value for 6MWD is the average of the 2 values collected during Screening. All 6MWTs performed from Visit 1 onward can be performed at the study visit day or within 10 days prior to study treatment administration. If the 6MWT is performed on the Day of the study visit, it must be performed before study treatment administration. Clinical worsening assessment, including the 6MWT/Borg Dyspnea Scale measurement, should be performed whenever a participant's symptoms and condition suggest the possibility of a clinical worsening event. NOTE: Document a single clinical worsening when consecutive doses of IV diuretics are administered within 24 hours during a hospitalization or when multiple doses are given at a single visit. If more than 24 hours pass between IV diuretic doses/SC furosemide administration, document an additional clinical worsening event.

j The QoL assessments include KCCQ, EQ-5D-5L, PGI-S, and PGI-C. The QoL assessments are to be completed before performing other study assessments if possible (6MWT, blood draws, AE discussions, and RHC).

k On days when study treatment is administered, samples for biomarker assessments (such as NT-proBNP, Activin A, ST2, etc.) will be collected prior to study treatment administration.

l On days when study treatment is administered, samples for ADA assessment will be collected prior to study treatment administration. 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.

m Samples for PK assessments will be collected predose.

n Echocardiogram parameters include but are not limited to TAPSE, RVFAC, LVEF, MCF, IVRT, E/e' ratio, and E/A ratio. All echocardiograms after Visit 1 may be performed within 7 days prior to or at the study visit.

o All study procedures must be done prior to study treatment administration. Dose must be calculated based on the participant's weight on the Day of dosing. If the participant has rapid weight change caused by fluid retention between visits (e.g., a weight gain of more than 1 kg within a 24-hour period), the Medical Monitor can be consulted for calculating the dose. Dose modification guidelines based on Hgb levels, platelet counts, and related AEs must be reviewed and implemented prior to dosing (Section 8.3).

p EOT will be performed in all participants 3 weeks after the last dose of study treatment or at the time of early discontinuation. EOS will be performed in the case of a participant's early discontinuation or for those participants who do not proceed to HARMONIZE.

q Optional ICFs should be collected when appropriate.

r Following the EOT and EOS Visits, or if the participant refuses to attend additional study visits, participants who discontinue study treatment early will receive quarterly telephone contacts for vital status, AE/SAE review, and concomitant medication review until study completion, provided that consent is not withdrawn (refer to Section 9.4).

s Participants who complete CADENCE between V9a and V34, and who have not discontinued study treatment early, will complete the EOT Visit (3 weeks after last CADENCE dosing visit) and may be eligible to transfer per treatment schedule to HARMONIZE. Transfer into HARMONIZE may occur on the same day as the EOT Visit in CADENCE. The participant should enter HARMONIZE at the next scheduled study treatment visit after EOT for CADENCE. If entry at the next scheduled study treatment visit is not feasible, please consult Sponsor.

3 INTRODUCTION: BACKGROUND AND STUDY RATIONALE

Pulmonary hypertension (PH) is a chronic disease of various etiologies, characterized by sustained elevation of pulmonary arterial pressure (PAP), eventually leading to right ventricular failure and death. The most recent World Health Organization (WHO) classification of PH has established 5 disease groups according to pathogenesis or comorbidity; Group 2 PH is due to left heart disease. As the largest of the PH groups, Group 2 PH represents a high unmet medical need. Group 2 PH has 3 primary etiologies: heart failure (HF) with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF), and valvular heart disease.

Heart failure is present in 1% to 3% of the population worldwide and has an annual incidence of > 650,000 in the United States of America (USA). The societal burden of HF is projected to increase due to the aging population [WRITING COMMITTEE MEMBERS., et al 2013]. In patients with clinical HF, studies estimate that the prevalence of HFpEF is approximately 50% worldwide (range: 40% to 71%) [WRITING COMMITTEE MEMBERS., et al 2013] [Owan, T. E., et al 2006] [Redfield, M. M. 2016]. Despite the high prevalence, morbidity, and mortality associated with HFpEF, treatment options are limited. The first approved treatment for HFpEF is Entresto, a combination of sacubitril and valsartan, which was approved for treatment of left ventricular ejection fraction (LVEF) below normal (a classification that includes HFrEF patients and some HFpEF patients) by the FDA in February 2021.

Among patients with HFpEF, up to 80% of patients develop PH [Hoeper, M. M., et al 2017]. Observational studies suggest that the development of PH in HF is an independent predictor of mortality in both HFrEF and HFpEF [Miller, W. L., et al 2014] [Lam, C. S. P., et al 2009]. Patients with HFpEF (or HFrEF) can be further differentiated by hemodynamic characteristics into 2 subtypes: isolated postcapillary PH (Ipc-PH) and combined postcapillary and precapillary PH (Cpc-PH) [Simonneau, G., et al 2019]. In WHO Group 2 PH, patients with Cpc-PH have a worse prognosis than those with Ipc-PH [Naeije, R., et al 2017]. Patients with HFpEF and Cpc-PH were found to have significantly lower exercise capacity and were more at risk for right ventricular failure, HF hospitalizations, and death, compared with HFpEF patients without additional precapillary PH [Barst, R. J., et al 2006]. Effective treatment for WHO Group 2 PH has the potential to improve patient functional status by removing exertional limitation with decongestion of pulmonary pressure and improve mortality and cardiopulmonary hospitalization by limiting progression to right HF.

3.1 Study Rationale

Study A011-16 is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sotatercept in adults with Cpc-PH due to HFpEF. The study is divided into a 28-Day Screening Period, a 24-week placebo-controlled Treatment Period, an 18-month Extension Period, and an 8-week Follow-up Period.

This Phase 2 study is supported by nonclinical data in 2 rodent Cpc-PH models [Joshi, S. R., et al 2023] and data from the Phase 2 PULSAR study (A011-09, NCT03496207) in patients

with pulmonary arterial hypertension (PAH), as described in Section 3.2. The rationale for this study is also consistent with the Framingham Heart Study, which showed that both circulating levels of follistatin like 3 protein (FSTL3) and activins increase with age and are positively correlated with the severity of left HF.

Sotatercept (ACE-011) is a first-in-class human recombinant, homodimeric fusion protein consisting of the extracellular domain (ECD) of human activin receptor type IIA (ActRIIA) linked to the fragment crystallizable (Fc) domain of human immunoglobulin (Ig) G1. Sotatercept acts as a ligand trap for members of the transforming growth factor (TGF)-β superfamily, including activin [Yung, L. M., et al 2020]. Aberrant TGF-β superfamily signaling is associated with a wide range of human pathologies, including autoimmune, fibrotic diseases, cancer, and cardiovascular disorders such as PAH.

The shared presence of precapillary PH in PAH and Cpc-PH suggests a pathophysiological overlap between the 2 diseases, including increased pulmonary vascular resistance (PVR), right heart dysfunction and increased mortality [Hoeper, M. M., et al 2017] [Gerges, M., et al 2015]. Genetic studies have also suggested that the Cpc-PH subgroup of WHO Group 2 patients more closely resembles WHO Group 1 (PAH) patients than patients with Ipc-PH [Assad, T. R., et al 2016]. Given these pathophysiological overlaps, the Sponsor hypothesizes that the efficacy of sotatercept observed in PAH might also be observed in WHO Group 2 participants with Cpc-PH due to HFpEF. Therefore, this study is designed to determine the efficacy and safety of sotatercept versus placebo in adults with Cpc-PH due to HFpEF.

This study will assess the effects of sotatercept on change from baseline in PVR (primary endpoint) and 6-minute walk distance (6MWD; key secondary endpoint). This study design allows for interrogation of the potential benefits of sotatercept in a population with few treatment options.

There is an unmet need for Cpc-PH therapies because limited treatment options are available, especially for patients with Cpc-PH due to HFpEF. Through a novel mechanism of action, sotatercept targets an imbalance in growth and differentiation factor (GDF)/activin and bone morphogenetic protein (BMP) pathway signaling, which could open a new treatment paradigm for Cpc-PH. This Phase 2 study is being conducted to evaluate the efficacy and safety of sotatercept in participants with Cpc-PH due to HFpEF.

3.1.1 Rationale for Participant Population

The proposed study population is adults (aged 18 to 85 years) with Cpc-PH due to HFpEF of New York Heart Association (NYHA) functional class (FC) II or III.

The study inclusion and exclusion criteria have been chosen to select for patients with high unmet medical need in WHO Group 2 (Cpc-PH due to HFpEF) who would most likely show improvement in PVR and 6MWD parameters and who would benefit from treatment with sotatercept over the duration of the A011-16 proposed study.

Because patients with Ipc-PH do not share the clinical characteristics (i.e., elevated PVR) of patients with PAH, who have been shown to benefit from sotatercept, patients with Ipc-PH will not be included in this study. In addition, although the diagnostic PVR criteria for Cpc-PH is > 3 Wood Units, the criterion of ≥ 4 Wood Units was chosen to enrich for participants with moderate to higher severity.

The Sponsor's pharmacokinetics/pharmacodynamics (PKPD) analyses have suggested that sotatercept pharmacokinetics (PK) are linear and identified participant body weight as the most important covariate influencing sotatercept clearance and volume of distribution. The WHO Group 2 PH participants in this proposed study will have significantly higher body weight than prior studies, which may impact sotatercept exposure. In addition, the obesity in WHO Group 2 participants may have an unknown influence on sotatercept absorption, due to a higher fat composition, and on total body clearance, due to other WHO Group 2-specific cardio-renal factors. The developed PK model parameters were used to simulate sotatercept PK profiles for participants with body weights 100 to 200 kg for dosing regimens 0.3 mg/kg every 3 weeks (Q3W) and 0.7 mg/kg Q3W. For the 0.3 mg/kg Q3W regimen, the steady-state exposure in participants with body weight ranging from 100 to 200 kg were within the observed exposures in WHO Group 1 participants in the PULSAR study following 0.3 mg/kg and 0.7 mg/kg Q3W. As shown in the PKPD model, the reduction in PVR is sotatercept concentration dependent; therefore, the higher sotatercept exposure following a starting SC dose of 0.7 mg/kg/Q3W may result in acute reduction in PVR in WHO Group 2 participants. The sotatercept SC dose titration starting from 0.3 mg/kg for the first 3 visits to a target active dose of 0.7 mg/kg Q3W mitigated this safety concern. Pulmonary vascular resistance profiles were simulated for a dosing regimen starting with an SC dose of 0.3 mg/kg Q3W for Visits 1 to 33, which was then escalated to 0.7 mg/kg Q3W at Visit 4. These simulations supported this dose titration scheme for better management of acute PVR reduction.

The NYHA FC is a categorization system used to classify patients' HF according to the severity of their symptoms [Dolgin, M., et al 1994]. The NYHA FC was selected as the stratification factor for this trial to ensure even distribution of participants with mild versus marked symptoms, which may impact assessment of Efficacy and Safety Endpoints in the proposed study.

3.1.2 Rationale for Study Endpoints

The primary efficacy endpoint of change from baseline in PVR at 24 weeks is intended to assess change in resistance to flow across the pulmonary vasculature; a reduction in PVR is anticipated based on the activity of sotatercept in animal models and PULSAR study results in WHO Group 1 participants with PAH. A similar mechanism of action and activity of sotatercept is hypothesized to occur in patients with Cpc-PH due to HFpEF. The scientific literature suggests that clinically important worsening symptoms in this patient population may reflect increases in PVR [Tampakakis, E., et al 2015] [Butler, J., et al 1999]. Numerous studies have associated pulmonary vascular remodeling in the setting of left heart disease (HFpEF or HFrEF) with higher patient morbidity or mortality. Accordingly, elevation in PVR is the hemodynamic characteristic that distinguishes Cpc-PH from Ipc-PH due to left heart disease.

In a right heart catheter-based study, the presence of increased PVR was associated with increased mortality [Gorlitzer, M., et al 2005]. A retrospective cohort study that enrolled over 1,200 patients, including those with Cpc-PH, confirmed that PVR is the most significant predictor of mortality among 3 hemodynamic parameters that have historically been used to define Cpc-PH (PVR, transpulmonary pressure gradient, and diastolic pressure gradient) [Tampakakis, E., et al 2015]. Furthermore, increased PVR is associated with reduced exercise capacity, which contributes to dyspnea on exertion [Butler, J., et al 1999]. These data indicate that PVR could minimally be a marker for how patients feel, function, and survive [Butler, J., et al 1999].

Measuring change in PVR at 24 weeks permits the observation of clinically meaningful changes in a shorter period of time compared with endpoints such as mortality and clinical worsening in participants with Cpc-PH due to HFpEF. Given the protocol design with placebo crossover and a right heart catheterization (RHC) assessment at Week 48 of the Extension Period, assessment of delayed start may also contribute to our understanding of and evidence of disease modification of sotatercept treatment effect.

Secondary endpoints in this study have been chosen to capture worsening of HF, functional status, and hemodynamic parameters; exploratory endpoints will include patient reported outcomes and biomarkers. The 6MWD is a key secondary endpoint. 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]. Tricuspid annular plane systolic excursion (TAPSE), 6MWD, and FC have been established as having significant mortality prognostic capacity [Forfia, P. R., et al 2006] [Gabler, N. B., et al 2012] [Farber, H. W., et al 2015]. Safety will be assessed by evaluating adverse events (AEs) and discontinuation of study treatment due to AEs.

3.1.3 Rationale for the Comparator

The choice of placebo as the comparator is to enable robust assessments of the effectiveness and safety of sotatercept in a controlled setting. Participants in the placebo group (and sotatercept groups) will be on stable doses of background therapies for HF or other underlying conditions, thus ensuring that participants randomized to the placebo arm are treated and managed as per established treatment guidelines.

3.1.4 Rationale for Dose and Frequency Selection

For the current study, doses of 0.3 and 0.7 mg/kg were selected and will be administered by subcutaneous (SC) injection Q3W.

The proposed sotatercept doses of 0.3 and 0.7 mg/kg Q3W have been previously studied for safety and efficacy in the ongoing PULSAR study (A011-09) as well as in the SPECTRA study (A011-10) in over 100 adult participants with PAH. Similar doses have also been previously tested in various other indications. Exposures from these doses have not only been associated with pharmacological activity related to TGF-β biology, but also have been shown to be efficacious in reducing PVR as well as improving 6MWD in the PULSAR study. The PULSAR study also demonstrated that both doses were generally well tolerated with

acceptable safety profiles. Therefore, for the current proposed study in WHO Group 2 participants with Cpc-PH due to HFpEF, doses of 0.3 and 0.7 mg/kg Q3W were selected; these 2 arms will be compared with 1 arm of placebo Q3W. For the arm with 0.7 mg/kg, a starting dose of 0.3 mg/kg will be administered at Visit 1, Visit 2, and Visit 3 and then escalated to 0.7 mg/kg at Visit 4. This dosing scheme was selected to manage any safety/tolerability issues due to acute PVR reduction that may happen with higher exposures of sotatercept in the first few dosing cycles if 0.7 mg/kg is given at the first visit. In addition, previous experience suggested starting with a lower dose and escalating to target dose of 0.7 mg/kg appeared to address rapid increases in hemoglobin (Hgb).

Sotatercept concentrations and pharmacodynamic (PD) data from the PULSAR study in WHO Group 1 participants with PAH have been analyzed using a population PKPD approach. The developed PKPD model has well described the relationship between sotatercept concentration, efficacy (PVR, 6MWD, and N-terminal prohormone B-type natriuretic peptide [NT-proBNP]), and safety (Hgb) in WHO Group 1 participants with PAH. The exposure-response analyses have suggested that a starting dose of 0.3 escalating to 0.7 mg/kg given Q3W will have a favorable benefit-risk balance in participants with WHO Group 2 PH.

3.2 Background

Diseases with shared clinical manifestations may help to inform the pathogenesis of WHO Group 2 PH. A substantial body of evidence exists implicating members of the TGF-β superfamily in the aberrant proliferation of pulmonary vascular endothelial cells and vascular smooth muscle cells, such as in the disease pathogenesis of PAH (WHO Group 1), which also includes a component of precapillary PH [Zabini, D., et al 2018] [Rol, N., et al 2018] [Medical Letter, Inc 2015]. In the context of WHO Group 2 PH, members of the TGF-β superfamily of signaling molecules have also been associated with the pathogenesis associated with left heart disease.

The TGF-β superfamily is implicated in differentiation and proliferation of various cell types, cell metabolism, motility, invasion, and death as well as extracellular matrix production [Derynck, R. and Budi, E. H. 2019]. Thirty-three ligands have been identified so far, comprising TGF-β isoforms, activins, GDFs, inhibins, nodal, anti-Mullerian hormone, and BMPs. The canonical TGF-β signaling pathway engages mothers against decapentaplegic homologs (receptor-regulated, R-SMAD) transcription factors, while the noncanonical pathway involves phosphorylation of various kinases [Moustakas A, Heldin CH 2005] [Zhang, Y. E. 2017]. Endothelial cells integrate TGF-β/activins/GDFs- and BMP-mediated signaling events in order to maintain vessel wall integrity. It is well-known that in the context of PAH, a defect in the BMP9-ALK1 bone morphogenetic protein type II receptor (BMPR2)-SMAD1/5/8 axis is associated with progression and severity of the disease [Assad, T. R., et al 2016] [Cogan, J. D., et al 2006] [Aldred, M. A., et al 2006] [Newman, J. H., et al 2004]. It is also known that other hyperactive proproliferative TGF- β pathways enhance proliferation through the phosphorylation of SMAD2/3 [Yung, L. M., et al 2020] [Yung LM, Nikolic I, Paskin-Flerlage SD, Pearsall RS, Kumar R, Yu PB 2016]

[Megalou AJ, Glava C, Oikonomidis DL, Vilaeti A, Agelaki MG, Baltogiannis GG 2010] [Megalou AJ, Glava C, Vilaeti AD, Oikonomidis DL, Baltogiannis GG, Papalois A 2012].

Sotatercept blocks activin ligands and GDFs and improves pulmonary vascular remodeling by restoring balance to SMAD signaling [Yung, L., et al 2018]. Trapping of activins and preventing them from binding to the cell surface type II receptor has been shown to rebalance the opposing SMAD signaling pathways and results in the reversal of the adverse remodeling of the pulmonary vasculature and right ventricle in nonclinical models of PAH. The magnitude of effects at the right ventricle supports the hypothesis that SMAD2/3 ligands could have a pathogenic role at the cardiac chambers.

In the murine transverse aortic constriction nonclinical model of pressure overload-induced cardiac hypertrophy, both levels of activin A and SMAD3 phosphorylation are increased in the heart and inhibition of the activin/ActRIIA pathway preserves and restores cardiac function, while enhancing activin A levels is sufficient to induce left heart dysfunction [Roh JD, Hobson R, Chaudhari V, Quintero P, Yeri A, Benson M 2019]. Data generated by the Sponsor have demonstrated that left heart dysfunction in the transverse aortic constriction (Cpc-PH) model subsequently leads to an increase in right ventricular systolic pressure and that a murine ortholog of sotatercept (RAP-011) significantly reduced 2 diagnostic parameters of diastolic dysfunction (the ratio of mitral inflow velocity [E] to mitral annular velocity [e] [E/e' ratio] and isovolumetric relaxation time [IVRT]) and had markedly lower right ventricular systolic pressure.

In addition, the effect of RAP-011 was evaluated in a ZSF1 rat model of Cpc-PH. Obese ZSF1 rats develop diastolic dysfunction together with many features of metabolic syndrome, such as hypertension, hyperglycemia, and insulin resistance, and closely resemble clinical features of HFpEF. When exposed to Sugen (SU5416), ZSF1 rats further develop PH with elevated PVR and remodeling [Lai, Y. C., et al 2016]. In that model, RAP-011 treatment significantly reduced the left ventricular filling pressure (E/e' ratio) and IVRT, 2 diagnostic parameters of diastolic dysfunction. In addition, RAP-011 treatment decreased right ventricular systolic pressure and reduced cardiac and lung fibrosis.

In humans, data from the Framingham Heart Study showed that both circulating levels of FSTL3 and activins increase with age and are positively correlated with the severity of left HF [Roh JD, Hobson R, Chaudhari V, Quintero P, Yeri A, Benson M 2019]. Hence, it is hypothesized that trapping of activins by sotatercept will provide significant benefits to this patient population.

The PULSAR study in patients with WHO Group 1 PH has demonstrated statistically significant reductions in PVR following 6 months of treatment with sotatercept, compared with placebo, as well as substantial improvement from baseline in 6MWD in sotatercept-treated participants compared to the placebo group. In addition, a statistically significant greater reduction in plasma NT-proBNP levels, a marker of cardiac stress, was observed in the sotatercept treatment groups compared with placebo, and a greater proportion of participants in the sotatercept treatment groups improved in FC compared with placebo participants.

Recent nonclinical data suggest that sotatercept (murine analog, RAP-011) may positively affect vascular remodeling in animal models of PAH. Affected animals treated with RAP-011 showed substantial improvements in pulmonary vascular and cardiac hemodynamic measurements that are comparable or superior to approved agents for the treatment of PAH. Importantly, the animal models provide evidence of a disease-modifying effect, a substantial reduction in the proliferation of pulmonary vascular smooth muscle cells in RAP-011-treated animals, as assessed by histologic evaluation, in both preventative and therapeutic disease models.

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

3.3 Risks and/or Benefits to Participants

The study will be conducted on participants with Cpc-PH due to HFpEF. The study design, inclusion/exclusion criteria, and procedures have been developed to protect participant safety.

The evidence for potential benefits comes from rodent models of Cpc-PH, observational data in humans, and clinical studies of patients with PAH. Given this pathophysiological overlap between PAH and Cpc-PH, it is hypothesized that the efficacy of sotatercept observed in PAH might also be observed in WHO Group 2 subset of participants with Cpc-PH due to HFpEF.

Results from the PULSAR study demonstrated a clinically significant improvement in PVR at 24 weeks when compared with baseline (the study's primary endpoint) [Badesch, D. B., et al 2020]. Pulmonary vascular resistance 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).

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

In addition, a greater proportion of participants in the sotatercept treatment groups improved in WHO FC compared with placebo.

Results from A011-11 (STELLAR), the pivotal Phase 3 study of sotatercept in PAH, further support those from PULSAR. STELLAR was a randomized, double-blind, placebo-controlled study in participants with PAH (WHO Group 1 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 nonfatal 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).

Existing nonclinical and clinical data support a mechanism of action of sotatercept that warrants clinical investigation to determine the potential benefit in patients with Cpc-PH due to HFpEF. Current knowledge and the totality of evidence suggest a favorable benefit-risk balance for the study of sotatercept in this patient population. The proposed study is designed to evaluate clinically meaningful changes in endpoints that inform how these patients feel and function.

Overall, sotatercept has been studied in participants in multiple indications and has been shown to be well tolerated and consistent in its known and potential risks. 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. More details about contraception and collection of pregnancy information can be found in Appendix 2. More detailed information about the known and expected benefits and risks of sotatercept may be found in the current IB.

4 STUDY OBJECTIVES

Placebo-controlled Treatment Period

- To evaluate the effect of sotatercept versus placebo on the change from baseline in PVR at Week 24.

  Hypothesis: at least one sotatercept dose is superior to placebo in reducing PVR from baseline at Week 24.

- To evaluate the effect of sotatercept versus placebo on the change from baseline in 6MWD at Week 24

  Hypothesis: at least one sotatercept dose is superior to placebo in improving 6MWD from baseline at Week 24.

- To evaluate the safety and tolerability of sotatercept as assessed by review of the accumulated safety data through Week 24.

Extension Period

- To continue the assessment of the disease-modifying effect of sotatercept past Week 24.

- To continue the assessment of the long-term safety and tolerability of sotatercept past Week 24.

Refer to Section 11.4 for analysis of Efficacy and Safety Endpoints in both the Placebo-controlled Treatment Period and Extension Period.

5 STUDY ENDPOINTS

Refer to Section 11.4 for analysis of Efficacy and Safety Endpoints in both the Placebo-controlled Treatment Period and Extension Period.

5.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Change from baseline in PVR at Week 24

Key Secondary Efficacy Endpoint

- Change from baseline in 6MWD at Week 24

Other Secondary Endpoints

- Time to first clinical worsening event (TTCW) assessed at Week 24, defined as the number of weeks from first dose date to any of the following:
  - Hospitalization due to a cardiopulmonary indication (a nonelective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or HF)
  - Administration of intravenous diuretics or SC furosemide
  - Death (all causes)
  - Decrease in 6MWD by ≥ 15% from baseline
- Change from baseline in hemodynamic and echocardiography (ECHO) parameters, including but not limited to mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP), TAPSE, right ventricular fractional area change (RVFAC), LVEF, IVRT, ratio of mitral inflow velocity I to mitral annular velocity'(e') (E/e' ratio), ratio of the peak velocity flow of the E wave in early diastole to peak velocity flow of the A wave in late diastole (E/A ratio) and myocardial contraction fraction (MCF) at Week 24
- Change from baseline in NT-proBNP at Week 24
- Change from baseline in NYHA FC at Week 24

Exploratory Endpoints

- Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) scores at Week 24
- Change from baseline in disease-related biomarkers (ST2 and Activin A) at Week 24
- Change from baseline in dyspnea score (assessed by Borg CR10 scale®) at Week 24
- Identification of molecular biomarkers (e.g., transcriptomics, metabolomics, and/or proteomics) that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of sotatercept and other treatments
- Composite endpoint including the following:
  - All-cause mortality,
  - Frequency of HF hospitalizations by Week 24,
  - Change from baseline to Week 24 in 6MWD (meters), and
  - Change from baseline to Week 24 in NT-proBNP (ng/L).

5.2 Safety Endpoints

Placebo-controlled Treatment Period

- AEs
- Discontinuation of study treatment due to AEs

5.3 Pharmacokinetic Endpoint

Placebo-controlled Treatment Period

- Population PK parameters of sotatercept and exposure-response relationships in participants with Cpc-PH due to HFpEF.

6 STUDY DESIGN

6.1 Study Description

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of sotatercept versus placebo in adults with Cpc-PH due to HFpEF.

Adult participants (age 18 to 85 years) enrolled in the study will have a clinical diagnosis of HFpEF with demonstrated Cpc-PH and a NYHA FC of II or III.

6.2 Duration of Study

Each participant will be enrolled in the study for up to a maximum of 114 weeks (approximately 26 months), as follows:

- The Screening Period will be up to 28 days (4 weeks)
- The placebo-controlled Treatment Period will be 6 months (approximately 24 weeks)
- The Extension Period will be up to 18 months (approximately 78 weeks)
- The Follow-up Period will be up to 2 months (approximately 8 weeks)

As of CADENCE Amendment MK-7962-007-06, the 18-month Extension Period is being removed from CADENCE and being placed in the extension study MK-7962-023 (HARMONIZE). Additional information on the transition to HARMONIZE is described in Section 6.3.

6.3 Study Design, Stratification and Treatment Assignment

This is a Phase 2, randomized, double-blind, placebo-controlled study. Participants who have provided documented consent and meet all eligibility criteria will be stratified by the following:

- NYHA FC (Class II or Class III) on the day of randomization (Visit 1), which will serve as the baseline for the study

A total of approximately 150 eligible participants will be randomly assigned to 1 of the 3 treatment groups (in a 1:1:1 ratio) for the placebo-controlled Treatment Period:

- Treatment Group 1: Placebo SC Q3W for 24 weeks
- Treatment Group 2: Sotatercept SC at a dose level of 0.3 mg/kg Q3W for 24 weeks
- Treatment Group 3: Sotatercept SC at a starting dose level of 0.3 mg/kg for 3 dosing visits (Q3W), then escalating to 0.7 mg/kg SC on the fourth dosing visit and Q3W for the remainder of the 24-week Treatment Period

Chronic medication for HF or for any underlying condition will need to be administered at a stable dose for ≥ 30 days prior to Visit 1. SGLT2 inhibitors and sacubitril/valsartan may be administered but must be at a stable dose for ≥ 30 days prior to Visit 1. Diuretics and/or

anticoagulants are excepted from this rule but should not be newly started or stopped within 30 days of Visit 1, and a prescribed dose change should not occur within 7 days of Visit 1. Anticoagulation may be suspended for RHC if necessary. Therapies specific for PAH are not allowed within 30 days of Visit 1.

A planned interim analysis (IA) (described in Section 11) will occur when approximately 75 participants across the 3 treatment groups have completed 24 weeks on the study or discontinued study treatment before 24 weeks. Details are described in Section 11.4.4.

Participants who remain on study treatment at the completion of the placebo-controlled Treatment Period may continue in the 18-month Extension Period as follows:

- Placebo participants will be re-randomized in a 1:1 ratio to 1 of the 2 sotatercept treatment groups utilized in the placebo-controlled Treatment Period, i.e. to receive either of the following:
  - Placebo-crossed Treatment Group 1: Sotatercept SC at a dose level of 0.3 mg/kg Q3W for up to 18 months in the Extension Period
  - Placebo-crossed Treatment Group 2: Sotatercept SC at a starting dose of 0.3 mg/kg for 3 dosing visits (Q3W), then escalating to 0.7 mg/kg at the next dosing visit and Q3W for the remainder of the Extension Period
- Participants who were treated with sotatercept in the placebo-controlled Treatment Period will continue on their current dose SC Q3W in the Extension Period.

Participants who have completed at least the 24-week placebo-controlled Treatment Period (through V9) and the EOT Visit, and who have not discontinued study treatment early, may be eligible to participate in HARMONIZE.

There are 3 categories of participants from CADENCE with respect to the transition to HARMONIZE:

Category 1: Participants who completed the 24-week double-blind placebo-controlled Treatment Period in CADENCE (Visit 9 and EOT Visit) and transfer per treatment schedule to the first visit of the Primary Extension (Visit 9a) in HARMONIZE.

Category 2: Participants who completed at least 1 visit in the 18-month Extension Period in CADENCE (at least Visit 9a and EOT) and transfer at the next feasible scheduled study treatment visit of the Primary Extension (from Visit 10 to Visit 34) per treatment schedule in HARMONIZE. The visit number associated with the first dose in HARMONIZE will vary for each participant.

Category 3: Participants who completed the 2-year period of CADENCE (Visit 34, EOT Visit, and EOS visit) on study treatment and enroll in the Secondary Extension of HARMONIZE (Visit 35) at any time after completion of CADENCE.

Enrollment into HARMONIZE will commence after the futility analysis for CADENCE (see Section 11.4.4). The Sponsor will inform sites about the start of enrollment in HARMONIZE following the interim analysis of CADENCE. Participants are expected to enroll in HARMONIZE within approximately 3 months of receiving notification from the Sponsor that enrollment may begin.

6.4 Randomization and Blinding

Participants who have documented consent and met all eligibility criteria will be stratified by baseline (Section 6.3) NYHA FC (Class II or III) and then randomized 1:1:1 to Treatment Group 1, Treatment Group 2, or Treatment Group 3 for the placebo-controlled Treatment Period (See Section 6.3). Randomization assignments will be generated through a computerized system, provided by interactive response technology (IRT). After the completion of the 24-week placebo-controlled Treatment Period, placebo participants will be re-randomized 1:1 to placebo-crossed Treatment Group 1 or placebo-crossed Treatment Group 2 (See Section 6.3) and sotatercept-treated participants will continue on their current dose in the Extension Period.

Among study personnel, the pharmacist or his/her designee who prepares the study treatment (sotatercept or placebo) will be unblinded to the participant treatment assignments during the placebo-controlled Treatment Period. All other study personnel (including but not limited to the study team, the Sponsor's representatives, investigators, study coordinators, nursing staff, and clinical monitors) and all participants will remain blinded to the study treatment assignments throughout the trial. Limited Sponsor personnel may be unblinded to the treatment-level results after the placebo-controlled Treatment Period. Details regarding the unblinding plan are outlined in the statistical analysis plan (SAP).

In the event of a medical emergency for an individual participant in which knowledge of the study treatment is critical to the participant's medical management, the investigator may break the blind for that participant by contacting IRT (see the IRT User Manual for further instructions). The investigator is free to break the blind if it is required to manage the participant's medical emergency, based on their judgment. In nonurgent situations, the investigator should consult with the study Medical Monitor prior to breaking the blind. Where the investigator has broken the blind without prior discussion, they must inform the Medical Monitor at the earliest opportunity. 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 treatment. The investigator should not inform the participant of their treatment assignment under any circumstances.

7 STUDY POPULATION

7.1 Inclusion Criteria

Participants must meet the following criteria to be enrolled in this study:

1. Age 18 to 85 years
2. Clinical diagnosis of HFpEF:
   - Left ventricular ejection fraction ≥ 50%, with no history of LVEF below 45% in more than 2 consecutive measurements under stable conditions
3. Demonstrated Cpc-PH by all of the following:
   - Baseline RHC performed within 28 days of randomization documenting a minimum PVR ≥ 320 dyn•sec/cm^5 (4 wood units) (see Section 9.2.1 for historic RHC requirements)
   - Mean pulmonary arterial pressure > 20 mm Hg
   - Pulmonary capillary wedge pressure > 15 mm Hg but < 30 mm Hg
4. NYHA FC of II or III
5. Six-Minute Walk Distance ≥ 100 meters repeated twice during Screening and both values within 15% of each other, calculated from the highest value (see Section 9.3.2 for details)
6. Chronic medication for HF or for any underlying condition, administered at a stable (per investigator) dose for ≥ 30 days prior to Visit 1. Diuretics and/or anticoagulants are excepted from this rule but should not be newly started or stopped within 30 days of Visit 1, and a prescribed dose change should not occur within 7 days of Visit 1. Anticoagulation may be suspended for RHC if necessary.
7. Women of childbearing potential (defined in Appendix 2) must:
   - Have 2 negative urine or serum pregnancy tests as verified by the investigator during the Screening Period; must agree to ongoing pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug
   - If sexually active with a male partner:
     - Use highly effective contraception without interruption for at least 28 days prior to starting the investigational product AND
     - Agree to use the same highly effective contraception in combination with a barrier method during the study (including dose interruptions), and for 16 weeks (112 days) after discontinuation of study treatment
   - Refrain from breastfeeding a child or donating blood, eggs, or ovum for the duration of the study and for at least 16 weeks (112 days) after the last dose of study drug

See Appendix 2 for additional contraceptive information.

8. Male participants must:
   - Agree to use a condom, defined as a male latex condom or nonlatex condom NOT made out of natural (animal) membrane (e.g., polyurethane), during sexual contact with a pregnant female or a WOCBP 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 (see Appendix 2 for additional contraceptive information)
   - Refrain from donating blood or sperm for the duration of the study and for 16 weeks (112 days) after the last dose of study drug
9. Ability to adhere to the study visit schedule and understand and comply with all protocol requirements
10. Agreement to not participate in any other trials of investigational drugs/devices while enrolled in the A011-16 study
11. Ability to understand and provide documented informed consent for participation.

7.2 Exclusion Criteria

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

1. A diagnosis of PH in WHO Group 1, WHO Group 3, WHO Group 4, or WHO Group 5
2. Clinically significant and active lung disease:
   - Chronic obstructive pulmonary disease with postbronchodilator forced expiratory volume in the first second (FEV1) < 60% predicted
   - Restrictive lung disease with total lung capacity <70% predicted
   - More than mild interstitial lung disease (ILD), with FVC <70% or FEV1< 60% predicted (still appropriate if absence of more than mild ILD, fibrosis, or COPD on computed tomography [CT] imaging)
3. Cardiovascular comorbidities, which include any of the following:
   - History of more than mild mitral or aortic stenosis, corrected mitral or aortic stenosis by a surgical or transcatheter method within 12 months from Visit 1. (Participants with corrected valvular disease may only be allowed after the Medical Monitor's review).
   - Ongoing more than mild mitral or aortic regurgitation, corrected mitral or aortic regurgitation by a surgical or transcatheter method within 12 months from Visit 1. (Participants with corrected valvular disease may only be allowed after the Medical Monitor's review.) NOTE: If an imaging report reads, "mild-to-moderate mitral regurgitation" the participant may still be enrolled if, in the opinion of the investigator, the mitral regurgitation is no more than mild.

- More than one valve replacement or repair (mechanical or biomechanical) or anticipation of any valve replacement or repair
- Severe tricuspid regurgitation due to primary valvular disease (e.g., from endocarditis, carcinoid, or mechanical destruction)
- Occurrence of myocardial infarction, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention within 180 days of Visit 1
- History of serious life-threatening or hemodynamically significant arrhythmia
- History of or anticipated heart transplant or ventricular assist device implantation
- History of implantable cardioverter defibrillator placement or anticipated implantation of pacemaker, pacemaker implantation within 30 days of Screening
- History of known pericardial constriction, hypertrophic cardiomyopathy, sarcoidosis, or amyloid cardiomyopathy
- Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 110 mm Hg during Screening after a period of rest
- Systemic hypotension as evidenced by sitting systolic blood pressure < 90 mm Hg or sitting diastolic blood pressure < 50 mm Hg during Screening
- Resting heart rate of < 45 bpm or > 115 bpm (including atrial fibrillation)
- Stroke within 90 days of Visit 1
- Acutely decompensated HF that required hospitalization within 30 days of Visit 1
- Electrocardiogram during Screening Period with Fridericia's corrected QT interval (QTcF) > 470 msec for males or > 480 msec for females, or > 500 msec if a ventricular conduction defect (right bundle branch block; left bundle branch block; or interventricular conduction delay) is present
- Personal or family history of Brugada syndrome, sudden cardiac arrest or unexplained sudden cardiac death or arrest
- Personal or family history of long QT syndrome unless the subject's ECG shows a normal QTc
- Arrhythmogenic right ventricular dysplasia (ARVD) unless the subject has a recent cardiac MRI that shows no evidence of this diagnosis.

4. Hospitalization for any worsening of medical conditions or any significant surgery per investigator within 30 days of Visit 1
5. Received any approved PAH-specific therapies (i.e., endothelin receptor antagonists, prostacyclin analogs, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators) within 30 days of Visit 1. The use of an oral phosphodiesterase-5 inhibitor, if only indicated for erectile dysfunction, is permitted, if not administered within 48 hours of a study visit or procedure.

6. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin, or levosimendan) within 30 days of Visit 1
7. Received erythropoietin within 6 months of Visit 1
8. Known history of chronic liver disease, including untreated hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication), with severe hepatic impairment and/or cirrhosis (e.g., hepatic encephalopathy)
9. Prior exposure to sotatercept or luspatercept
10. 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 consent
11. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days of Visit 1 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)
12. Any of the following clinical laboratory values prior to Visit 1 as specified:
    - Hemoglobin above the gender-specific upper limit of normal (ULN) per local laboratory test within 28 days of Visit 1 or < 10 g/dL per local laboratory within 28 days of Visit 1
    - Serum alanine aminotransferase or aspartate aminotransferase levels > 3× ULN or total bilirubin > 3× ULN within 28 days of Visit 1
    - Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (4-variable Modification of Diet in Renal Disease equation) within 28 days of Visit 1 or required renal replacement therapy within 90 days of Visit 1
    - Glycated hemoglobin (HbA1c) > 10% within 28 days of Visit 1
    - Platelet count < 75,000/mm^3 within 28 days of Visit 1
13. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in the investigational product
14. Major surgery within 60 days of Visit 1. Participants must have completely recovered from any previous surgery prior to Visit 1
15. Prior organ transplantation (e.g., heart, lung, liver, kidney), bone marrow transplantation, or life expectancy of < 12 months
16. Pregnancy or breastfeeding in females
17. Active malignancy, with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in situ, or ≤ 2 squamous cell carcinomas of the skin
18. History of clinically significant (as determined by the investigator) endocrine, hematologic, hepatic, (auto)immune, infectious (requiring chronic antibiotics), metabolic, urologic, pulmonary, neurologic, neuromuscular, dermatologic, psychiatric, renal, and/or another disease that may limit participation in the study.

19. Body mass index $\geq$ 50 kg/m^2
20. More than mild obstructive sleep apnea (treated or untreated)
21. Any noncardiopulmonary condition or acute/chronic impairment(s) (other than dyspnea) that limits the ability to perform 6-minute walk test (6MWT)

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

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

8 STUDY TREATMENT

8.1 Study Treatment Description

Sotatercept is a homodimeric recombinant fusion protein consisting of the ECD of the ActRIIA linked to the human IgG1 Fc domain. Sotatercept is the generic name assigned to ActRIIA-IgG1Fc. The laboratory code is ACE-011. The Chemical Abstracts Service Registry number for sotatercept is 1001080-50-7; the United States 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 during the placebo-controlled Treatment Period, as described in Section 6.4.

Therapy for HF or any other underlying condition will not be provided as study medication during the study. To be enrolled in the study, participants must be on stable background therapy according to local practice.

8.1.2 Formulation

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

8.2 Study Drug Management

8.2.1 Storage

The clinical supply kits for sotatercept lyophilized drug product and matching placebo must be stored under refrigerated conditions (2 °C to 8 °C or 36 °F to 46 °F). 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 identification (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 1:1:1 ratio to 1 of the following 3 treatment groups for the placebo-controlled Treatment Period:

- Treatment Group 1: Placebo SC Q3W for 24 weeks
- Treatment Group 2: Sotatercept SC at a dose level of 0.3 mg/kg Q3W for 24 weeks
- Treatment Group 3: Sotatercept SC at a starting dose level of 0.3 mg/kg for 3 dosing visits (Q3W), then escalating to 0.7 mg/kg SC on the fourth dosing visit and Q3W for the remainder of the 24-week Treatment Period

Refer to the Pharmacy Manual for specific dosing information.

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.

Participants who remain on study treatment at the completion of the placebo-controlled Treatment Period may continue in the 18-month Extension Period as follows:

- Placebo participants will be re-randomized in a 1:1 ratio to 1 of the 2 sotatercept treatment groups utilized in the placebo-controlled Treatment Period, i.e., to receive either of the following:
  - Placebo-crossed Treatment Group 1: Sotatercept SC at a dose level of 0.3 mg/kg Q3W for approximately 18 months in the Extension Period
  - Placebo-crossed Treatment Group 2: Sotatercept SC at a starting dose of 0.3 mg/kg for 3 dosing visits (Q3W), then escalating to 0.7 mg/kg at the next dosing visit and Q3W for the remainder of the Extension Period
- Participants treated with sotatercept in the placebo-controlled Treatment Period will continue on their current dose SC Q3W in the Extension Period.

As of CADENCE Amendment MK-7962-007-06, the 18-month Extension Period is being removed from CADENCE and being placed in HARMONIZE. Participants who have completed at least the 24-week placebo-controlled Treatment Period (through V9) and the EOT Visit, and who have not discontinued study treatment early, may be eligible to participate in HARMONIZE.

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 (Treatment Group 1)	Placebo Comparator	Placebo	Placebo	Injection, Powder, Lyophilized, For Solution	0 mg	0 mg Q3W	SC	V1 to V8	Placebo	IMP	Central
Sotatercept (Treatment Group 2)	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 mg/kg Q3W	SC	V1 to EOT/EOS	Test Product	IMP	Central
Sotatercept (Treatment Group 3)	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 and 0.7 mg/kg Q3W	SC	0.3 mg/kg (V1 to V3) 0.7 mg/kg (V4 to EOT/EOS)	Test Product	IMP	Central
Placebo-crossed Treatment Group 1	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 mg/kg Q3W	SC	V9 to EOT/EOS	Test Product	IMP	Central
Placebo-crossed Treatment Group 2	Experimental	Sotatercept	Biological/Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 and 0.7 mg/kg Q3W	SC	0.3 mg/kg (V9 to V11) 0.7 mg/kg (V12 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; TBD = to-be-determined; V = Visit.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the 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 delays or reductions (from 0.7 to 0.3 mg/kg) due to a safety event are described in Section 8.3.1. Sotatercept dose re-escalation may occur according to Section 8.3.3.

8.3 Dose Modification

Dose delays and reductions can be implemented for safety reasons at any time per investigator's assessment and are not restricted to the dose modification guidance provided. The investigator will perform and document a risk-benefit assessment for action taken in regard to study treatment and notify the Medical Monitor.

If a dose delay is required, the participant will not be dosed. All other study procedures should be performed as scheduled (see Section 2). The participant will return Q3W for assessment of hematology results and AEs until the participant is eligible to receive the next dose of study treatment (e.g., if the participant delays dose at Visit 5 and the issue is resolved based on evaluation at Visit 6, then they would resume dosing at Visit 6).

Guidance for dose modifications and dose delays is summarized in [Table 5].

Local laboratory test results for the hematology panel must be evaluated prior to study treatment administration. Blood samples may be taken and assessed for Hgb and platelet count levels on the same day as study treatment administration or up to 3 days prior, if available.

8.3.1 Dose Delay, Reduction, or Discontinuation

Dose delay and/or reduction or discontinuation may be required in any treatment arm (sotatercept or placebo). Guidance for dose delays due to an increase in Hgb and a decrease in platelets is summarized Section 8.3 and [Table 5]. There are 4 doses available for the study (0.7, 0.3, 0.1, and 0.05 mg/kg). When dose reduction is necessary, 0.7 mg/kg reduces to 0.3 mg/kg, 0.3 mg/kg reduces to 0.1 mg/kg, and 0.1 mg/kg reduces to 0.05 mg/kg.

A maximum of 3 consecutive dose delays is allowed during the study, though there is no limit on the number of nonconsecutive dose delays. If a fourth consecutive dose delay is required, the investigator discontinues study treatment.

In this study, participants are permitted no more than 2 consecutive dose reductions, meaning 2 dose reductions without an increase in dosage in between. Additional dose reductions may be allowed after Medical Monitor notification.

Table 5 Dose Modifications Due to Safety Events

Event	Severity/Condition	Action
Telangiectasia	≥Moderate	• If the severity is ≥ moderate, delay dose for 1 visit. If no progression in the severity, the dosing may be resumed at the previous dose level.
Hgb increase	Hgb >4.0 g/dL above participant baseline value	• Investigator to perform and document a risk-benefit assessment for continuing study treatment. Notify the Medical Monitor.
	Hgb >2.0 g/dL above gender-specific ULN	• Dose delay for 1 visit.
	Hgb >2.0 g/dL above the participant's level from the last dosing visit **and** above gender-specific ULN	• Dose delay for 1 visit.
Reduced Platelets	Platelet <50,000/mm^3	• Dose delay for 1 visit.
	Platelet ≥50,000/mm^3 following each dose delay visit	• At the visit following each dose delay, if platelet count is more than 50,000/mm^3, reduce the dose and restart study treatment.
SAEs of Bleeding	Serious active bleeding	• Dose delay until event of serious bleeding resolves and notify the Medical Monitor if the serious bleeding persists beyond one dose delay to discuss study treatment discontinuation.

HGB=hemoglobin; SAE=serious adverse events; ULN=upper limit of normal.
NOTE: When dose reduction is necessary: 0.7 mg/kg reduces to 0.3 mg/kg; 0.3 mg/kg reduces to 0.1 mg/kg; 0.1 mg/kg reduces to 0.05 mg/kg.
NOTE: A maximum of 3 consecutive dose delays is permitted during the study. After the third consecutive dose delay, the investigator discontinues the study treatment.
NOTE: Baseline is defined as the Hgb value at Screening.

8.3.2 Escalation to Target Dose (0.7 mg/kg)

All participants taking sotatercept will begin treatment at a starting dose of 0.3 mg/kg for the first 3 dosing visits starting with Visit 1 (Q3W). For participants in Treatment Group 3, at the fourth dosing visit, 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 modification criteria as described in Section 8.3 are met.

In the Extension Period (protocol versions MK-7962-007-05 or earlier), participants in both placebo-crossed treatment groups will begin taking sotatercept at a starting dose of 0.3 mg/kg for 3 dosing visits starting with Visit 9a. For participants in placebo-crossed Treatment Group 2, at the fourth dosing visit, 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 Extension Period, unless dose modification criteria as described in Section 8.3 are met.

8.3.3 Dose Re-escalation Following Dose Reduction

In all treatment groups, dose re-escalation may be considered after dose reduction if the following criteria are met:

- In cases when the investigator implements a dose reduction due to a safety concern, the dose can be re-escalated when the concern is resolved.
- In cases of dose reduction due to increases in Hgb, the dose will be re-escalated to the previous dose level after 2 consecutive visits at which Hgb values are stable and equal to or lower than the gender-specific ULN.
- Similarly, in cases of dose reduction due to decrease in platelet count, the dose will be re-escalated to the previous dose level after 2 consecutive visits at which platelet counts are stable and more than 50,000/mm^3, with no association with AEs of bleeding.

8.3.4 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, kept in a secure location, and stored as described in Section 8.2.1. Refer to the Pharmacy Manual for additional details. 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 the Sponsor at the end of the study, or the study drug may be destroyed at the clinical site after Sponsor 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

The study procedures are detailed in the SoEs (Section 2).

9.2.1 Screening Period (Up to 4 Weeks Prior to Visit 1)

Potential participants must document an ICF before any study-specific Screening procedures are conducted. Informed consent must be provided before any Screening procedures are undertaken.

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

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

Any Screening clinical laboratory values considered abnormal may be repeated once during the Screening Period, but prior to the RHC (RHC should be performed last and after all other Screening procedures are done, when possible, as described in the SoE). Use of historic RHC for Screening is discouraged. Exception is for historic RHC done within 14 days from the start of the Screening Period, with the review and approval of the Medical Monitor.

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, and collection of demographics, race, ethnicity, and medical record requests for relevant external procedures.

9.2.2 Double-blind, Placebo-controlled Treatment Period

Study procedures for the double-blind placebo-controlled Treatment Period (Visit 1 through Visit 9) vary depending on the visit number. Study procedures/assessments should be performed prior to the administration of the study drug except where noted otherwise.

Visit 1 will be on Study Day 1 (Week 0). Study drug administration will occur at Visit 1 and Q3W ± 3 days through Visit 8 unless there is a dose delay (see Section 8.3 for dose modification guidelines). Visit 1a, Visit 2a, and Visit 4a will be at 6 to 10 days after Visit 1, Visit 2, and Visit 4, respectively.

Note that Week 24 involves 2 clinic visits (Visit 9 and Visit 9a), which are to be on the same Day (protocol versions MK-7962-007-05 or earlier). Visit 9 is part of the double-blind placebo-controlled Treatment Period and Visit 9a is part of the Extension Period (see Section 9.2.3). The Visit 9 assessments are considered the 24-week assessments.

As of the CADENCE Amendment MK-7962-007-06, the 18-month Extension Period is being removed from CADENCE and is being placed in HARMONIZE. Participants who complete the double-blind placebo-controlled Treatment Period at Week 24 (Visit 9) and the EOT Visit, and who have not discontinued early, in CADENCE have the option to transfer at the next feasible study treatment visit to HARMONIZE. Transfer into HARMONIZE may occur on the same day as the EOT Visit in CADENCE. Participants should enter HARMONIZE at the next scheduled study treatment visit for CADENCE after HARMONIZE approval. If entry at the next scheduled study treatment is not feasible, please consult the Sponsor.

9.2.3 Extension Period

Study procedures for the Extension Period (Visit 9a through Visit 34) vary depending on the visit number. Study procedures/assessments should be performed prior to the administration of the study treatment except where noted otherwise.

Visit 9a will be on the same Day as Visit 9 (Week 24). Study treatment administration will occur at Visit 9a and Q3W ± 3 days through Visit 34 unless there is a dose delay (see Section 8.3 for dose modification guidelines). Visits 9b, 10a, and 12a will be at 6 to 10 days after Visits 9a, 10, and 12, respectively.

As of the CADENCE Amendment MK-7962-007-06, the 18-month Extension Period is being removed from CADENCE and is being placed in HARMONIZE. Participants who complete CADENCE between Visit 9a and Visit 34, and who have not discontinued study treatment early, will attend the EOT Visit in CADENCE and have the option to transfer at the next feasible treatment visit to HARMONIZE. The visit number associated with first dose in HARMONIZE will vary for each participant. Participants should enter HARMONIZE at the next feasible scheduled study treatment visit for CADENCE after HARMONIZE approval. If entry at the next scheduled study treatment is not feasible, please consult the Sponsor.

9.2.4 End of Treatment Visit

The End of Treatment (EOT) Visit should occur 3 weeks (± 7 days) after the last study treatment administration or at early discontinuation. Discontinuation of study treatment administration can occur at any visit during the placebo-controlled Treatment Period or the Extension Period. Reasons for early discontinuation are described in Section 9.4.1.

For participants who enroll in HARMONIZE without treatment interruption, the initial dosing visit in HARMONIZE may occur on the same day as the EOT Visit in CADENCE (after all CADENCE assessments have been performed).

9.2.5 End of Study Visit

The End of Study (EOS) Visit will be completed by participants who do not enroll into MK-7962-023 within 5 weeks post EOT Visit (including participants who discontinue treatment early and who withdraw consent). The participants who discontinue treatment early should also complete their EOT Visit assessments as described in Section 9.4.1 prior to the EOS Visit as long as consent is not withdrawn.

9.3 Description of Study Procedures

9.3.1 Pulmonary Vascular Resistance

The participant's PVR will be measured during the RHC procedure. There will be a total of up to 3 RHCs to assess PVR. The first RHC must be performed within 28 days of randomization (see Section 9.2.1 for historic RHC requirements), and the second RHC should be performed within 14 days prior to or at Week 24 (Visit 9) (during the Treatment Period). The third RHC should be performed within 14 days of or at Week 48 (Visit 17) (during the Extension Period). If a participant discontinues the study early, before Week 24 (Visit 9), an RHC should be performed. If a participant discontinues the study early, after Week 24 (Visit 9) and prior to or at Week 48 (Visit 17), the final RHC should be offered prior to the EOS Visit. If performed on the same Day at any of these timepoints, the RHC should take place after other assessments have been completed and prior to dosing.

The site investigators will measure PVR/mPAP/PCWP during the Screening Period and the local values analyzed at the investigative sites will be used to determine eligibility. All RHC data will be transferred to a central vendor for interpretation according to the RHC manual.

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

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

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

The participant's PVR will be calculated and populated in the eCRF. Right ventricle pressure data from the RHC with simultaneously recorded ECG recordings may be collected and digitally stored.

9.3.2 Six-minute Walk Test

The 6MWD will be measured by the 6MWT during the Screening Period and at multiple timepoints throughout the study [American Thoracic Society 2002], as described in Section 2. During the Screening Period, the 6MWT is to be performed twice, at least 4 hours but no more than 1 week apart, and the distances must be within 15% of each other, based on the longer distance. If the difference between the first and second tests is >15%, the test may be repeated once more, provided the repeat test is within 1 week of the previous test. If the difference between the distances remains >15%, the participant will be considered a screen failure.

If occurring on the same Day, the 6MWT should be performed after quality of life (QoL) assessments and before RHC. Appendix 3 provides further instructions on 6MWT. For evaluation of clinical worsening as indicated by the 6MWT, a decrease of ≥15% in 6MWD at any timepoint as compared to Screening must be confirmed by a second 6MWT performed at least 4 hours, but no more than 6 weeks, apart from the first. The baseline value for 6MWD is the average of the 2 values collected during Screening. If the Screening 6MWT is performed within 10 days of Visit 1, an additional 6MWT is not required at Visit 1.

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. All attempts should be made to perform the 6MWT under the same conditions, at least between Screening and the 24-week assessment (Visit 9), including oxygen therapy, the use a of walking aid, and/or face covering. However, if the circumstances have changed, if it is clinically warranted, or due to changes in local restrictions, the reason for the change in the 6MWT conduct must be documented in the eCRF. All 6MWTs performed from Visit 1 onward can be performed at the study visit Day or within 10 days prior to study treatment administration.

9.3.3 Borg Dyspnea Scale (CR10)

The Borg CR10 scale® will be used to assess dyspnea pre- and post-6MWT. The Borg Dyspnea Scale is a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT. Scores range from 0 (for the best condition) to 10 (for the worst condition). Refer to the Appendix 3 for more details.

9.3.4 New York Heart Association Functional Class Assessment for Pulmonary Hypertension

The NYHA FC system is used to provide information about how affected an individual is by HF [Dolgin, M., et al 1994]. The 4 FCs used to rate symptom severity are detailed in [Table 6].

Table 6 New York Heart Association Functional Class Assessment

NYHA FC	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.

FC = functional class; HF = heart failure; NYHA = New York Heart Association.
Source: American Heart Association [Dolgin, M., et al 1994a].

9.3.5 Clinical Worsening Assessment

The occurrence of clinical worsening events after the first dose of study treatment must be assessed by the investigator at each study visit and recorded on the case report form (eCRF). A participant may experience multiple clinical worsening events based on the categories below.

Clinical worsening assessments should be conducted in accordance with the SoE and whenever there are indications of potential clinical deterioration in the participant's symptoms and condition. Clinical worsening must be assessed using the following criteria:

- Hospitalization due to a cardiopulmonary indication (a nonelective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or HF)
- Administration of intravenous diuretics or SC furosemide
- Death (all causes)
- Decrease in 6MWD by ≥15% from baseline confirmed by 2 tests at least 4 hours, but no more than 6 weeks, apart

NOTE: Document a single clinical worsening when consecutive doses of IV diuretics are administered within 24 hours during a hospitalization or when multiple doses are given at a single visit. If more than 24 hours pass between IV diuretic doses/SC furosemide administration, document an additional clinical worsening event.

NOTE: The baseline value for 6MWD is the average of the 2 values collected during Screening.

Investigators will also assess clinical worsening events, including the 6MWT, whenever a participant’s symptoms and condition suggest the possibility of a clinical worsening event between scheduled study visits.

9.3.6 Echocardiography Parameters

Two-dimensional ECHO parameters will include but not limited to TAPSE, RVFAC, LVEF, IVRT, E/e' ratio, E/A ratio and MCF.

During the Screening Period, either a new or historical ECHO will be used for Screening. LVEF and other ECHO parameters will be analyzed locally at the investigative sites to determine eligibility. If an ECHO is performed during the Screening Period, these values may be used as the baseline for this study, and an additional ECHO is not required for these participants at Visit 1. If a historical ECHO is evaluated during the Screening Period, the participant must receive an ECHO at Visit 1, which will serve as the baseline for the study for these participants (provided that it is consistent with the historical ECHO). All ECHOs after Visit 1 may be performed within 7 days prior to or at the study visit.

Review of the ECHO parameters will be performed by a central vendor according to the vendor manual.

9.3.7 Quality of Life Assessments

9.3.7.1 Patient Global Impression of Severity and Patient Global Impression of Change

The PGI-S is a single-item questionnaire used to rate the participant's impression of the severity of his/her condition.

The PGI-C is a self-reported measure that reflects a participant's perspective on his or her overall health status with respect to the study treatment. The assessment rates the participant's perceived overall improvement or deterioration while receiving study treatment.

Participants will complete the PGI-S assessment prior to study treatment administration during the study visits outlined in Section 2. The PGI-C assessment should not be conducted at Screening or Visit 1 as it is dependent on a participant's study treatment. The PGI-S and PGI-C should be completed before performing other study assessments (6MWT, blood draws, AE discussions, and RHC), if possible.

9.3.7.2 EuroQoL 5-Dimension 5-Level Assessment

The EQ-5D-5L is a widely used standardized measure of health status that provides a descriptive profile to appraise respondents' health status. The measure was designed for both clinical and economic appraisal and has been validated in numerous clinical populations. The EQ-5D-5L consists of 5 single-item dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These dimensions are measured on a 5-level scale: "No problems," "Slight problems," "Moderate problems," "Severe problems," and "Extreme problems."

The EQ-5D-5L also contains a visual analog scale (VAS) to assess the participant's overall health on a scale of 0 ("The worst health you can imagine") to 100 ("The best health you can imagine").

Participants will complete the EQ-5D-5L questionnaire prior to study treatment administration during the study visits outlined in Section 2. The EQ-5D-5L is to be completed before performing other study assessments (6MWT, blood draws, AE discussions, and RHC), if possible.

9.3.7.3 Kansas City Cardiomyopathy Questionnaire

The KCCQ is a 23-item, self-administered, health-related QoL survey validated for HF that quantifies physical limitations, symptoms, self-efficacy, social interference and QoL [Green, C. P., et al 2000]. Respondents' responses are arrayed on a Likert scale with clinically meaningful gradations between categories. It is scored by assigning each response an ordinal

value, beginning with 1 for the response that implies the lowest level of functioning, and summing items within each domain.

Participants will complete the KCCQ prior to study treatment administration during the study visits outlined in Section 2. The KCCQ is to be completed before performing other study assessments (6MWT, blood draws, AE discussions, and RHC) if possible.

9.3.8 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.

9.3.9 Vital Signs

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

- Temperature, pulse rate, respiratory rate, blood pressure, and weight will be assessed at study visits as outlined in the SoEs (Section 2). Weight will be measured in indoor clothing, but without shoes. Dose must be calculated based on the participant's weight on the day of dosing. If the participant has rapid weight change caused by fluid retention between visits (e.g., a weight gain of more than 1 kg within a 24-hour period), the Medical Monitor can be consulted for calculating the dose.
- Blood pressure and pulse measurements will be assessed (in triplicate) while seated after a period of rest in a quiet setting with no distractions (e.g., television, cell phones). The same method of collection (manual or automated) should be used throughout the study. Manual techniques will be used only if an automated device is not available.
- Pulse rate, if performed manually, must be measured in the brachial/radial artery for at least 30 seconds. The average of 3 pulse rate assessments will be used for the final result.
- Three consecutive blood pressure measurements will be recorded at intervals of approximately 2 minutes apart and averaged for the final result. The time, positioning, and arm used will be recorded for each measurement.
- Clinically significant abnormal findings will be reported as AEs (Section 10.1).

9.3.10 Planned Exploratory Biomarker Research

Details on collection and management of exploratory biomarker samples are in Appendix 4.

9.3.10.1 Proteomics, Immunoassay, and Flow Cytometry

Samples from this study may undergo additional proteomic analyses. Therefore, samples may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. Additionally, flow cytometry may be used to quantify multiparameter cellular phenotypes. These approaches could identify novel protein and other cellular biomarkers that could aid in patient selection for therapy.

9.3.10.2 Other Blood-derived Biomarkers

In addition to expressing on the tissue, tissue-derived proteins can be released into the blood. Assays such as enzyme-linked immunosorbent assays measure such proteins in serum. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood. This research would serve to develop such assays for future clinical use.

9.3.10.3 Blood RNA Analyses

Both genome-wide and targeted mRNA expression profiling may be performed to define gene signatures that correlate to clinical response to treatment with therapies. Specific gene sets (e.g., those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (e.g., interleukin-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

9.3.10.4 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (e.g., protein, RNA, metabolites) and other circulating molecules will be collected from all participants in this study as specified in Section 2.

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

9.3.11 Planned Biomarkers

Planned biomarkers for this trial may include the following. Disease-related biomarkers include N-terminal Prohormone B-type Natriuretic Peptide (NT-proBNP) and Suppressor of Tumorigencity 2 (ST2). Glycated hemoglobin (HbA1c) is measured to understand its correlation with cardiovascular events. Activin A is included as a target-engagement biomarker.

9.3.11.1 N-Terminal Prohormone B-type Natriuretic Peptide

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

Samples for NT-proBNP analysis will be collected as described in Section 2 and will be shipped and analyzed by a central laboratory. All central laboratory NT-proBNP results will be masked after randomization through study completion. If mandated for clinical management (e.g., occurrence of a CV event), investigators may evaluate NT-proBNP at a local laboratory during the study.

9.3.11.2 Activin A

Sotatercept acts to block activin ligands and improve pulmonary vascular remodeling by restoring balance to SMAD signaling. The assessment of the ligand-trapping activity of sotatercept is therefore important and can provide better understanding in its role in disease modification.

Serum activin levels correlate with sotatercept ligand-trapping activity. Samples for analysis of activin and other TGF-β ligands as needed will be collected as described in Section 2 and will be shipped and analyzed by a central laboratory.

9.3.11.3 Suppressor of Tumorigenicity 2

The HF biomarker suppressor of tumorigenicity 2 (ST2) is a member of the interleukin-1 receptor family. In patients with acute HF, an elevated level of serum ST2 is strongly associated with the presence and severity of the disease and is an independent predictor of long-term and short-term mortality [Shah, R. V. 2010].

Samples for ST2 analysis will be collected as described in Section 2 and will be shipped and analyzed by a central laboratory.

9.3.11.4 Glycated Hemoglobin

The levels of HbA1c represent the average blood glucose concentrations over the preceding 2 to 3 months, making this a well-established clinical biomarker for diabetes. The HbA1c level is also an independent risk factor for cardiovascular events in people without diabetes [Liu, Y., et al 2011].

Samples for HbA1c analysis will be collected as described in Section 2 and will be shipped and analyzed by a central laboratory.

9.3.12 Anti-Drug Antibody Assessments

Anti-drug antibody samples will be collected as described in Section 2 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.

9.3.13 Pharmacokinetics Measurements

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

Instructions for the collection and handling of biological samples will be provided by the Sponsor. Samples will be used to evaluate the PK of sotatercept. Samples collected for analyses of sotatercept serum concentration may also be used to evaluate safety or efficacy 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. Samples collected for analyses of sotatercept serum concentration may also be used to determine concentrations of concomitant medications.

9.3.14 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 the Sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the SoEs. Please refer to Section 2 for the timing and frequency of clinical laboratory tests.

9.3.14.1 Hematology

Hematology (complete blood count) laboratory assessments will be collected and analyzed locally at the investigative sites and will be evaluated at the Screening Visit (for eligibility purposes), every dosing visit, and EOT as outlined in Section 2. Complete blood cell count

includes red blood cells, absolute white blood cells, Hgb, hematocrit, and platelet count. Results must be evaluated prior to study treatment administration.

9.3.14.2 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 Section 2 and should be drawn prior to dosing. Blood urea, creatinine, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, glucose, magnesium, follicle-stimulating hormone, bicarbonate (HCO_3), and albumin will be measured. Investigators must review the results to monitor the participant's safety.

9.3.14.3 Urinalysis (Dipstick)

Urinalysis will be performed per Section 2 using dipsticks provided to sites by the central laboratory to evaluate pH, specific gravity, protein, glucose, bilirubin, ketones, blood, leukocytes, urobilinogen, and nitrite. If a positive/abnormal dipstick result occurs, the urine sample will be sent to the central laboratory for further analysis.

9.3.14.4 Pregnancy Testing

Pregnancy testing (urine or serum) will be performed per Section 2 for all women of childbearing potential (WOCBP) prior to each dose administration. See Appendix 2 for further information.

9.3.15 Twelve-Lead Electrocardiogram

A single 12-lead ECG will be obtained at study visits as outlined in Section 2 and will be transferred to a central vendor for reading and interpretations. QT interval and QTcF will be analyzed locally at the investigative sites to determine eligibility. Parameters obtained will include but will not be limited to heart rate as well as QRS and QT:QTcF interval.

- 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.

9.4 Discontinuation and Withdrawal Criteria

The reason for early discontinuation must be recorded in the corresponding participant's eCRF. The investigator must notify the Sponsor and Medical Monitor when a participant has discontinued treatment or has withdrawn from the study.

9.4.1 Early Discontinuation of Study Treatment

Early discontinuation of study treatment refers to permanently stopping and it does not represent withdrawal from the study.

Participants who discontinue study treatment prior to completion of the double-blind Treatment Period:

- Should be encouraged to have a RHC as soon as possible after the last dose of study treatment (this will replace the Week 24 PVR).
- Should be encouraged to continue to be followed for all remaining study visits as outlined in the SoE (Section 2) through the completion of Week 24.
- Participants who have a new or higher-titer positive ADA result at EOS will be asked to complete the additional ADA testing described in Section 9.3.12.
- After Week 24 or if the participant refuses to attend additional study visits, they will receive quarterly telephone contacts for vital status, AE/SAE review, and concomitant medication review until study completion, provided that consent is not withdrawn.

Participants who discontinue study treatment during the Extension Period:

- If the participant discontinues after Visit 9 (Week 24) and prior to or at Visit 17 (Week 48), the final RHC should be offered prior to the EOS Visit.
- Participant treatment should complete the assessments scheduled for the EOS Visit at the time of study treatment discontinuation.
- Participants who have a new or higher-titer positive ADA result at EOS will be asked to complete the additional ADA testing described in Section 9.3.12.

Following the EOS, or if the participant refuses to attend the EOT/EOS visits, participant will receive quarterly telephone contacts for vital status, AE/SAE review, and concomitant medication review until study completion, provided that consent is not withdrawn. Reasons that may lead to discontinuation of study treatment include the following:

- Adverse event: If a participant discontinues due to a treatment-related serious adverse event (SAE) or other medical reason(s), the participant should be followed at regular intervals until the AE normalizes or the participant returns to their baseline condition, as per Section 10.6.
- Participant’s unwillingness or inability to comply with the protocol.
- More than 3 consecutive dose delays required per dose adjustment guidelines (Section 8.3).
- Pregnancy.
- QTcF > 470 msec for males or > 480 msec for females (or >550 ms if ventricular conduction defect [right bundle branch block, left bundle branch block, or interventricular conduction delay] is present) during the Treatment Period.

- Women of childbearing potential not using adequate combination of effective contraception methods throughout the study.
- Men with a partner of childbearing potential not accepting to use contraceptive methods throughout the study.
- Study terminated by Sponsor.
- Lost to follow-up.
- The participant or participant's legally acceptable representative requests to discontinue study treatment.

The Sponsor may terminate the study after consultation with the external Data Monitoring Committee (eDMC) at any time for safety or administrative reasons. The Sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the participants.

9.4.2 Participant Withdrawal from the Study

A participant will be withdrawn from the study if he/she withdraws consent. If the participant withdraws consent, no further evaluations are to be performed and no additional data are to be collected. The timepoint when withdrawal of consent occurs will be recorded as the EOS Visit. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

For participants who have withdrawn consent from further study follow-up, collection of clinical event and vital status data will be completed by review of medical or public records in accordance with participant informed consent and local regulations.

9.4.3 End of Study Definition

CADENCE will be complete once both criteria have been met:

1. All participants have completed Week 24 or discontinued from the study
2. Approximately 3 months after all sites have received approval for both MK-7962-007-06 and HARMONIZE.

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. If a participant is continuing into HARMONIZE, only the EOT Visit is required. The end of the CADENCE is defined as when the last participant completes the last visit.

9.5 Participants Lost to Follow-up

A participant will be considered lost to follow-up if he/she stops attending scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant stops attending study visits:

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

9.6 Concomitant Medication and Therapy During Study Conduct

During Screening and throughout the study, participants may continue taking stable doses of medications for HF and other chronic conditions (e.g., beta blockers, statins, ACE inhibitors). Prior to randomization and throughout the study, PAH background therapies (i.e., endothelin receptor antagonists, prostacyclin analogs, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators) are discouraged. However, administration of oral phosphodiesterase-5 inhibitors only, for erectile dysfunction, is allowed if given more than 48 hours before a study visit or procedure. If there is a clinical need to prescribe a new medication or a new dosage of an existing medication during the study, concurrent therapy may be administered at the discretion of the investigator. The investigator may consult the Medical Monitor regarding the addition of new HF therapies and/or therapies for treating PH, including the use off-label PAH therapies. Live vaccines and coronavirus disease 2019 (COVID-19) vaccines are allowed during the study. Information regarding concomitant medications will be collected in the eCRF beginning after documenting the ICF and will include all medications taken during Screening Period to the EOS.

9.7 Treatment Compliance

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

9.8 Criteria for Study Termination

Both the Sponsor and the Principal Investigator reserve the right to terminate the study at any time. Should this be necessary, the Sponsor 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, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

9.8.1 Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor'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 Definition of Adverse Event

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

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

10.1.1.1 Unexpected Adverse Events

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

10.1.1.2 Events Not Considered as Adverse Events

Preexisting medical conditions/signs/symptoms present 30 days prior to the initial study treatment 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, 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.

Disabling/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 treatment 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 treatment dependency or treatment 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 treatment and the occurrence of an AE/SAE as "not suspected" or "suspected" as defined below. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of study treatment including PK

properties of sotatercept, known side effects of study treatment, medical history, concomitant therapy, course of the underlying disease, and pertinent study procedures. Median time to reach 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 treatment administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- **Suspected:** Means there is a reasonable possibility that the administration of study treatment caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study treatment and the AE.

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 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 the Sponsor or designee.

For overdose and cancer (serious and nonserious) 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 paper SAE Report Form. If the participant was hospitalized, a summary from the investigator should be included as part of the participant medical file. In all instances, the investigator should follow-up with participants until the outcome of the SAE is known.

10.6 Reporting Serious Adverse Events

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

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

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, 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 the Sponsor 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 the Sponsor and (as applicable) to allow the Sponsor to meet regulatory timelines associated with expedited reporting obligations.

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

For overdose and cancer (serious and nonserious) 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 paper SAE Report Form. If the participant was hospitalized, a summary from the investigator should be included as part of the participant medical file. In all instances, the investigator should follow-up with participants until the outcome of the SAE is known.

10.6.1 Reporting Period and Monitoring of Participants with Adverse Events

All AEs must be recorded in the eCRF from the documenting of the informed consent up until the EOS Visit. All participants who took at least 1 dose of study treatment, whether they completed the Treatment Period or not, should complete the EOS Visit unless they are transitioning into a future long-term follow-up study.

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

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

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

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

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

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

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

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 the Sponsor 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. The pregnancy information will be recorded on the appropriate form and must be submitted to the Sponsor within 24 hours of learning of the pregnancy. The participant or partner will be followed for the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported as an AE. Abnormal pregnancy outcomes (e.g., spontaneous abortion [includes miscarriage and missed abortion], fetal death, stillbirth, congenital anomalies, ectopic pregnancy, neonatal death) are considered SAEs. Any neonatal death that occurs within 1 month of birth should be reported, without regard to causality, as an SAE. Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 16 weeks (112 days) after the last dose.

If a pregnancy is reported, the investigator must inform the Sponsor within 24 hours of learning of the pregnancy. If pregnancy is reported, the participant will be discontinued from the study treatment (see Appendix 2 for details regarding pregnancy).

10.9 Monitoring of Adverse Events of Special Interest

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

Laboratory data and vital signs are monitored on an ongoing basis by the investigator and Medical Monitor in the study. Laboratory data and AEs are measured as per study schedule or upon an unscheduled visit if applicable. Details regarding dose modifications due to decreases in platelets, increases in Hgb and events of moderate or severe telangiectasia are provided in Section 8.3.

Additional reviews will be performed periodically as part of standard safety signal detection and medical monitoring. Finally, an independent eDMC will be convened to monitor the safety of the study participants.

10.9.1 Adverse Events of Special Interest

Telangiectasia (spider veins, spider naevi) and intrapulmonary right-to-left shunting or pulmonary capillary dilatation are considered AESIs in this study.

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

11 STATISTICAL ANALYSES

11.1 Overview

This Phase 2, double-blind, randomized, placebo-controlled study will evaluate the efficacy and safety of sotatercept versus placebo in adults with Cpc-PH due to HFpEF.

Planned statistical analyses to be conducted are outlined in the sections that follow. Additional detail will be described in the 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

Power and sample size are based on the mean change from baseline in PVR at Week 24. Assuming that the true mean decrease from baseline in PVR at Week 24 is approximately 92 dyn•sec/cm^5 for each sotatercept dose versus 0 for placebo and assuming a common standard deviation (SD) of 154, a sample size of 45 per group provides 80% power to demonstrate superiority for each of the sotatercept treatment comparisons using a one-sided alpha=0.025. Through 24 weeks post randomization, drop-out is expected to be approximately 10% in each treatment group. To account for the assumed drop-out rate, this study will randomize 150 participants in a 1:1:1 ratio into sotatercept 0.3 mg/kg arm, sotatercept 0.7 mg/kg arm, and placebo arm, respectively. Power was computed based on the two-sample t-test assuming equal variance using PASS 16 and verified based on the Aligned Rank Stratified Wilcoxon (ARSW) test via 1000 simulations performed in SAS 9.4.

Given a sample size of 45 per group as determined above, power for the key secondary efficacy endpoint of change from baseline in 6MWD at Week 24 is based on the effect size. Assuming that the true mean increase from baseline in 6MWD at Week 24 is 33 meters for each sotatercept dose versus 0 for placebo and assuming a common SD of 60, a sample size of 45 per group provides 73% power to demonstrate superiority for each of the sotatercept treatment comparisons using a one-sided alpha=0.025. Power was computed based on the two-sample t-test assuming equal variance using PASS 16.

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

- **PK Population:** PK population will include all participants who have received at least 1 dose of sotatercept and have sufficient PK samples collected and assayed for PK analysis.

11.4 Statistical Analyses

The SAP will be developed and finalized before database lock for Week 24 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.

11.4.1 Analysis of Efficacy

Statistical analyses of efficacy data will be performed on the FAS. Efficacy data for the Extension Period will be summarized in the CADENCE clinical study report (CSR) separately from the DBPC.

11.4.1.1 Primary Endpoint

Following the ICH E9(R1) guidance, the estimand for the primary efficacy endpoint contains the following attributes:

- Target Population: Males or females between 18 and 85 years of age with Cpc-PH due to HFpEF.
- Treatment Condition: Sotatercept 0.7 mg/kg, sotatercept 0.3 mg/kg, pooled sotatercept or placebo.
- Variable/Endpoint: Change from baseline in PVR at 24 weeks, with death prior to Week 24 represented quantitatively by any fixed worst-rank change from baseline to reflect the worst clinical outcome.
- 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 difference between treatment groups is referred to in statistical terms as the location-shift parameter.
- Intercurrent events: There are 2 intercurrent events:
  - Death: A *composite strategy* will be implemented, in which the occurrence of death is incorporated into the definition of the endpoint.
  - Changes in the use of sotatercept, placebo (dose reduction, dose delay, or discontinuation): A *treatment policy* strategy will be implemented, such that the actual outcome is of interest regardless of any changes in the use of these treatments.

The change from baseline in PVR at Week 24 will be analyzed using the ARSW test [Hodges, J. L., Jr. and Lehmann, E. L. 1962] [Mehrotra, D. V., et al 2010] with the randomization stratification factors as strata. Prior to performing the ARSW test, the change from baseline in PVR at Week 24 will be aligned across the randomization strata using the

stratum-level Hodges-Lehmann location-shift estimates, and the aligned values will then be analyzed using a Wilcoxon rank sum test. The output from this analysis will be used to provide a 1-sided unadjusted *p*-value and corresponding Hodges-Lehmann location-shift estimate of the overall treatment difference (sotatercept minus placebo) with 95% CI.

The following steps will be taken to perform the primary analysis, including imputation for missing data. Mean change from baseline in PVR at Week 24 is the response variable:

- Death will be assigned as the worst-rank score among all observed data
- Missing data due to a nonfatal clinical worsening event, the next worst-rank score among all observed data will be used to impute the missing data [Lachin, J. M. 1999]
- Missing data due to reasons other than death or a nonfatal clinical worsening event (other than death), a standard Multiple Imputation (MI) method will be used to impute missing data:

The Missing at Random (MAR) assumption is made to perform standard MI. It has been shown that MAR-based imputation under non-MAR conditions is unlikely to impact the overall treatment-level mean ranks[Mogg, R. and Mehrotra, D. V. 2007]. For missing points, Fully Conditional Specification (FCS) regression [van Buuren, S., et al 2006] [van Buuren, S. 2007] is used to fill in the missing points in the order of timepoints using measurements calculated at the previous timepoints. The analysis involves the following steps:

1. The missing data are filled in *m* times to generate *m* complete datasets using an FCS regression model accounting for the baseline measurement and treatment group separately for each stratum, where *m*=100.
2. The *m* complete datasets are analyzed by using the analysis.
3. The results from the *m* complete datasets are combined for the inference.

The random number seed used for all imputations will be 7962007.

Descriptive statistics will be provided for baseline, Week 24, and the change from baseline at Week 24 for PVR. A boxplot of the change from baseline in PVR at Week 24 will be provided for each treatment group. This will be based on the observed data.

A line plot (mean ± standard error of the mean [SEM]) of the change from baseline in PVR by visit will be provided for each treatment group. This will be based on the observed data.

Additional analyses for PVR will be specified in the SAP.

11.4.1.2 Secondary Endpoints

[Table 7] presents an overview of the analysis strategy for the secondary efficacy endpoints. Details of the analyses can be found below.

Table 7 Analysis Strategy for the Secondary Efficacy Endpoints

Endpoint	Type	Statistical Method	Missing Data Approach
Secondary Endpoints			
Change from baseline in 6MWD at Week 24	P	ARSW	MI[a]
Time to first clinical worsening event assessed at Week 24	P	Cox regression	If no clinical worsening event or death, subject will be censored at Visit 9, or at the last visit while on study if earlier
Change from baseline in selected hemodynamic and echocardiography parameters at Week 24	P	ARSW	MI[a]
Change from baseline in NT-proBNP at Week 24	P	ARSW	MI[a]
Change from baseline in NYHA FC at Week 24	P	Stratified CMH	Due to public health concerns (e.g., COVID-19): take subject out of denominator and not consider Not due to public health concerns (e.g., COVID-19): Impute as non-responder

ARSW = Aligned Rank Stratified Wilcoxon; CMH = Cochran-Mantel-Haenszel; MI = multiple imputation; P = primary.
[a]Participants who died prior to the analysis timepoint will be represented with the worst-rank. Missing due to a nonfatal clinical worsening event will receive the next worst-rank.

Change from Baseline in 6MWD

The change in 6MWD will be estimated at each timepoint at which 6MWD is collected. Treatment effects of change from baseline at Week 24 are of interest.

The estimand and treatment difference of the change from baseline in 6MWD at Week 24 will be estimated using the ARSW test with the randomization stratification factors as strata, as described for the primary endpoint.

Time to First Clinical Worsening or Death

The estimand for this endpoint contains the following attributes:

- Target population: As defined for the primary endpoint
- Treatment condition: As defined for the primary endpoint
- Variable/Endpoint: TTCW or death
- Population-level summary: The hazard ratio (sotatercept vs. placebo)

- Intercurrent events: Changes in the use of sotatercept, placebo (dose reduction, dose delay, or discontinuation). A *treatment policy* strategy will be implemented, such that the actual outcome is of interest regardless of any changes in the use of these treatments.

- Time to first clinical worsening event or death through Week 24 will be analyzed using a Cox proportional hazards model stratified by the randomization stratification factor to estimate the hazard ratio of sotatercept versus placebo and the corresponding 95% CI. The covariates will include treatment group. The *p*-value based on the log-rank test of the treatment difference of sotatercept versus placebo with the randomization stratification factor as strata will also be provided but will not be used to perform inference. In addition, Kaplan-Meier curves will be generated for each arm.

If a participant has no clinical worsening event, the participant will be censored at Visit 9, or at the last visit while on the study if earlier.

Change from Baseline in NT-proBNP and in Selected Hemodynamic and Echocardiography Parameters

The estimand and the analysis approach for these endpoints are analogous to that for the primary endpoint.

Change from Baseline in NYHA FC

- Target population: As defined for the primary endpoint.
- Treatment condition: Sotatercept 0.7 mg/kg, sotatercept 0.3 mg/kg, or placebo.
- Variable/Endpoint: Indicator variable (Yes/No) for maintaining and/or improving in the NYHA FC.
- Population-level summary: Odds ratio (sotatercept/placebo) comparing the proportion of participants with change in NYHA FC.
- There are 2 intercurrent events:
  - Death: A *composite strategy* will be implemented, in which the occurrence of death is incorporated into the definition of the endpoint.
  - Changes in the use of sotatercept, placebo (dose reduction, dose delay, or discontinuation): A *treatment policy* strategy will be implemented, such that the actual outcome is of interest regardless of any changes in the use of these treatments.
  - If a response is missing due to public health concerns (e.g., COVID-19), then the individual subject will be taken out of the denominator and not be considered, otherwise the subject with missing data not due to public health concerns (e.g., COVID-19) will be considered a non-responder.

11.4.1.3 Exploratory Endpoints

Details will be provided in the SAP.

11.4.2 Analysis of Safety

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. All safety analyses will be performed on the Safety population.

All AEs reported from the point of documented consent to the EOS Visit will be collected. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs that started after the first administration of study drug up to 8 weeks after the last dose will be considered as TEAEs. All TEAEs will be 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.

The point estimates and 95% CIs for the differences between treatment groups in the percentages of participants will be provided for selected AE summaries that occur in at least 4 participants in any treatment group. This threshold was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when fewer participants per group have events and thus would add little to the interpretation of potentially meaningful differences. Confidence intervals for differences between treatment groups will be provided using the Miettinen and Nurminen method [Miettinen, O. S. 1985].

Clinical laboratory results will be summarized descriptively by treatment group. Clinically significant laboratory abnormalities will be listed and summarized by treatment arm. Chemistry and hematology laboratory tests will be collected regularly and reviewed periodically. Descriptive statistics (mean, SD, standard error of the mean, median, minimum, and maximum) will be provided for each timepoint of the collection by treatment arm for each timepoint analyzed.

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

For the safety analyses, in addition to comparisons between each dose versus placebo, the pooled sotatercept will be compared to placebo.

Missing safety parameters, unless otherwise specified, will be handled using the data as observed approach, that is, any participant with a missing value at a given timepoint will be excluded from the analysis for that timepoint. Change from baseline summaries require a baseline value. For analysis purposes, baseline is defined as the last measurement before the first dose of study treatment, except for 6MWD, which is the mean of the 2 Screening values (see [Table 5] for the definition of baseline Hgb as related to dose modification). In the rare event when baseline data are missing, the value obtained at the most recent Screening Visit will be used as baseline, when available. If no baseline result is available, that participant will not be included in the summary.

Safety data for the Extension Period will be summarized in the CADENCE CSR separately from the DBPC.

Immunogenicity (incidence/titer of ADAs) will also be analyzed with descriptive statistics.

11.4.3 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. Empirical 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/PD Data Analysis Plan.

11.4.4 Interim Analysis

The eDMC will serve as the primary reviewer of the results of the IA and will make recommendations for discontinuation of the study or modification to the executive oversight committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee and potentially other limited Sponsor personnel may be unblinded to the treatment-level results in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of IAs will be documented by the study team. Additional details will be provided in the eDMC Charter.

Treatment-level results of the IA will be provided by the external unblinded statistician to the eDMC. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol or statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

One IA will be conducted when approximately 75 participants across the 3 treatment groups have completed 24 weeks of treatment in the placebo-controlled Treatment Period or discontinued study treatment before 24 weeks. For the IA, all available efficacy and safety data for all randomized participants at the time of the Week 24 IA will be reviewed. The IA will be performed by an unblinded independent statistics provider. Results of the IA will be reviewed by the eDMC.

The purpose of the IA is to allow an early stop for futility. The recommended futility criterion is that if the Hodges-Lehmann location-shift for the treatment difference (sotatercept minus placebo) in PVR at Week 24 is greater than 0 dyn•sec/cm^5 for both

sotatercept dose levels, consideration may be given to stop the study. The estimate will be based on the Aligned Rank Stratified Wilcoxon (ARSW) test. [Table 8] shows the operating characteristics of the futility criterion for various sizes of the true treatment difference.

Table 8 Operating Characteristics of the Futility Criterion for Various True Treatment Differences

True Treatment Difference[a] (dyn•sec/cm^5)	Probability of Meeting the Futility Criterion[b] (%)
-92	0.1
-80	0.4
-60	1.9
-40	6.5
-20	16.6
0	33.0

[a] Hodges-Lehmann location-shift
[b] Futility criterion = the estimated Hodges-Lehmann location-shift for the treatment difference is greater than 0 for both dose groups using the ARSW test (assessed via 1000 simulations per scenario).

The eDMC will be responsible for periodic interim safety reviews as specified in the eDMC charter. An interim safety analysis will be performed 3 months after the 15th participant is randomized, or 6 months after the first participant is dosed, whichever occurs first. Afterwards, the eDMC will review safety data periodically in the study. Interim safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the eDMC charter.

11.4.5 Multiplicity

A gatekeeping method will be used to control the family-wise Type I error rate in the primary and key secondary efficacy endpoints by testing starting with the primary efficacy endpoint and then proceeding to the key secondary efficacy endpoint as listed in Section 5.1. For each endpoint, there are 2 treatment group comparisons that may be tested to address the corresponding hypothesis. Testing will be done using a 1-sided alpha=0.025 level in a sequential manner, in descending order of endpoint priority (primary, then key secondary), in descending order of sotatercept dose group (0.7 mg/kg vs. placebo, then 0.3 mg/kg vs. placebo) within each endpoint, stopping at the point statistical significance is not achieved.

The multiplicity strategy controls the family-wise Type I error rate at 2.5% (1-sided) to address the primary and key secondary hypotheses.

11.4.6 Subgroup Analysis

Analyses of the primary endpoint will be conducted on the following subgroups provided the sample size in the subgroup category is at least 10:

- Sex
- NYHA FC at baseline (II, III)
- Diabetes at baseline (Y, N)
- Atrial fibrillation at baseline (Y, N)
- Atrial fibrillation type (paroxysmal, persistent, permanent)

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

12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1 Study Monitoring

The Sponsor 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

The Sponsor 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 the Sponsor.

13 ETHICS AND RESPONSIBILITIES

13.1 Good Clinical Practice

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

13.2 Regulatory and Ethical Considerations

The following regulatory and ethical considerations will be applied:

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

13.3 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to ensure that the appropriate IRB/IEC has reviewed and approved this protocol prior to initiating the study. The investigator must provide the Sponsor or the Sponsor's representative with current and revised IRB/IEC membership rosters that include the members' occupations and qualifications. Sites within the USA may provide a copy of the USA 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 the Sponsor with the dated IRB/IEC approval of the amended documents as soon as available.

13.4 Informed Consent

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

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

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

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

The following data quality assurance considerations will be applied:

- All participant data relating to the study will be recorded on an eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically documenting the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification as indicated to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including 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 the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

15 STUDY REPORT AND PUBLICATIONS

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of the Sponsor is discussed in the investigator's Clinical Research Agreement.

All information concerning sotatercept is considered confidential and shall remain the sole property of the Sponsor. The investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without the written approval of the Sponsor. The investigator agrees not to disclose the Sponsor's confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and nonuse.

It is understood by the investigator that the information developed from this clinical study will be used by the Sponsor in connection with the development of sotatercept and therefore may be disclosed as required to regulatory agencies. To allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except as specified in a separate, written agreement between the Sponsor and the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practices, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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 documented consent is gained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, the Sponsor, 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

The following data protection considerations will be applied:

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor. will contain the identifier only; participant names or any information 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 the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

16.2 Site Monitoring/Scientific Integrity

- Investigative trial sites are monitored to assess compliance with the trial protocol and GCP. The clinical data are reviewed for accuracy, completeness, and consistency. Per Sponsor policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or clinical trial-related significant quality issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.
- For investigators located in countries with serious breach reporting requirements, the investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol, which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

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18 APPENDICES

Appendix 1. Abbreviations and Specialist Terms

6MWD	6-minute Walk Distance
6MWT	6-minute Walk Test
ActRIIA	Human Activin Receptor Type IIA
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ARSW	Aligned Rank Stratified Wilcoxon
BMP	Bone Morphogenetic Protein
BMPR2	Bone Morphogenetic Protein Type II Receptor
BNP	B-type Natriuretic Peptide
CDL	Chen-DeMets-Lan
CHW	Cui-Hung-Wang
CI	Confidence Interval
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
Cpc-PH	Combined Postcapillary and Precapillary Pulmonary Hypertension
CSR	Clinical Study Report
E/A ratio	Ratio of the Peak Velocity Flow of the E Wave in Early Diastole to Peak Velocity Flow of the A Wave in Late Diastole
ECD	Extracellular Domain
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECHO	Echocardiogram
eDMC	External Data Monitoring Committee
E/e' ratio	Ratio of Mitral Inflow Velocity (E) To Mitral Annular Velocity (E')
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
EU CT	European Union Clinical Trial registration

FA	Final Analysis
FAS	Full Analysis Set
Fc	Fragment Crystallizable
FC	Functional Class
FCS	Fully Conditional Specification
FDA	United States Food and Drug Administration
FEV1	Forced expiratory volume in the first second (FEV1)
FSTL3	Follistatin Like 3 Protein
GCP	Good Clinical Practice
GDF	Growth and Differentiation Factor
HbA1c	Glycated Hemoglobin
Hct	Hematocrit
HF	Heart Failure
HFpEF	Heart Failure With Preserved Ejection Fraction
HFrEF	Heart Failure With Reduced Ejection Fraction
Hgb	Hemoglobin
HRT	Hormone Replacement Therapy
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
Ig	Immunoglobulin
ILD	Interstitial Lung Disease
Ipc-PH	Isolated Postcapillary Pulmonary Hypertension
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRT	Isovolumetric Relaxation Time
KCCQ	Kansas City Cardiomyopathy Questionnaire
LS	Least Squares
LVEF	Left Ventricular Ejection Fraction

MAR	Missing at Random
MCF	Myocardial Contraction Fraction
MedDRA	Medical Dictionary For Regulatory Activities
mPAP	Mean Pulmonary Arterial Pressure
NT-proBNP	N-Terminal Prohormone B-Type Natriuretic Peptide
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PH	Pulmonary Hypertension
PK	Pharmacokinetic(s)
PKPD	Pharmacokinetic(s)/Pharmacodynamic(s)
PLT	Platelets
PVR	Pulmonary Vascular Resistance
Q3W	Every 3 Weeks
QoL	Quality Of Life
QTcF	Fridericia's Corrected QT Interval
RBC	Red Blood Cell
RHC	Right Heart Catheterization
RVFAC	Right Ventricular Fractional Area Change
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard Deviation
SEM	Standard Error of the Mean
SGLT2	Sodium-Glucose Cotransporter-2
SMAD	Mothers Against Decapentaplegic Homolog
SpO_2	Oxygen Saturation
SoE	Schedule of Events

ST2	Suppressor of Tumorigenicity 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEAE	Treatment-Emergent Adverse Event
TGF	Transforming Growth Factor
t_{max}	Time to Reach Maximum Sotatercept Concentration
TTWC	Time to Clinical Worsening
ULN	Upper Limit of Normal
USA	United States of America
VAS	Visual Analog Scale
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

Appendix 2. Contraceptive Guidance and Collection of Pregnancy Information

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone 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 follicle-stimulating hormone measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal 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 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 9]. 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 study treatment, while participating in the study and agree to use the same highly effective contraception in combination with a barrier method and for at least 16 weeks (112 days) after the last dose of study treatment.

Examples of the barrier method are:

- Male or female condom with or without spermicide
- Cervical cap, diaphragm, or sponge with spermicide

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 9 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
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • 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.

IUD = intrauterine device; WOCBP = woman of childbearing potential.

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

Pregnancy Testing

- A WOCBP should only be included in the study after 2 confirmed negative pregnancy tests (2 urine, 2 serum, or 1 urine and 1 serum) during Screening Period.
- Additional pregnancy testing (1 urine or 1 serum) should be performed prior to study treatment administration at each dosing visit during the study and as required locally.
- Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary documented consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (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 poststudy pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 10.8. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

Appendix 3. Six-minute Walk Test

The 6-minute walk test (6MWT) [American Thoracic Society 2002] 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

- Countdown timer (or stopwatch)
- Mechanical lap counter
- Two small cones to mark the turnaround points
- A chair that can be easily moved along the walking course
- Worksheets on a clipboard
- A source of oxygen
- Sphygmomanometer
- Telephone
- Automated electronic defibrillator
- Portable pulse oximeter

Participant Preparation

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

Measurements

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The participant should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Record in the source documents.

4. Measure and record baseline heart rate and oxygen saturation (SpO_2) and follow the manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.
5. Have the participant stand and rate their baseline dyspnea using the Borg Dyspnea Scale.
   a. Show the scale to the participant and ask the participant this: "Please grade your level of shortness of breath using this scale." Record the pre-walk Borg dyspnea level.
   b. At the end of the exercise, remind the participant of the breathing number that they chose before the exercise and ask the participant to grade their breathing level again.

Instruct the Participant as Follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. "

"You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking 1 lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready."

1. Position the participant at the starting line. You should also stand near the starting line during the test. Do not walk with the participant. As soon as the participant starts to walk, start the timer.
2. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the participant. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.
3. After the first minute, tell the participant the following (in even tones): "You are doing well. You have 5 minutes to go."
4. When the timer shows 4 minutes remaining, tell the participant the following: "Keep up the good work. You have 4 minutes to go."
5. When the timer shows 3 minutes remaining, tell the participant the following: "You are doing well. You are halfway done."

6. When the timer shows 2 minutes remaining, tell the participant the following: "Keep up the good work. You have only 2 minutes left."
7. When the timer shows only 1 minute remaining, tell the participant: "You are doing well. You have only 1 minute to go."
8. Do not use other words of encouragement (or body language to speed up).
9. 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.
10. 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.
11. 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."
12. 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 postwalk Borg dyspnea level.
2. Measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
3. Record the number of laps from the counter.
4. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides.
5. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
6. Congratulate the participant on good effort and offer a drink of water.

Appendix 4. Collection and Management of Exploratory Biomarker Samples

1. Definitions
   a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]
   b. RNA: Ribonucleic acid.[2]
2. Scope of Exploratory Biomarker Research[3, 4]

   The specimens consented and/or collected in this study as outlined in Section 9.3.11 will be used in various experiments to understand:

   - The biology of how drugs work
   - Biomarkers responsible for how a drug enters and is removed by the body
   - Other pathways with which drugs may interact
   - The biology of disease

   The specimen(s) may be used for assay development and/or drug/vaccine development.

   It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to treatments, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.
3. Summary of Procedures for Exploratory Biomarker Research[3, 4]
   a. Informed Consent

      Informed consent will be obtained during Screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Documented consent forms will be kept at the clinical study site under secure storage for regulatory reasons.

      A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.
   b. Exploratory Biomarker Research Specimen(s)

      Collection of biomarker specimens will be performed as outlined in the SoE.
4. Confidential Participant Information for Exploratory Biomarker Research[3, 4]
   a. In order to optimize the research that can be conducted with biomarker research specimens, it is critical to link participants' clinical information with test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

b. To maintain privacy of information collected from biomarker research specimens, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

c. At the clinical study site, unique codes will be placed on the biomarker research specimens. This code is a random number, which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

   Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the biomarker research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in the protocol and consent. Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Retention of Specimens[3, 4]

   Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

   Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

7. Data Security[3, 4]

   Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

8. Reporting of Exploratory Biomarker Research Data to Participants[3, 4]

   No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

   If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be

identified by name in any published reports about this study or in any other scientific publication or presentation.

9. Risks Versus Benefits of Exploratory Biomarker Research Research[3, 4]

   The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

10. Questions

    Any questions related to biomarker research should be emailed directly to clinical.specimen.management@MSD.com.

11. References (Appendix 4 only)

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council for Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

Appendix 5. Protocol Nomenclature Mapping

Acceleron Protocol Description (A011-16) CADENCE	Date	Merck Number (MK-7962-007)
Original Protocol (v1.0)	26 April 2021	MK-7962-007-01
Original Protocol (v1.0) France	12 January 2022	MK-7962-007-02
Global Amendment 01 (v2.0)	22 September 2022	MK-7962-007-03
Global Amendment 02 (v3.0)	04 December 2023	MK-7962-007-04
Global Amendment 03 (v4.0)	23 April 2024	MK-7962-007-05
Global Amendment 04 (v5.0)	07 November 2024	MK-7962-007-06
Amendment 05 (v6.0) EEA	18 March 2025	MK-7962-007-07
Global Amendment 06 (v7.0)	01 May 2025	MK-7962-007-08
Global Amendment 07 (v8.0)	19 September 2025	MK-7962-007-09