Official Protocol Title:	A Phase 3 Non-randomized, Non-controlled, Open Label Clinical Study to Evaluate the Efficacy and Safety of MK-7962 (Sotatercept) add-on to Background Therapy in Japanese Participants with Pulmonary Arterial Hypertension (PAH)
NCT Number:	NCT05818137
Document Date:	24-Apr-2024

TITLE PAGE

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Protocol Title: A Phase 3 Non-randomized, Non-controlled, Open Label Clinical Study to Evaluate the Efficacy and Safety of MK-7962 (Sotatercept) add-on to Background Therapy in Japanese Participants with Pulmonary Arterial Hypertension (PAH)

Protocol Number: 020-01

Compound Number: MK-7962

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

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IND	Not Applicable

Approval Date: 24 April 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	24-APR-2024	This amendment was created primarily to add dose modification instructions in the event of serious bleeding events and to update the risk/benefit section.
Original Protocol	01-FEB-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

This amendment was created primarily to add dose modification instructions in the event of serious bleeding events and to update the risk/benefit section.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 6.6.5, Dose Delays Due to SAEs of Bleeding	New treatment modification guidance for the participants who experienced serious bleeding events included.	This change was made to reflect the potential risk of serious bleeding as added to the sotatercept core risk profile.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other changes and their reasons are included for completeness.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.
Section 2.1, Study Rationale	New information added.	New data have become available.
Section 2.2.2, Preclinical and Clinical Studies	New information added.	Refer to Section 2.1 rationale.
Section 2.3, Benefit/Risk Assessment	New information added.	Refer to Section 2.1 rationale.

Section Number and Name	Description of Change	Brief Rationale
Section 9.2, Responsibility for Analyses/In-house Blinding	Reference to an additional analysis after all participants have completed Week 54 or discontinued prior to Week 54 was added.	To obtain an additional data cut for evaluation of selected efficacy and safety data.
Section 9.4.1, Efficacy Endpoints	The endpoints of WHO FC have been updated from “improvement or maintenance” to “improvement”.	To correct description errors and align with study objectives.
Section 9.6.1, Statistical Methods for Efficacy Analyses	The endpoints of WHO FC have been updated from “improvement or maintenance” to “improvement”.	Refer to Section 9.4.1 rationale.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Non-randomized, Non-controlled, Open Label Clinical Study to Evaluate the Efficacy and Safety of MK-7962 (Sotatercept) add-on to Background Therapy in Japanese Participants with Pulmonary Arterial Hypertension (PAH)

Short Title: A Phase 3 Study of Sotatercept in Japanese PAH Participants

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for this study.

The study has the following objectives in patients aged ≥ 18 years with WHO Group 1 PH (PAH) who are on stable background therapy.

Note: The primary population of this study consists of participants with WHO functional class (FC) II and III. Participants with WHO FC I or IV are considered as other populations and will be evaluated separately.

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of sotatercept in reducing PVR at Week 24	PVR
To evaluate the safety and tolerability of sotatercept	-AEs -Discontinuation of study intervention due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of sotatercept in improving 6MWD at Week 24	6MWD
To evaluate the efficacy of sotatercept based on the functional improvements at Week 24	WHO FC
To evaluate the efficacy of sotatercept based on the prognostic biomarker at Week 24	NT-proBNP

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Pulmonary arterial hypertension
Population	Adult Japanese Participants with WHO Group1 PAH and currently on stable background therapy
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 35 PAH participants with WHO FC II or III will be allocated and evaluated as primary population. PAH participants with WHO FC I or IV are able to be enrolled in this study and evaluated separately as other populations.

Enrollment of participants using infusion prostacyclin will not exceed approximately 50% of primary population.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Sotatercept	MK-7962 (sotatercept)	60 mg/vial	0.3 mg/kg, Q3W	SC	V2	Test Product
Sotatercept	MK-7962 (sotatercept)	60 mg/vial	0.7 mg/kg, Q3W	SC	V3 to EOT	Test Product

EOT=End of Treatment; Q3W=every 3 weeks; SC=subcutaneous; V=visit

All participants receive sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg every 3 weeks.

Dose delay, reductions (from 0.7 to 0.3 mg/kg) due to safety events and dose re-escalation are described in Section 6.6

Other current or former name(s) or alias(es) for study intervention(s) are as follows: ActRIIA-IgG1Fc, ACE-011.

Total Number of Intervention Groups/Arms	1
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final contact as follows. After a screening phase of up to 4 weeks, each participant will receive study intervention for 24 weeks as Primary Treatment Period and is able to continue until approval of sotatercept in Japan. If participants discontinue early, they will be followed for approximately 8 weeks after End of Treatment visit.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

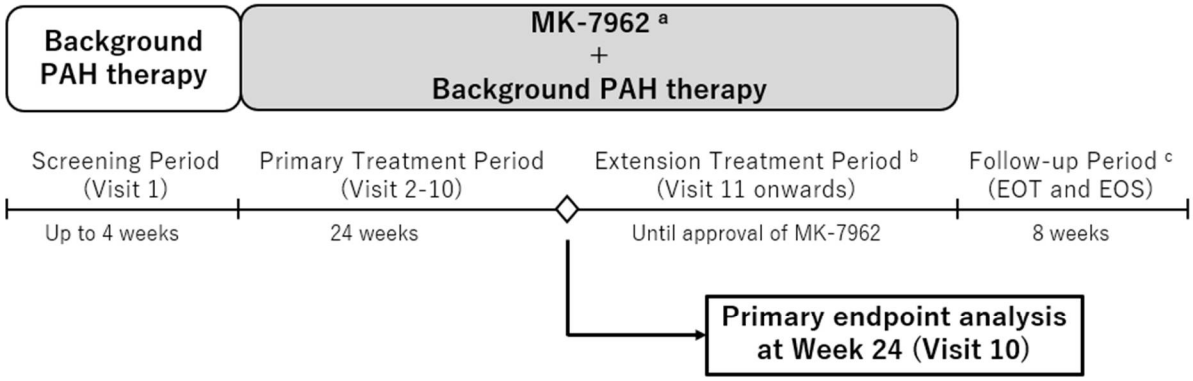
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



[a] MK-7962 at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered subcutaneously every 3 weeks (see Section 6.6 for details).

[b] Participants who are eligible for, trained for and willing to self-administration may be allowed to return to the site every 4 visits (12 weeks) after Visit 12 at the earliest. (see Section 8.1.8.1 for details).

[c] Participants who discontinue early should complete both End of Treatment (EOT) and End of Study (EOS) visits.

1.3 Schedule of Activities

Study Period	Screening	Primary Treatment Period						Extension Treatment Period [a]				Follow-up		Notes
Visit Number	1	2	3	4, 5	6	7-9	10 (1°EP Evaluation)	11	12	13-15	16-70	End of Treatment (EOT)	End of Study (EOS)	During the Treatment Period, visit intervals (21 days ± 3 days) are relative to the date of the previous dose of study intervention.
Scheduled Week		0 (Day 1)	3	6, 9	12	15, 18, 21	24	27	30	33, 36, 39	every 3 weeks	3 weeks from the last dose	8 weeks from EOT	
Visit Window	≤28 days		±3 days									±7 days		
Administrative Procedures														
Informed Consent	X													
CCI														
Inclusion/ Exclusion Criteria	X	X									Repeat V12 to V15.			
Participant Identification Card	X													
Medical History (includes disease history of PAH)	X													
Prior/ Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		X	X	
Allocation		X												
Study intervention Administration/ Dispensing		X	X	X	X	X	X	X	X	X				All study procedures must be done prior to study intervention administration. Dose must be calculated based on the participant's weight on the day of dosing. Dose modification guidelines are in Section 6.6. Eligible participants start self-administration from Visit 12 or later. Refer to the details in Section 8.1.8.1.

Study Period	Screening	Primary Treatment Period						Extension Treatment Period [a]				Follow-up		Notes
Visit Number	1	2	3	4, 5	6	7-9	10 (1°EP Evaluation)	11	12	13-15	16-70	End of Treatment (EOT)	End of Study (EOS)	During the Treatment Period, visit intervals (21 days ± 3 days) are relative to the date of the previous dose of study intervention.
Scheduled Week		0 (Day 1)	3	6, 9	12	15, 18, 21	24	27	30	33, 36, 39	every 3 weeks	3 weeks from the last dose	8 weeks from EOT	
Visit Window	≤28 days		±3 days									±7 days		
Self-administration Training (Optional)							X	X	X	X	Repeat V12 to V15.			Training for self-administration can be start from Visit 10 or later if participants eligible and wish to self-administration. Participants will be trained at least 3 consequent visits. Refer to the details in Section 8.1.8.1
Study Intervention Accountability Confirmation for Self-administration										X				
Efficacy Procedures														
Right heart catheterization	X						X				Repeat V12 to V15.	(X)		RHC at EOT visit should be done for participants who discontinued prior to Visit 10, but in other case, it is optional.
6MWT/Borg Dyspnea Scale (pre and post 6MWT)	X		X		X		X		X			X	X	
WHO FC assessment	X		X		X		X		X			X	X	

Study Period	Screening	Primary Treatment Period						Extension Treatment Period [a]				Follow-up		Notes
Visit Number	1	2	3	4, 5	6	7-9	10 (1°EP Evaluation)	11	12	13-15	16-70	End of Treatment (EOT)	End of Study (EOS)	During the Treatment Period, visit intervals (21 days ± 3 days) are relative to the date of the previous dose of study intervention.
Scheduled Week		0 (Day 1)	3	6, 9	12	15, 18, 21	24	27	30	33, 36, 39	every 3 weeks	3 weeks from the last dose	8 weeks from EOT	
Visit Window	≤28 days		±3 days									±7 days		
Clinical worsening assessment			X		X		X		X		Repeat V12 to	X	X	Clinical worsening events occurs between the prespecified assessment visits should also be reported.
CCI [redacted]														
Safety Procedures														
Physical examination including height and weight	X	X	X	X	X	X	X	X	X	X	Repeat V12 to V15.	X	X	Perform full physical examination at Screening, Visit 10, and at the EOT/EOS visits. For all other visits, perform targeted cardiopulmonary and skin examinations. Height is measured only at Visit 1
Vital Signs	X	X	X	X	X	X	X	X	X	X		X	X	Includes pulse, blood pressure, temperature, and respiratory rate.
12-lead ECG	X		X		X		X		X			X		
Pulmonary function test	X													PFT will be done if the most recent test was performed more than 6 months prior to the screening visit.
Echocardiogram	X				X		X		X			X	X	

Study Period	Screening	Primary Treatment Period						Extension Treatment Period [a]				Follow-up		Notes
Visit Number	1	2	3	4, 5	6	7-9	10 (1°EP Evaluation)	11	12	13-15	16-70	End of Treatment (EOT)	End of Study (EOS)	During the Treatment Period, visit intervals (21 days ± 3 days) are relative to the date of the previous dose of study intervention.
Scheduled Week		0 (Day 1)	3	6, 9	12	15, 18, 21	24	27	30	33, 36, 39	every 3 weeks	3 weeks from the last dose	8 weeks from EOT	
Visit Window	≤28 days		±3 days									±7 days		
Urine Pregnancy Test (POCBP only)	X	X	X	X	X	X	X	X	X	X	Repeat V12 to V15.	X	X	Confirm with serum test if urine test is positive. A negative pregnancy test is required for POCBP prior to every study drug administration including self-administration at home.
FSH - (as needed in PONCBP only)	X													
Hematology	X		X	X	X	X	X	X	X	X		X	X	
Urinalysis	X						X		X			X	X	
Chemistry	X				X		X		X			X	X	
AE/SAE review		X	X	X	X	X	X	X	X	X		X	X	Include injection-site reactions.
Pharmacokinetics/Pharmacodynamics/Biomarkers														
CCI [redacted]														

follicle-stimulating hormone; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; PFT=pulmonary function test; PK=pharmacokinetic; POCBP=participant of childbearing potential; PONCBP= participant of nonchildbearing potential; RHC=right heart catheterization; SAE=serious adverse event; WHO=World Health Organization; V=Visit; 6MWT=six-minute walk test;

[a] For participants who are eligible and trained for self-administration may be allowed to return to the study site every 4 visits (12 weeks) after Visit 12 at the earliest.

2 INTRODUCTION

Pulmonary hypertension (PH) is a chronic disease with a variety of etiologies, which if not treated, leads to right heart failure and death due to sustained elevation of pulmonary arterial pressure [Rubin, L. J. 1997]. According to the latest clinical classification, PH is divided into 5 types, and pulmonary arterial hypertension (PAH) is classified into WHO group 1 [Simonneau, G., et al 2013]. In Japan, PAH is designated as a specific disease (intractable disease) defined by Ministry of Health, Labour and Welfare (MHLW), and it is reported that the number of patients who received the certificate for the recipient of the specific medical expenses (designated intractable/rare diseases) for PAH in 2020 was 4320 [Japan Intractable Diseases Information Center 2020]. Currently, treatment of PAH is mainly drug therapy with PAH-specific drugs while providing supportive care with diuretics and oxygen. Although drugs have been approved for the treatment of PAH and widely used in Japan, all of them are vasodilators targeting the pathways that directly or indirectly increase blood flow in the pulmonary vascular system. Existing drugs for the treatment of PAH fall into three main classes: prostacyclin analogues or receptor agonists, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors. The combination of these drugs has improved the survival rate of patients with PAH. However, a recent study also reported that the transplant-free survival rate at 5 years was 74.0% even though most PAH patients received the best treatment with combination of 2 or 3 PAH drugs including prostacyclin injection [Kozu, K., et al 2020]. In other words, there is a certain number of patients who do not sufficiently respond to vasodilators alone. The underlying cause of PAH is the unregulated growth of pulmonary vascular smooth muscle cells (VSMCs) in the pulmonary artery, leading to progressive pulmonary vascular remodeling and increased pulmonary vascular resistance (PVR). New drugs targeting the root causes of PAH could potentially be disease-modifying agents as well as improving symptoms. The development of therapeutic drugs for disease-modifying PAH is extremely important and it was mentioned at the 6th World Symposium on Pulmonary Hypertension [Sitbon, O., et al 2019].

Sotatercept (ActRIIA-IgG1Fc, ACE-011 or MK-7962) is a novel first-in-class fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1, and is being developed for treatment of PAH.

2.1 Study Rationale

This is an open-label uncontrolled study to evaluate the efficacy and safety of sotatercept in Japanese patients with PAH.

As described above, there is an unmet need for additional PAH therapies because, despite available therapeutic options, the disease continues to progress in most patients. Through a novel mechanism of action, sotatercept targets an imbalance in activin/growth and differentiation factors (GDF) and bone morphogenetic protein (BMP) pathway signaling, opening a new treatment paradigm for PAH (see 2.2.1 and IB for details).

Currently, in participants with PAH, two global phase 2 studies (PULSAR [PN001] and SPECTRA [PN002] trials) and one phase 3 study (STELLAR [PN003]) have been

completed, and three global phase 3 studies (HYPERION [PN005], ZENITH [PN006] and SOTERIA [PN004] trials) are ongoing overseas.

In Japan, this local Phase 3 study is planned to confirm the efficacy and safety in Japanese PAH participants. The primary population of this study is Japanese PAH participants with WHO FC II or III while the study includes PAH participants with WHO FC I or IV as other populations.

2.2 Background

Refer to the IB for detailed background information on MK-7962 (sotatercept).

2.2.1 Pharmaceutical and Therapeutic Background

Members of the TGF-β superfamily have been implicated in the abnormal proliferation of pulmonary vascular endothelial cells and pulmonary VSMCs that underlie the pathogenesis of PAH. It is reported that genetic mutations in the BMP type II receptor (BMPR2) are associated with the majority of the familial form of PAH and approximately 25% of idiopathic PAH [Morrell, N. W. 2006] [Thomson, J. R., et al 2000]. Specifically, impairment of the BMPR2-associated signal pathway appears to lead to uncontrolled proliferation of pulmonary VSMCs, the principal cause of PAH.

Sotatercept traps Activin A, Activin B, and GDF-11, which are its family members, and ligands for ActRIIA, and by blocking pro-proliferative signaling, restores the balance between anti-proliferative signaling mediated by BMPs and BMPR2. As a result, it prevents abnormal remodeling of the pulmonary vascular system and improves pulmonary hemodynamics. PAH drugs available in the markets are drugs that improve symptoms by their vasodilating actions, however, since sotatercept acts on the underlying pathogenesis of PAH with a novel mechanism of action, it is expected not only to improve symptoms but also to be a disease-modifying drug.

2.2.2 Preclinical and Clinical Studies

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

Results from the PULSAR trial demonstrated a statistically significant improvement in PVR at 24 weeks when compared to baseline (the study's primary endpoint). PVR was reduced in both sotatercept dose groups versus placebo (least squares mean difference [standard error])

(sotatercept 0.3 mg/kg: −145.8 [48.6] dyn·s/cm^5, p = 0.0027; sotatercept 0.7 mg/kg: −239.5 [45.8] dyn·s/cm^5, p < 0.0001). Six-Minute Walk Distance (6MWD) was the key secondary endpoint at 24 weeks. The least squares mean increase from baseline in 6MWD was 58.1 m for sotatercept 0.3 mg/kg, 50.1 m for sotatercept 0.7 mg/kg, and 28.7 m for placebo. Combined, sotatercept produced a least squares mean difference versus placebo of 24.9 m (95% confidence interval [CI]: 3.1, 46.6 m). Sotatercept also improved N-terminal proB-type natriuretic peptide (NT-proBNP) levels. In addition, a greater proportion of participants in the sotatercept treatment groups improved in WHO functional class (FC) compared with placebo.

The most commonly reported AEs in clinical studies with sotatercept include headache, nausea, vomiting, hypertension and diarrhoea, and tended to occur at similar rates in sotatercept versus placebo arms in the PULSAR trial. Haemoglobin increased, however, was reported in 10.8% of participants receiving sotatercept versus 0 on placebo. Increases in hemoglobin are related to the mechanism of action of sotatercept. Thrombocytopenia was reported in 9.5% of participants receiving sotatercept vs 0 in placebo. There was no apparent association with bleeding. The emerging safety profile of sotatercept in the PAH population is reasonably well tolerated and manageable with routine clinical monitoring and dose modifications.

In the STELLAR trial, a Phase 3 study subsequently conducted after PULSAR, sotatercept also demonstrated the efficacy and was well-tolerated. In this trial, sotatercept significantly improved exercise capacity, increasing 6MWD by 40.8 meters (95% CI, 27.5-54.1; p<0.001) from baseline at week 24 comparing the placebo group, the study's primary endpoint. In addition, sotatercept demonstrated statistically significant and clinically meaningful improvements in eight of nine secondary outcome measures, including improvements in WHO functional class (WHO FC) and pulmonary vascular resistance (PVR). Sotatercept reduced the risk of clinical worsening or death by 84% compared to placebo with a median follow-up of 32.7 weeks (HR=0.16 [95% CI, 0.08-0.35]; p<0.001). The safety profile of sotatercept was generally consistent with that observed in previous studies with sotatercept.

Overall, the preclinical and clinical pharmacology findings suggest that sotatercept may have a therapeutic effect in the treatment of PAH. Further details may be found in the IB.

2.2.3 Ongoing Clinical Studies

P019 is a Phase 1, double-blind, randomized, placebo-controlled study in healthy Japanese participants to evaluate the safety, tolerability, and PK of single SC doses of sotatercept 0.3 mg/kg and 0.7 mg/kg. This phase 3 study (P020) will proceed if there is no safety concern, and there is no obvious difference in safety and pharmacokinetics between Japan and ex-Japan studies.

For PAH, there are three ex-Japan trials ongoing:

SOTERIA trial is a Phase 3 open-label long-term follow-up study to evaluate the effects of sotatercept when added to background PAH therapy for the treatment of PAH participants rolling over from parent PAH sotatercept clinical studies.

HYPERION trial is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate sotatercept when added to background PAH therapy in newly diagnosed intermediate-and high-risk PAH participants.

ZENITH trial is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate sotatercept when added to maximum tolerated background therapy in participants with PAH WHO FC III or FC IV at high risk of mortality.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

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

Treatment with sotatercept in addition to background PAH therapies was well tolerated, with thrombocytopenia and increased hemoglobin levels being the most common drug-related side effects. The treatment-induced increases in hemoglobin levels and decreases in platelet count observed in the PULSAR trial are consistent with effects of sotatercept in previous clinical studies. Each of these risks were monitored during the PULSAR and STELLAR trials, and dosing adjustments were made as necessary to mitigate these 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. Another important potential risk in this study is recurrent medication error by health care practitioner (HCP)-trained lay user causing overdose and leading to erythrocytosis. Potential risks of reproductive effects and renal injury were also monitored, and no clinically meaningful changes were observed. Anti-drug antibodies (ADA) were detected but without associated adverse effects. As other potential risk, cutaneous telangiectasia emerged and these events have been carefully monitored in phase 3 program.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no hypotheses for this study.

The study has the following objectives in patients aged ≥ 18 years with WHO Group 1 PH (PAH) who are on stable background therapy.

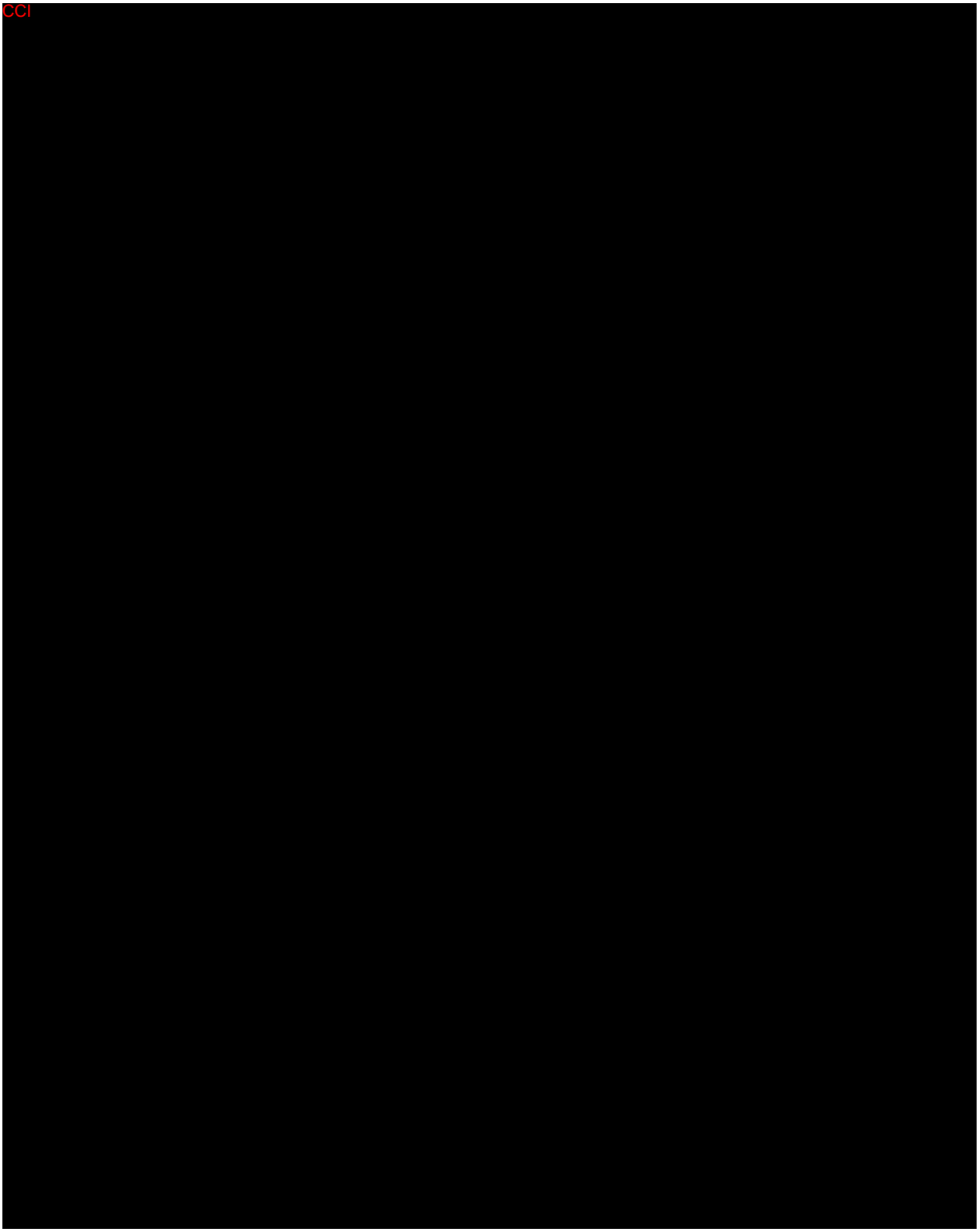
Note: The primary population of this study consists of participants with WHO functional class (FC) II and III. Participants with WHO FC I or IV are considered as other populations and will be evaluated separately.

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of sotatercept in reducing PVR at Week 24	PVR
To evaluate the safety and tolerability of sotatercept	-AEs -Discontinuation of study intervention due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of sotatercept in improving 6MWD at Week 24	6MWD
To evaluate the efficacy of sotatercept based on the functional improvements at Week 24	WHO FC
To evaluate the efficacy of sotatercept based on the prognostic biomarker at Week 24	NT-proBNP

CCI

[redacted]

CCI



4 STUDY DESIGN

4.1 Overall Design

This is a non-randomized, non-controlled, multisite, open-label study of Sotatercept in Japanese participants with PAH.

The study is divided into a Screening Period (up to 4 weeks), Primary Treatment Period (24 weeks), Extension Treatment Period (until approval or participants discontinue the study treatments), and a Follow-Up Period (at least 8 weeks). Each study eligible participant will be assigned allocation number and initiate the study intervention. Sotatercept is administered subcutaneously (SC) starting at a dose of 0.3 mg/kg with a target dose of 0.7 mg/kg every 3 weeks (21days) along with background PAH therapy that participants have been taking prior to study entry. Please refer to the details of background therapy in Section 6.5.1.

Escalation to target dose and dose modification (delay, reduction, or discontinuation) is performed according to the guidance prespecified in this protocol (Section 6.6). Dose modifications may occur at any time per the investigator's assessment and are not limited to the dose modification guidance. Blood samples must be taken and assessed for Hgb and platelet count on the same day of study intervention administration or up to 3 days prior to that day if available.

Participants who complete the Primary Treatment Period and are considered eligible for optional self-administration of study intervention at home will receive appropriate training (including successful self-administration on-site under the supervision of investigators). Actual self-administration can be determined and started at Visit 12 (±3 days) or later. The details of requirement and procedure for self-administration is provided Section 8.1.8.1.1.

Participants who complete the Primary Treatment Period but do not wish to participate in the extension period or who discontinue the study treatment before this study is completed will complete the Follow-up Period consisting of the End of Treatment (EOT) and the End of Study (EOS) visits.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Hemodynamic improvements, especially PVR, are one of the efficacy parameters commonly used for development of PAH drugs as well as confirming the treatment effects in clinical practice. Decreases in PVR in response to treatment have been associated with long-term transplant-free survival [Tiede, H., et al 2013]. The primary endpoint of change from baseline in PVR at 24 weeks is designed to assess reduction in resistance to flow across the

pulmonary vasculature, which is anticipated based on the activity of sotatercept in animal models and the hypothesized mechanism of action and activity of sotatercept in patients with PAH. In addition to that, PVR is an objective parameter measured by right heart catheterization (RHC), it is an appropriate primary endpoint given that this is an open-label non-randomized study. Other hemodynamic parameters are also used for efficacy evaluation as exploratory endpoints.

The 6MWD has been commonly used as an endpoint in clinical trials of PH therapies [Barst, R. J., et al 1996] and is an important prognostic factor in the risk scores[Galiè, N., et al 2016].

NT-proBNP is secreted by cardiomyocytes in response to ventricular stretch and is an established noninvasive marker of ventricular dysfunction in patients with PAH. Plasma NT-proBNP levels correlate with functional capacity, right ventricular function, and echocardiographic and hemodynamic variables, and this biomarker has been consistently shown to be an independent predictor of survival in PAH [Souza, R., et al 2007] [Souza, R., et al 2005].

The WHO FC, despite its interobserver variability, remains one of the most powerful predictors of survival, not only at diagnosis but also during follow-up [Sitbon, O., et al 2002] [Nickel, N., et al 2012] [Barst, R. J., et al 2013]. A worsening FC is one of the most alarming indicators of disease progression, and should trigger further diagnostic studies to identify the causes of clinical deterioration.

4.2.1.2 Safety Endpoints

AEs, AEs leading to discontinuation of study intervention, physical examinations (including vital signs), laboratory tests (ADA, hematology, chemistry, and urinalysis) and electrocardiogram (ECG) will be assessed to provide a comprehensive safety evaluation of sotatercept in Japanese participants with PAH. Potential drug-induced liver injury (DILI) events and AEs of telangiectasia will be captured as events of clinical interest (ECIs) per the standard requirement of Sponsor studies (Section 8.4.7). AEs will be evaluated at each visit and assessed according to the guidelines in Section 8.4 and Appendix 3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

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4.3 Justification for Dose

The same dosing method for ex-Japan Phase 3 studies is used in this study.

The PULSAR study demonstrated that both the 0.3 mg/kg and 0.7 mg/kg sotatercept doses are pharmacologically active and that both resulted in statistically significant improvements across several study endpoints compared to placebo. However, comprehensive E-R analyses demonstrated that a concentration-effect relationship exists for PVR, 6MWD, and NT-proBNP for efficacy and Hgb for safety. Simulations based on these E-R models suggest a higher probability of achieving clinically meaningful targets for 6MWD, PVR, and NT-proBNP with the 0.7 mg/kg dose level compared to 0.3 mg/kg.

While a concentration-effect relationship was also demonstrated for Hgb increases, no significant difference at steady state was observed between sotatercept dose levels in the PULSAR study; mean change from baseline in Hgb at Week 24 was 1.2 g/dL and 1.5 g/dL in

the 0.3 mg/kg and 0.7 mg/kg groups, respectively. The PULSAR study demonstrated that excursions in Hgb concentration above the upper limit of normal (ULN) can be effectively managed by sotatercept dose modification guidelines.

Clinical trial simulations from the pharmacokinetic (PK)/pharmacodynamic (PD) model for Hgb suggested that the probability of having Hgb ≥ 18 g/dL and an increase in Hgb ≥ 2 g/dL is higher during the first 21 days after a dose of 0.7 mg/kg than after a dose of 0.3 mg/kg. Therefore, for this study, a starting dose of 0.3 mg/kg was selected and will be administered at Visit 2 and a target dose of 0.7 mg/kg will be administered at Visit 3 and for the remainder of the treatment period. All doses will be administered subcutaneously every 3 weeks in accordance with dose modification guidelines (Section 6.6).

Prior to the initiation of Japan Phase 3 study (P020), the data from P019, a Japan Phase 1 study, will be evaluated to determine if there are any differences in the safety and PK between Japanese and non-Japanese populations. There is unlikely to be ethnic difference in the PK of sotatercept because sotatercept, a fusion protein, is mainly eliminated through catabolic pathways. In addition, sotatercept is administered as a dose per body weight, which can reduce the effect of body size on the changes of the exposure.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Documented diagnostic RHC at any time prior to screening confirming the diagnosis of WHO PAH Group 1 in any of the following subtypes:

- Idiopathic PAH
- Heritable PAH
- Drug/toxin-induced PAH
- PAH associated with connective tissue disease
- PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair

2. PAH classified as WHO FC I or symptomatic PAH classified as WHO FC II to IV
3. Baseline RHC performed during the Screening Period documenting a minimum PVR of ≥ 400 dyn·sec/cm^5 （5 Wood unit）
4. On stable doses of background PAH therapy (i.e., patient-specific dose goal for each therapy already achieved) and diuretics (if applicable) for at least 90 days prior to screening (Refer to Section 6.5 for details).
5. 6MWD ≥ 150 and ≤ 500 m repeated twice at screening (measured at least 4 hours apart, but no longer than 1 week), and both values are within 15% of each other (calculated from the highest value).

Demographics

6. Is an individual of any sex/gender and ≥18 years of age at the time of providing informed consent.

Participants Assigned Male Sex at Birth

7. If capable of producing sperm, the participant, agrees to the following during the intervention period and for at least 16 weeks (112 days) after the last dose of study intervention:

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview):

  - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant and should also be advised of the benefit for that partner to use an additional method of contraception, as a condom may break or leak.
    Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

  - Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Participants Assigned Female Sex at Birth

8. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP

  OR

- Is a POCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 16 weeks (112 days) after the last dose of study intervention.The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for

those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

- Has a negative highly sensitive pregnancy test (as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

- Abstains from breastfeeding during the study intervention period and for at least 16 weeks (112 days) after study intervention.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

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Additional Categories

10. If participants assigned male sex at birth, agrees to refrain from donating blood or sperm for the duration of the study and for 16 weeks (112 days) after the last dose of study intervention.
11. If participants assigned female sex at birth, agrees to refrain from 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 intervention.
12. Ability to adhere to study visit schedule and understand and comply with all protocol requirements.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Diagnosis of PH WHO Groups 2, 3, 4, or 5.
2. Diagnosis of the following PAH Group 1 subtypes:

• human immunodeficiency virus (HIV)-associated PAH

- PAH associated with portal hypertension
- schistosomiasis-associated PAH
- PAH with features of significant venous/capillary (PVOD/PCH) involvement

3. Is on the waiting list for lung transplant

   Note: patient who was registered to the list within 12 months prior to the screening or currently pending (temporally out of) the waiting list is eligible.

4. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure > 160 mmHg or sitting diastolic blood pressure > 100 mmHg during screening visit after a period of rest
5. Baseline systolic blood pressure < 90 mmHg at screening.
6. Pregnant or breastfeeding women.
7. History of full or partial pneumonectomy.
8. Pulmonary function test (PFT) values of forced vital capacity (FVC) < 60% predicted at the screening visit or within 6 months prior to the screening visit.
9. Initiation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to the screening visit or planned initiation during the study (participants who are stable in the maintenance phase of a program and who will continue for the duration of the study are eligible).
10. History of more than mild obstructive sleep apnea that is untreated.
11. Known history of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication), defined as mild to severe hepatic impairment (Child-Pugh Class A-C).
12. History of restrictive, constrictive, or congestive cardiomyopathy.
13. History of atrial septostomy within 180 days prior to the screening visit.
14. ECG with Fridericia's corrected QT interval (QTcF) > 500 ms during the Screening Period.
15. Personal or family history of long QT syndrome (LQTS) or sudden cardiac death.
16. Left ventricular ejection fraction (LVEF) < 45% on historical ECHO within 6 months prior to the screening visit or pulmonary arterial wedge pressure (PAWP) > 15mmHg at the baseline RHC performed during the Screening Period.
17. Any symptomatic coronary disease events (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the screening visit. Note: Anginal pain can be ignored as an exclusion criterion if coronary angiography shows no obstructions.
18. Cerebrovascular accident within 3 months prior to the screening visit.
19. Acutely decompensated heart failure within 30 days prior to the screening visit, as per investigator assessment.
20. Significant (≥ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease, mitral stenosis and more than mild aortic valve stenosis.

21. Prior exposure to sotatercept or luspatercept or history of allergic or anaphylactic reaction or hypersensitivity to recombinant proteins (including sotatercept or luspatercept) or excipients in investigational product.

Prior/Concomitant Therapy

22. Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the screening visit.

Prior/Concurrent Clinical Study Experience

23. Currently enrolled in or have completed any other investigational product study within 30 days for small-molecule drugs or within 5 half-lives for biologics prior to the date of signed informed consent.

Diagnostic Assessments

24. Has exclusionary laboratory values at the screening visit as listed in the table below.

Laboratory Assessment	**Exclusionary Values**
AST	>3 × ULN
ALT	>3 × ULN
Total bilirubin	>3 × ULN
Estimated glomerular filtration rate (eGFR)	<30 mL/min/m^2 based on the calculation with formula: eGFR (mL/min/1.73 m^2) = 194 x $Cr^{-1.094}$ x $Age^{-0.287}$ (x0.739 if female)
Hemoglobin	> gender-specific ULN
Platelet count	<50,000/ mm^3

25. Weight at the screening is over 85 kg.

Other Exclusions

26. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.
27. Has a severe, acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or Sponsor, would make the participant inappropriate for entry into this study.

5.3 Lifestyle Considerations

5.3.1 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study intervention(s) provided by the Sponsor] will be packaged to support enrollment of study participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study is outlined in Table 1.

Table 1 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
Sotatercept	Experimental	MK-7962 (sotatercept)	Biological/ Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.3 mg/kg, Q3W	SC	V2	Test Product	IMP	Central
Sotatercept	Experimental	MK-7962 (sotatercept)	Biological/ Vaccine	Injection, Powder, Lyophilized, For Solution	60 mg/vial	0.7 mg/kg, Q3W	SC	V3 to EOT	Test Product	IMP	Central

EEA=European Economic Area; EOT=End of Treatment; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; SC=subcutaneous; 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.
Note: Sotatercept dose delay, reductions (from 0.7 to 0.3 mg/kg) due to a safety events and dose re-escalation are described in Section 6.6.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Medical Devices

No medical devices are tested in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by non-random assignment using IRT. There is 1 study intervention arm.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Each dose of study intervention will be administered by SC injection(s) and will be documented in the appropriate eCRF and source documents. Interruptions from the protocol-specified treatment plan are acceptable for participants who dose delay due to a safety event, as described in Section 6.6. Study sites should consult with the Sponsor Clinical Director for participants who meet study intervention discontinuation criteria (Section 7.1) due to dose delays (see Section 6.6).

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

During screening and throughout the study, participants may take stable doses of medications for chronic conditions. If there is an immediate clinical need during the study to prescribe a

new medication or a new dosage of an existing medication for either a new or worsening preexisting condition, concurrent therapy may be administered at the discretion of the investigator. The investigator may consult the Sponsor Clinical Director regarding what constitutes a stable dose or a chronic condition.

6.5.1 Background PAH Therapy and Diuretics

Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or double- or triple- combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, or prostacyclin analogues or receptor agonists. Background PAH therapy as well as diuretics used as supportive therapy should be stable at least 90 days prior to screening and remain stable throughout the study. For infusion prostacyclin, dose adjustment within 10% of optimal dose is allowed per medical practice. If the patient is on diuretic therapy, stable diuretic therapy is defined as no addition of a new diuretic and no switching of a pre-existent oral diuretic to parenteral administration; however, dose adjustments (up or down) in pre-existent oral diuretics are acceptable.

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

Participants under investigator's supervision can substitute, add, or increase the dose (for infusion prostacyclin, increase the dose by 10% or more) of background therapy for PAH-worsening including diuretics and supplemental oxygen. Clinical worsening must be captured if background therapy is increased due to PAH-worsening.

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.2 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

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

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

6.6.1 Escalation to Target Dose (0.7 mg/kg)

All participants will begin treatment at a starting dose of 0.3 mg/kg at Visit 2. At Visit 3, the dose will be escalated to the target dose of 0.7 mg/kg and remain at 0.7 mg/kg for the duration of the treatment period, unless dose reduction criteria as described in Section 6.6.2 and Section 6.6.3 are met. However, if at Visit 3 Hgb increases by more than 2.0 g/dL from baseline and this value is above the gender-specific ULN per local laboratory test, dosing should be delayed. All other study procedures, with the exception of study intervention administration, should be performed. At Visit 4, if Hgb has increased by less than 2.0 g/dL from baseline or Hgb value is below the gender-specific ULN per local laboratory test, dosing should be restarted at 0.3 mg/kg. At Visit 5, if Hgb has increased by less than 2.0 g/dL from baseline or Hgb value is below the gender-specific ULN per local laboratory test, the dose will be escalated to the target dose of 0.7 mg/kg. Refer to Figure 2 for additional details.

6.6.2 Dose Modifications Due to Hemoglobin Increase

From Visit 4 onward, if Hgb increases by more than 2 g/dL from the previous dosing visit, and this value is above the gender-specific ULN per local laboratory test, then a maximum of 3 consecutive dose delays are allowed during the study treatment period. After the third dose delay, if Hgb persists at more than 2 g/dL above the previous dosing visit, and this value is above the gender-specific ULN per local laboratory test then the dose should be reduced to 0.3 mg/kg. If the participant is already at a dose of 0.3 mg/kg, the Sponsor Clinical Director should be consulted, and study intervention discontinuation should be considered.

If Hgb increases more than 4 g/dL above the participant's baseline value, the Sponsor Clinical Director should be consulted, and study intervention discontinuation should be considered. Refer to for Figure 3 additional details.

6.6.3 Dose Modifications Due to Low Platelet Count

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

6.6.4 Dose Modifications Due to AE of Telangiectasia

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

intervention dosing has been delayed, the investigator should consult the Sponsor Clinical Director and consider discontinuation from study intervention.

6.6.5 Dose Delays Due to SAEs of Bleeding

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

6.6.6 Dose Re-escalation Following Dose Reduction

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

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

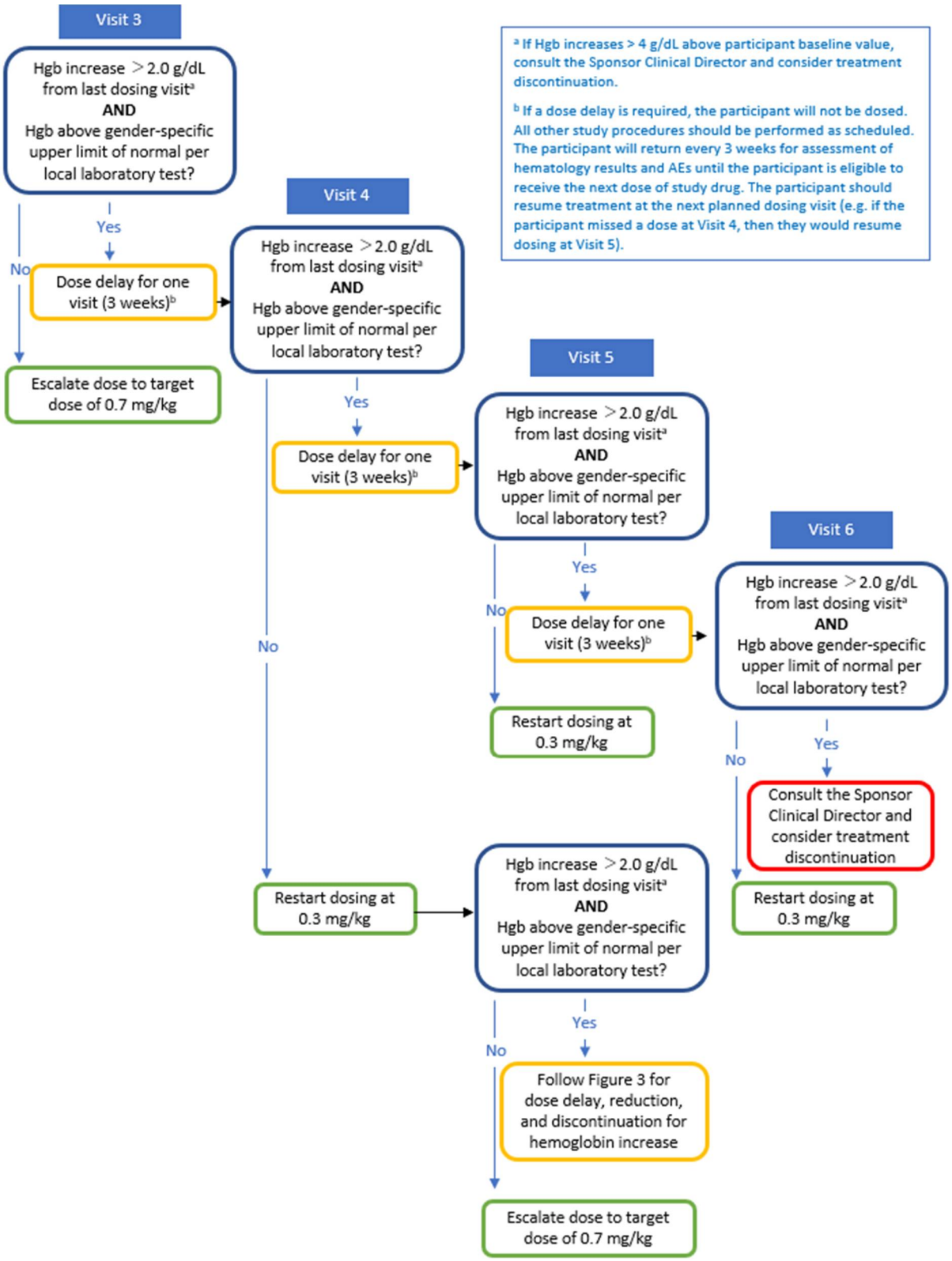


Figure 3 Guidelines for Dose Modification Due to Hemoglobin Increase

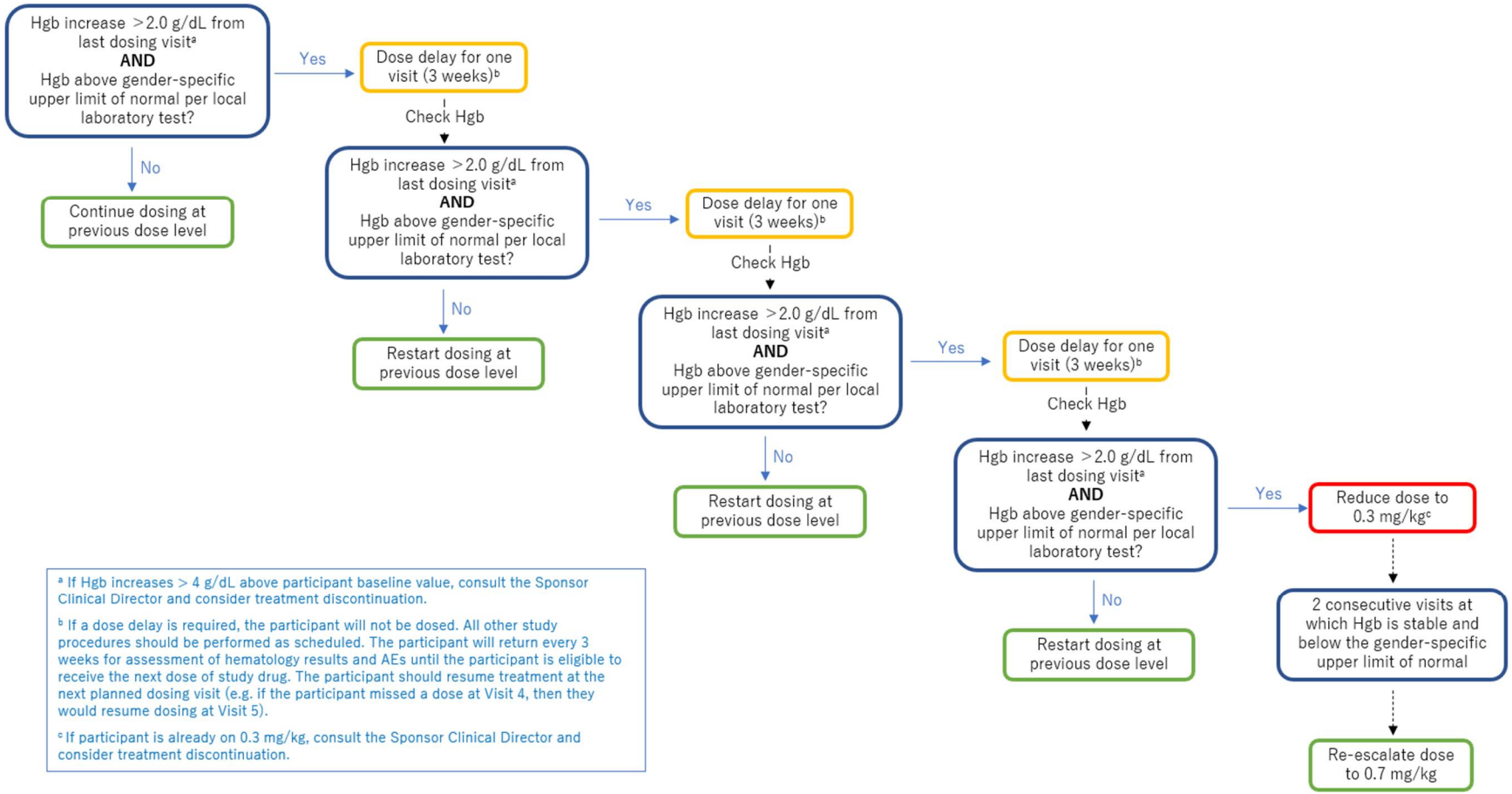
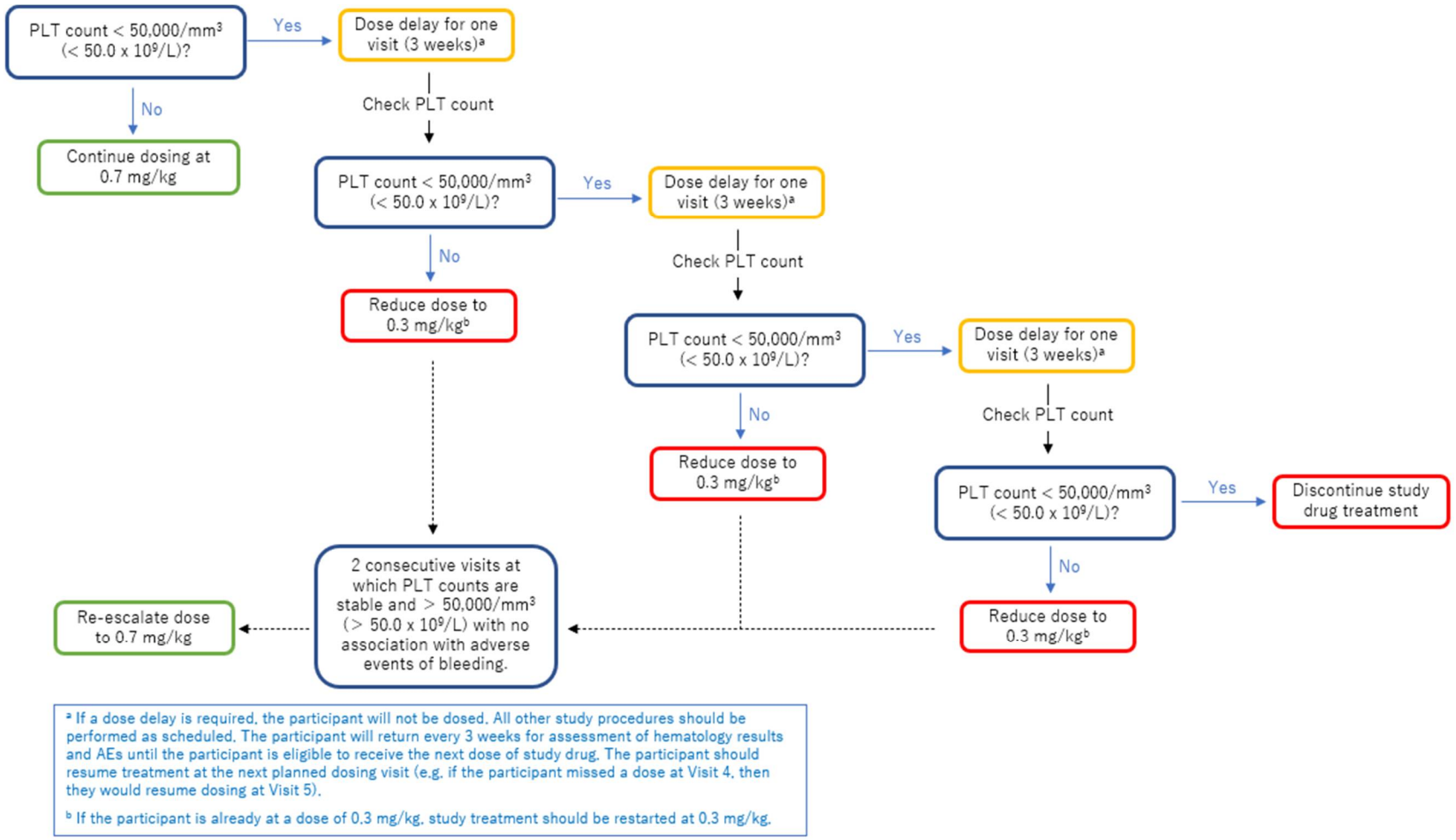


Figure 4 Guidelines for Dose Modification Due to Low Platelet Count



6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.4 unless the participant has withdrawn from the study as specified in Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant meets study intervention discontinuation criteria or decided to discontinue as a result of consultation with the Sponsor Clinical Director according to dose modification guidelines (Section 6.6)

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as CCI [redacted] are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return

for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected for central laboratory tests from each participant will be approximately 130 mL in Screening Period and Primary Treatment Period and 23 mL per visit in Extension treatment Period (only for visits with blood sampling) and Follow-up Period (see appendix 2)). The amount of blood collected for local laboratory tests varies according to each laboratory requirements.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

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8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 28 days before the first dose of study intervention.

Regardless of timing, all prior PAH therapy used must be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/allocation number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/allocation number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/allocation number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee according to the specifications within the pharmacy manual.

8.1.8.1 Timing of Dose Administration

Study intervention will be provided as per Table 1 (Section 6.1) and dispensed through the IRT system at visits indicated in the SoA (Section 1.3).

The first dose of study intervention will be administered at the study site at Visit 2 (Day 1). Subsequent dosing will be performed once per 3 weeks at the study site.

8.1.8.1.1 Optional self-administration

Participants who complete the Primary Treatment Period and are eligible for self-administration (see below for criteria) can start training for consecutive 3 visits at Visit 10 or later. By the investigators' judgement, participants considered eligible and well trained can start self-administration from Visit 12 at the earliest. Those participants may be allowed to return to the study sites every 4 visits after start of self-administration.

At the visit in which self-administration is started (i.e., Visit 12 or later), participants will self-administer the study intervention at the study site and then will be dispensed up to 3 additional doses for self-administration at home.

Participants who meet all of the following criteria may be eligible for voluntary subsequent self-administration of study intervention at home:

- Successfully completed on-site visits through Visit 10
- Received the provided training for self-administration of study intervention (including successful self-administration on-site under the supervision of the investigators)
- Have stable Hgb and platelet count for at least 3 consecutive visits and throughout the duration of the training period

Each self-administration of study intervention at home will be accompanied by a phone call from the study site to confirm proper storage, dosing, and administration of study intervention and to document medication ID numbers, concomitant medications, as well as incidence of any AEs, medication errors, accidental exposure of others, or product inquiries.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.4.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

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8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

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

8.2.2 Six-Minute Walk Test (6MWT)

The distance walked in 6 minutes (the 6MWD) will be measured during the Screening Period and at multiple timepoints throughout the study as per the SoA. During Screening Period, the 6MWT is to be performed twice-at least 4 hours and no longer than 1 week apart; the distances must be within 15% of each other, based on the longer distance. If the difference between the first and second tests is > 15%, the test may be repeated once more, provided that the repeat test is within 1 week of the previous test. If the difference between the distances remains > 15%, the participant will be considered a screen failure.

The 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. The 6MWT should be performed under the same conditions at least between Screening and Visit 10, including chronic oxygen therapy, use of walking aids or face coverings. All 6MWTs performed from Visit 1 onward can be performed at the study visit day or within 10 days prior to study intervention administration. If possible, the 6MWT should be performed at approximately the same time of day to avoid diurnal variation. For each 6MWT, blood pressure, pulse rate and percutaneous oxygen saturation (SpO_2) will also be measured pre and post 6MWT. Refer to Appendix 8 for additional details.

For evaluation of clinical worsening as indicated by the 6MWT, a decrease of ≥ 15% in 6MWD at any timepoint, as compared to screening, must be confirmed by a second 6MWT performed at least 4 hours and no more than 1 week apart from the first. Average of two 6MWT measurements at screening will be used as baseline 6MWD.

8.2.3 World Health Organization Functional Class Assessment for Pulmonary Hypertension

The WHO class system is used to provide information about how affected an individual is by their disease. The 4 FCs that are used to rate how ill a PAH participant is are detailed in Table 2.

Table 2 World Health Organization Functional Class Assessment for Pulmonary Hypertension

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

FC=functional class; PH=pulmonary hypertension; WHO=World Health Organization
Adapted from the New York Heart Association functional assessment.

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8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 2.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. At minimum, assessments of the skin as well as cardiovascular, respiratory, gastrointestinal, and neurological systems will be performed.

A full physical examination will be completed at Screening, Visit 10, and at the EOT/EOS visits. At all other visits, a targeted physical examination, which is consist of cardiopulmonary and skin examinations, will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

Height (only at Visit 1) and weight will also be measured and recorded.

8.3.2 Vital Signs

- Axillary temperature, PR, RR, and BP will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 21 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted as per SoA for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for participant's contraception as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is: 8 weeks.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation through 11 weeks after cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 3 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events or outcomes not qualifying as an AE or SAE.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

2. An AE of telangiectasia (spider veins, spider naevi)
   Note: Investigators are strongly encouraged to have the participant evaluated by a dermatologist, or other appropriate specialist, and to consider photo-documentation of the affected skin.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the prescribed dose.

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 within 5 calendar days of learning of event and be fully documented as an AE in the CRF.

There is no antidote for sotatercept and it is not dialyzable from blood. Therefore, in case of overdose, participants should be monitored/treated as per clinical practice based on symptoms of potential risks as described in the IB.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

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8.10 Health Economics Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Approximately 4 weeks before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

8.11.2 Rescreening

If a participant screen-fails (Section 5.4), the participant may be rescreened once based on investigator judgment, and after consultation with the Sponsor. Participants who are rescreened will retain the same screening number assigned at the initial screening visit (Section 8.1.6).

8.11.3 Treatment Period Visit

All procedures and their timing should be completed as per the SoA (Section 1.3).

The treatment period consists of 24 weeks of Primary Treatment Period and Extension Treatment Period (until approval or participants discontinue the study treatments).

Visit intervals (21 days ± 3 days) are relative to the date of the previous dose of study intervention.

8.11.3.1 Primary Treatment Period (Visit 2 to 10)

Study procedures/assessments for Visits 2 to 10 vary depending on the visit number and will be completed per the SoA (Section 1.3). All study procedures/assessments should be performed before administration of the study intervention. Study intervention should not be administered until after results from local Hgb and platelet assessments are available from a sample taken at the same visit or within 3 days before the visit.

8.11.3.2 Extension Treatment Period (Visit 11 and later)

Participants who complete the 24-week Primary Treatment Period on study intervention will be encouraged to continue treatment in the Extension Treatment Period. Study procedures for this period vary depending on the visit type and will be completed per the SoA (Section 1.3).

All study procedures/assessments should be performed before administration of the study intervention. Study intervention should not be administered until after results from local Hgb and platelet assessments are available from a sample taken at the same visit or within 3 days before the visit.

Participants who are eligible (refer to Section 8.1.8.1.1 for details) for self-administration can start training for 3 consecutive visits at the time of Visit 10 or later. By the investigators' judgement, participants considered eligible and well trained can start self-administration from Visit 12 at the earliest. Those participants may be allowed to return to the study sites every 4 visits after start of self-administration. Even in this case, a negative pregnancy test is required for POCBP prior to each self-administration at home.

All participants, regardless of opt-in for self-administration are required to return to the study site at Visit 11 and Visit 12 and every 4 visits thereafter (i.e., Visit 16, Visit 20, etc.). All those visits occur on a 21 ± 3 days cycle.

8.11.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

A participant must be discontinued from study intervention but continue to be monitored for any of the reasons listed in Section 7.1. Once a participant discontinues from the study, they will not be eligible to re-enter the study.

When it is determined that discontinuation from study intervention is appropriate, the participant should have both an EOT visit (Section 8.11.4.1) and an EOS visit (Section 8.11.4.2) conducted. After the visit procedures are completed, the participant will be withdrawn from the study and managed for treatment of PAH by the investigator per local standard-of-care.

8.11.4.1 End of Treatment Visit

Participants who discontinue treatment for any reason should have an EOT visit as outlined in Section 1.3. If discontinuation occurs during the timeframe of a scheduled study visit, the assessments for the EOT visit should be conducted.

8.11.4.2 End of Study Visit

Participants who discontinue treatment should have EOS visit approximately 8 weeks after the EOT visit as outlined in Section 1.3.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to the database lock for the primary timepoint analysis will be documented in a supplemental statistical analysis plan (SAP) and referenced in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3 Non-randomized, Non-controlled, Open Label Clinical Study to Evaluate the Efficacy and Safety of MK-7962 (Sotatercept) add-on to Background Therapy in Japanese Participants with Pulmonary Arterial Hypertension (PAH)
Treatment Assignment	All eligible participants will be treated with sotatercept.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT) The primary participant population of interest is WHO FC II and III
Primary endpoint	Change from baseline in PVR at Week 24
Key secondary endpoint	Change from baseline in 6MWD at Week 24
Statistical Methods for Key Efficacy Analyses	<u>WHO FC II and III</u> The mean and the corresponding 95% CI based on a t-distribution will be calculated for change from baseline in PVR at Week 24, the primary efficacy endpoint for the study. If a serious departure from normality is observed, the median and the corresponding 95% CI based on the Hodges-Lehmann method will be provided instead. The key secondary endpoint, change from baseline in 6MWD at Week 24, will be analyzed using the Hodges-Lehmann method. <u>WHO FC I, IV</u> The individual data will be listed. If the number of participants enrolled warrants statistical analysis, the point estimates and 95% CIs will be calculated in the same manner as WHO FC II and III.
Statistical Methods for Key Safety Analyses	The overall safety evaluation will include a summary of the number and percentage of participants with at least one AE, drug-related AE, SAE, drug-related SAE, discontinuation from study intervention due to an AE, and an AE resulting in death. The number and percentage of participants with specific AEs, including telangiectasia (event of special interest), will also be provided.
Interim Analyses	No interim analysis is planned.
Multiplicity	No adjustment for multiplicity is planned.

Sample Size and Power	A minimum of 35 participants with WHO FC II and III will be enrolled and receive study intervention. With 35 participants enrolled, it is expected that change from baseline in PVR at Week 24 will be obtained from 31 participants, assuming a discontinuation rate of ~10%. If the standard deviation (SD) estimate is 200 (400) dyn·sec/cm^5, the half-width of the 95% CI will be 73 (147) dyn·sec/cm^5.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a non-randomized, open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The primary timepoint analysis will be performed after all participants have completed Week 24 or discontinued. The data available at that point, including the data beyond Week 24 that are collected on or before the cutoff date, will be used to prepare the CSR. An additional analysis will also be performed to provide selected efficacy and safety results after all participants have completed Week 54 or discontinued prior to Week 54. After the Extension Treatment Period has been completed, the CSR will be amended to include those results.

If population PK analysis is performed, a separate analysis plan will be prepared by the Quantitative Pharmacology and Pharmacometrics group, and the analysis results will be provided as a separate report.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within-treatment differences are listed below. Unless otherwise noted, baseline is defined as the last available measurement prior to the first dose of study intervention, which is typically the measurement at Visit 1 (Screening) or Visit 2 depending on the endpoint.

9.4.1 Efficacy Endpoints

Primary endpoint

- The primary efficacy endpoint will be change from baseline in PVR at Week 24. Percent change from baseline in PVR at Week 24 will also be evaluated as a supportive approach.

Secondary endpoints

The key secondary efficacy endpoint will be change from baseline in 6MWD at Week 24. The average of two measurements at screening, which are within 15% of each other, will be used as baseline. Percent change from baseline in 6MWD at Week 24 will also be evaluated as a supportive approach.

The other secondary efficacy endpoints include:

- Proportion of participants with improvement in WHO FC at Week 24
- Change from baseline in NT-proBNP at Week 24

Exploratory endpoints

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9.4.2 Safety Endpoints

Refer to Section 4.2.1.2 Safety Endpoints.

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9.5 Analysis Populations

The primary participant population of interest is WHO FC II and III.

9.5.1 Efficacy Analysis Populations

Efficacy analyses will be conducted in the FAS population, which consists of all participants who received at least one dose of study intervention. The number of participants contributing to the analyses may vary by endpoint, depending on the degree of missing data.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all participants who received at least one dose of study intervention.

9.6 Statistical Methods

All analyses will be conducted separately by WHO FC [(1) WHO FC II and III, (2) WHO FC I, (3) WHO FC IV] at baseline.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

WHO FC II and III

The mean and the corresponding 95% CI based on a t-distribution will be calculated for change from baseline in PVR at Week 24, the primary efficacy endpoint for the study. If a serious departure from normality ($p < 0.001$ with a Shapiro-Wilk test) is observed, the median and the corresponding 95% CI based on the Hodges-Lehmann method will be provided instead.

As a supportive approach, percent change from baseline in PVR at Week 24 will also be evaluated. The individual ratios (Week 24/baseline) will be natural log-transformed, and the mean and the corresponding 95% CI based on a t-distribution will be calculated. The results will be transformed back to the original scale for reporting.

The key secondary efficacy endpoint, change from baseline in 6MWD at Week 24, will be analyzed using the Hodges-Lehmann method. Percent change from baseline at Week 24 will be analyzed in the same manner as PVR.

CCI [redacted]

The data obtained after the addition, increase or substitute of background PAH therapy will be excluded from the analysis. As a supportive approach, the analysis without excluding the data obtained after the addition, increase or substitute of background PAH therapy will also be performed.

Missing data will not be imputed for any analyses.

WHO FC I, IV

The individual data will be listed. If the number of participants enrolled warrants statistical analysis, the point estimates and 95% CIs will be calculated in the same manner as WHO FC II and III.

Table 4 summarizes key efficacy analyses.

Table 4 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, time Point)	Primary vs. Supportive	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective				
Change from baseline in PVR at Week 24	P	CI based on t-distribution/ Hodges-Lehmann method [a]	FAS	Data as observed
Percent change from baseline in PVR at Week 24	S	CI based on t-distribution	FAS	Data as observed
Secondary Objective #1				
Change from baseline in 6MWD at Week 24	P	Hodges-Lehmann method	FAS	Data as observed
Percent change from baseline in 6MWD at Week 24	S	CI based on t-distribution	FAS	Data as observed
Secondary Objective #2				
Proportion of participants with improvement in WHO FC at Week 24	P	CI based on the method of Clopper and Pearson	FAS	Data as observed
Secondary Objective #3				
Change from baseline in NT-proBNP at Week 24	P	CI based on t-distribution/ Hodges-Lehmann method [a]	FAS	Data as observed

P = primary, S = supportive.
[a] Methods that will be used under serious departure from normality ($p < 0.001$ with a Shapiro-Wilk test)

9.6.2 Statistical Methods for Safety Analyses

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary of the number and percentage of participants with at least one AE, drug-related AE, SAE, drug-related SAE, discontinuation from study intervention due to an AE, and an AE resulting in death.

The number and percentage of participants with specific AEs, system organ classes and predefined limits of change (PDLCs) will also be provided.

For continuous safety measures, such as change from baseline in laboratory, vital signs and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided.

Immunogenicity (incidence/titer of ADA) will also be analyzed.

9.6.2.2 Assessment of Safety Topics of Special Interest

The AE of telangiectasia (spider veins, spider naevi) will be considered an event of special interest in this study. The number and percentage of participants with an event will be summarized.

Table 5 summarizes analysis strategy for safety endpoints in this study.

Table 5 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics
Overall Safety Assessment	Any AE Any drug-related AE Any SAE Any drug-related SAE Discontinuation from study intervention due to an AE AE resulting in death Specific AEs, system organ classes, PDLCs Change from baseline results (labs, vital signs, ECGs) CCI	X
AE of Special Interest	AE of telangiectasia (spider veins, spider naevi)	X

9.6.3 Summary of Baseline Characteristics, Demographics, and Other Analyses

Demographic variables and other baseline characteristics, participant disposition, medical history, as well as prior and concomitant medications, will be summarized either by descriptive statistics or categorical tables.

CCI

9.7 Interim Analyses

No interim analysis is planned.

9.8 Multiplicity

No adjustment for multiplicity is planned.

9.9 Sample Size and Power Calculations

A minimum of 35 participants with WHO FC II and III will be enrolled and receive study intervention. If this is achieved in less than 1 year from the first dose of study intervention in the study, the enrollment will continue until either of the following has been achieved:

- One (1) year has elapsed from the first dose of study intervention in the study
- Forty (40) participants have been enrolled and received study intervention

The proportion of participants using infusion prostacyclin will not exceed approximately 50% of the WHO FC II and III participants enrolled.

No minimum or maximum number of participants will be pre-specified for WHO FC I or IV.

9.9.1 Sample Size and Power for Efficacy Analyses

With 35 participants enrolled and treated, it is expected that change from baseline in PVR at Week 24 will be obtained from 31 participants, assuming a discontinuation rate of ~10%. The half-widths of 95% CIs for change from baseline given various SD estimates will be as follows. For example, if the SD estimate is 200 (400) dyn·sec/cm^5, the half-width of the 95% CI will be 73 (147) dyn·sec/cm^5.

Table 6 Half-Widths of 95% CIs for Change From Baseline in PVR (dyn·sec/cm^5) at Week 24 Given Various SD Estimates (31 Participants)

SD Estimate	Half-width of 95% CI
115	42
200	73
300	110
400	147
500	183
600	220
700	257

9.9.2 Sample Size and Power for Safety Analyses

There is a >99% chance of observing at least one SAE among 35 participants if the underlying incidence of SAE is approximately 24% (1 of every ~4.2 participants receiving the study intervention), which is consistent with the 0.7 mg/kg group in the PULSAR trial. If no SAEs are observed among 35 participants, this study will provide 95% confidence that the underlying percentage of participants with an SAE is less than approximately 8.2% (one in every 12.2 participants).

9.10 Subgroup Analyses

The consistency of the treatment effect will be assessed descriptively via summary statistics by subgroup for the classification variables listed below.

- Sex (male, female)
- PAH Etiological Subgroups (iPAH [idiopathic PAH], hPAH [heritable PAH], Drug/Toxin, Connective Tissue Disease, congenital heart disease with s/p Shunt Repair)
- Background PAH therapy at baseline (monotherapy, double combination, triple combination)
- WHO FC at baseline (II, III)
- PVR (dyn·sec/cm^5) at baseline (≤800, >800)

The subgroup analysis will be performed for the primary and key secondary efficacy endpoints in participants with WHO FC II and III.

9.11 Compliance (Medication Adherence)

Percent compliance will be calculated according to the following formula and summarized using descriptive statistics.

$$\text{Compliance (\%)} = 100\text{x} \frac{\text{Number of visits where study intervention was administered}}{\text{Number of visits in the treatment period where study intervention should have been administered}}$$

The study intervention is administered every 3 weeks. For a participant who is followed for the entire study treatment period, the "Number of visits in the treatment period where study intervention should have been administered" is the total number of visits that should be done from allocation to the last scheduled day for treatment administration for that participant, excluding the number of dose delays/holds per protocol. For a participant who discontinues from the study treatment, the "Number of visits in the treatment period where study intervention should have been administered" is the total number of visits that should be done from allocation to the date of the last visit, excluding the number of dose delays/holds per protocol.

9.12 Extent of Exposure

The duration of exposure and the total dose administered (mg) will be summarized with descriptive statistics.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD 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.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this

process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

There are no committees in this study.

10.1.5 Publication Policy

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

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, 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.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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 review and verification to confirm that data entered into the CRF 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 participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion 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.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- Hematology parameters listed in Table 7 will be collected and analyzed locally.
- Except for hematology parameters, parameters in Table 7 will be analyzed by a central laboratory. Local assessment may be performed in the event that the central laboratory results are not available in time for study intervention administration and/or response evaluation. Additionally, if local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Magnesium
	Uric acid			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)			
Other Screening Tests	• FSH (as needed in PONCBP only)			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; POCBP=Participants of childbearing potential; PONCBP=Participants of nonchildbearing potential; WBC=white blood cell

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Blood volumes for central laboratory tests are listed in Table 8.

Table 8 Blood volumes for central laboratory tests

Study Period	Screening	Primary Treatment Period							Extension Treatment Period				Follow-up	
Visit Number	1	2	3	4	5	6	7-9	10 (1°EP Evaluation)	11	12	13-15	16, 20, 24	End of Treatment (EOT)	End of Study (EOS)
Scheduled Week		0 (Day 1)	3	6	9	12	15, 18, 21	24	27	30	33, 36, 39	every 12 weeks	3 weeks from the last dose	8 weeks from EOT
Visit Window	≤28 days		±3 days										±7 days	
NT-proBNP/ Activin A		4	4			4		4		4		4	4	4
Chemistry	7					7		7		7		7	7	7
CCI														
Total	19	24.5	16	12	12	23	0	23	0	23	0	23	23	23

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT

RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

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

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one 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.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• IUS[a,b] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner(s) (vasectomized or secondary to medical cause). All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Penile/external condoms must be used in addition to POCBP's hormonal contraception. [b] IUS is a progestin releasing IUD.

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[redacted]

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

The specimen(s) may be used for future 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 drugs/vaccines, 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 Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) 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. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant 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.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future 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 is critical to understanding clinical context of analytical results.

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that 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 future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, 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 future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

CCI [redacted]

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[redacted]

CCI

[redacted]

8. 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.

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[redacted]

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.

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Manual for 6MWT

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

Required Equipment

a. Countdown timer (or stopwatch)

b. Mechanical lap counter

c. Two small cones to mark the turnaround points

d. A chair that can be easily moved along the walking course

e. Worksheets on a clipboard

f. A source of oxygen

g. Sphygmomanometer

h. Telephone

i. Automated electronic defibrillator

j. Portable pulse oximeter

Participant Preparation

a. Comfortable clothing should be worn.

b. Appropriate shoes for walking should be worn.

c. Participants should use their usual walking aids during the test (eg, cane, walker, etc.).

d. The participant's usual medical regimen should be continued.

e. A light meal is acceptable before early morning or early afternoon tests.

f. Participants should not have exercised vigorously within 2 hours of beginning the test.

Measurements

a. Repeat testing should be performed about the same time of day to minimize intraday variability.

b. A "warm-up" period before the test should not be performed.

c. 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 ensure that clothing and shoes are appropriate. Record in the source documents.

d. Measure and record baseline heart rate and SpO_2, and follow the manufacturer's instructions to maximize the signal and minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

e. Have the participant stand and rate their baseline dyspnea using the Borg dyspnea scale (Borg CR10 Scale).

   - 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.

   - 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 should resume walking as soon as you are able to do so.

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 objective is to walk AS FAR AS POSSIBLE for 6 minutes but not run or jog. Start now or whenever you are ready."

a. 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.

b. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the participant. Do not get distracted and lose count of

the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the participant the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the participant: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the participant: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the participant: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the participant: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language) to speed up.

If the participant stops walking during the test and needs a rest, tell them: "You can lean against the wall if you would like, then continue walking whenever you feel able to do so." Do not stop the timer.

If the participant stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the participant to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, tell the participant: "In a moment, I am going to tell you to stop. When I do, just stop right where you are, and I will come to you."

When the timer rings (or buzzes), tell the participant: "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

a. Remind the participant of their breathing number pretest and ask the participant to rate their level of shortness of breath again. Record the post-walk Borg dyspnea level.

b. Measure SpO_2 and pulse rate from the oximeter and then remove the sensor.

c. Record the number of laps from the counter.

d. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides.

e. Calculate the total distance walked rounding to the nearest meter and record it on the worksheet.

f. Congratulate the participant on good effort and offer a drink of water.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
6MWD	six-minute walk distance
6MWT	six-minute walk test
CCI [redacted]	
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
BMP	bone morphogenetic protein
CI	confidence interval
CO	cardiac output
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CCI [redacted]	
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
E-R	exposure response
FC	functional class
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FSH	follicle-stimulating hormone

Abbreviation	Expanded Term
FVC	forced vital capacity
GCP	Good Clinical Practice
GDF	growth and differentiation factors
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
NT-proBNP	N-terminal proB-type natriuretic peptide
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PAWP	pulmonary artery wedge pressure
PD	pharmacodynamic
PDLC	predefined limits of change
PK	pharmacokinetic
POCBP	participant/participants of childbearing potential
PONCBP	participant/participants of nonchildbearing potential
PRO	patient-reported outcome
PVR	pulmonary vascular resistance
QoL	quality of life
RAP	right atrial pressure
RHC	right heart catheterization
RNA	ribonucleic acid

Abbreviation	Expanded Term
RVP	right ventricular pressure
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SpO2	percutaneous oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
SvO2	mixed venous saturation of oxygen
ULN	upper limit of normal
VAS	Visual Analog Scale
VSMC(s)	vascular smooth muscle cell(s)
WHO	World Health Organization

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