Official Protocol Title:	A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety of MK-5475 in Adults with Pulmonary Arterial Hypertension
NCT number:	NCT04732221
Document Date:	07-NOV-2023

TITLE PAGE

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Protocol Title: A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety of MK-5475 in Adults with Pulmonary Arterial Hypertension

Protocol Number: 007-03

Compound Number: MK-5475

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):

NCT	04732221
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JRCT	Not applicable
WHO	Not applicable
UTN	U1111-1278-4977
IND	149503

Approval Date: 07 November 2023

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 3	07-NOV-2023	Amended to 1) extend the duration of the Phase 2 Cohort Extension Period to allow participants continued access to study intervention; and 2) add a provision to collapse all treatment groups in the Phase 2 Cohort Extension Period to a single dose group after selection of the Phase 3 dose.
Amendment 2	18-OCT-2022	Amended to add an interim analysis for the Phase 2 Cohort Base Period.
Amendment 1	17-MAR-2022	Amended to add a blinded Extension Period to the Phase 2 Cohort, to evaluate the longer-term safety and tolerability of MK-5475.
Original Protocol	13-NOV-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

This protocol was amended to 1) extend the duration of the Phase 2 Cohort Extension Period to allow participants continued access to study intervention; and 2) add a provision to collapse all treatment groups in the Phase 2 Cohort Extension Period to a single dose group after selection of the Phase 3 dose.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reasons for Amendment		
Section 1.1, Synopsis	Duration of the Phase 2 Cohort Extension Period extended by 16 months.	To allow participants continued access to study intervention.
Section 1.2, Schema		
Section 1.3.1, Phase 2 Cohort Schedule of Activities		
Section 4.1, Overall Design		
Section 6.1, Study Intervention(s) Administered		
Section 1.1, Synopsis	Provision added to collapse all treatment groups into a single group for the remainder of the Phase 2 Cohort Extension Period after the Phase 3 dose is selected.	To permit Phase 2 participants to receive the selected Phase 3 dose.
Section 1.2, Schema		
Section 2.1, Study Rationale		
Section 4.1, Overall Design		
Section 6.1, Study Intervention(s) Administered		
Section 6.3.1, Intervention Assignment		
Section 6.6, Dose Modification		
Section 9.1, Statistical Analysis Plan Summary		

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 relevant changes and their primary reasons are included for completeness.
Title Page	Regulatory Agency identifying numbers updated.	To comply with current industry regulations and guidelines.
Section 1.2, Schema	Phase 2 Cohort Extension Period scheduled visit frequency updated.	To align with updated information about the stability of MK-5475.
Section 1.3, Schedule of Activities	Clinic in-person visit guidance updated.	To clarify that clinic in-person visits may be replaced by telephone, video, or home visits using site staff or a nursing service after consultation with the Sponsor.
	Option for home delivery of study intervention added.	To prevent study intervention interruption during exceptional situations.
	Reference to Appendix 7 for country-specific requirements added.	To align with country-specific pregnancy testing requirements.
Section 1.3.1 Phase 2 Cohort Schedule of Activities	Phase 2 Cohort Extension Period scheduled visit frequency updated.	Refer to Section 1.2 rationale regarding scheduled visit frequency.
Section 4.4.1, Clinical Criteria for Early Study Termination	Criteria for early study termination updated.	To clarify that early study termination of both the Phase 2 and/or Phase 3 cohorts may be the result of the Sponsor's plan to modify or discontinue the development of MK-5475 in PAH.
Section 5.1, Inclusion Criteria	Contraception requirements updated.	New data available.
Section 6.2.2, Handling, Storage, and Accountability	Option for home delivery of study intervention added.	Refer to Section 1.3 rationale regarding optional home delivery.
Section 8, STUDY ASSESSMENTS AND PROCEDURES	Clinic in-person visit guidance updated.	Refer to Section 1.3 rationale regarding replacement of clinic in-person visits.
Section 8.1.8.4, Dispense Double-blind Study Intervention	Phase 2 Cohort Extension Period scheduled visit frequency updated.	Refer to Section 1.2 rationale regarding scheduled visit frequency.
Section 8.3.7, Pregnancy Testing	Reference to Appendix 7 for country-specific requirements added.	Refer to Section 1.3 rationale regarding country-specific pregnancy testing requirements.
Section 8.4.4, Regulatory Requirements for SAEs	Reference to Appendix 7 for country-specific requirements added.	To clarify that notification to the Sponsor of SAEs and AESIs must occur immediately without exceeding 24 hours.
Section 8.11.4, Treatment Period	Phase 2 Cohort Extension Period scheduled visit frequency updated.	Refer to Section 1.2 rationale regarding stability of MK-5475.
	Clinic in-person visit guidance updated.	Refer to Section 1.3 rationale regarding replacement of clinic in-person visits.
Section 9.7, Interim Analyses	Futility analysis plan corrected.	To correct typographical errors.
Section 10.5.2, Contraceptive Requirements	Contraception requirements updated.	New data available.

Section Number and Name	Description of Change	Brief Rationale
Section 10.7, Appendix 7: Country-specific Requirements	Country-specific requirements added.	Refer to Section 1.3 rationale regarding country-specific pregnancy testing requirements and Section 8.4.4 rationale regarding regulatory requirements for SAEs and AESIs.
Section 10.8, Appendix 8: Approximate Blood Volume Tables, Table 11	Phase 2 Cohort Extension Period scheduled visit frequency updated.	Refer to Section 1.2 rationale regarding scheduled visit frequency.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety of MK-5475 in Adults with Pulmonary Arterial Hypertension

Short Title: Phase 2/3 Study of MK-5475 in Adults with Pulmonary Arterial Hypertension

Acronym: INSIGNIA-PAH

Hypotheses, Objectives, and Endpoints:

This study will be carried out in 2 parts, a Phase 2 dose selection cohort and a Phase 3 confirmatory cohort. Each cohort includes a Base Period and an Extension Period.

In men and women aged 18 to 75 years (inclusive) with pulmonary arterial hypertension (PAH):

Primary Objectives	**Primary Endpoints**
Phase 2 Cohort – to evaluate the effect of MK-5475 versus placebo on the pulmonary vascular resistance (PVR) at Week 12. Hypothesis: at least one MK-5475 dose is superior to placebo in reducing PVR from baseline at Week 12.	PVR (centrally assessed)
Phase 3 Cohort – to evaluate the effect of MK-5475 versus placebo on 6-minute walk distance (6MWD) at Week 12. Hypothesis: MK-5475 is superior to placebo in increasing 6MWD from baseline at Week 12.	6MWD
Secondary Objectives	**Secondary Endpoints**
Phase 2 Cohort - to evaluate the effect of MK-5475 versus placebo on 6MWD at Week 12.	6MWD

Phase 2 Cohort - to evaluate the effect of MK-5475 versus placebo on hemodynamic parameters other than PVR at Week 12.	-Mean right arterial pressure (mRAP) -Cardiac index -Stroke volume index (SVI)
Phase 3 Cohort – to evaluate the effect of MK-5475 versus placebo on 6MWD at Week 24.	6MWD
Phase 3 Cohort - to evaluate the effect of MK-5475 versus placebo on the WHO functional PAH class at Week 12.	WHO functional class
Phase 2 and Phase 3 Cohorts (independently) – to evaluate the safety and tolerability of MK-5475.	-Adverse Events (AEs) -Discontinuation of study intervention due to AEs

Overall Design:

Study Phase	Phase 2/3
Primary Purpose	Treatment
Indication	Pulmonary arterial hypertension
Population	Men and women aged 18 to 75 years (inclusive) with PAH.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Sponsor Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 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 450 participants will be randomized in this operationally seamless adaptive Phase 2/3 study. Approximately 164 participants will be randomized in the Phase 2 dose selection cohort and approximately 286 participants will be randomized in the Phase 3 confirmatory cohort.

Intervention Groups and Duration:

In the Phase 2 Cohort Base Period, participants will be randomized in a 1:1:1:1 ratio to once-daily dosing with 1 of 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) or placebo. In the Phase 2 Cohort Extension Period, the participants who received placebo during the Base Period will initially be assigned randomly in a 1:1:1 ratio to 1 of the 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) and will be given new randomization numbers. Participants who received MK-5475 during the Base Period will initially receive the same MK-5475 doses in the Extension Period and will be assigned new randomization numbers, to maintain the study blinding.

After selection of the MK-5475 dose for Phase 3, the 3 MK-5475 dose groups in the Phase 2 Cohort Extension Period will be collapsed into a single dose group for the remainder of the Phase 2 Cohort Extension Period.

In the Phase 3 Cohort, participants will be randomized in a 1:1 ratio to once-daily dosing with either placebo or one of the 3 doses of MK-5475 selected in the Phase 2 Cohort Base Period.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Phase 2 Cohort Group 1	MK-5475	380 µg	380 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and for ~40 months Extension Period	Test Product
Phase 2 Cohort Group 2	MK-5475	100 µg	100 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and for ~40 months Extension Period	Test Product
Phase 2 Cohort Group 3	MK-5475	32 µg	32 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and for ~40 months Extension Period	Test Product
Phase 2 Cohort Group 4	Placebo	0 µg	0 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period	Placebo

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Phase 2 Cohort Group 4a (before Phase 3 dose selection)	MK-5475	380 µg	380 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product
Phase 2 Cohort Group 4b (before Phase 3 dose selection)	MK-5475	100 µg	100 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product
Phase 2 Cohort Group 4c (before Phase 3 dose selection)	MK-5475	32 µg	32 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product
Phase 2 Cohort Group 4a, 4b, & 4c (after Phase 3 dose selection)	MK-5475	380 µg OR 100 µg OR 32 µg	380 µg OR 100 µg OR 32 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product
Phase 3 Cohort Group 1	MK-5475	380 µg OR 100 µg OR 32 µg	380 µg OR 100 µg OR 32 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and up to 60-month Extension Period	Test Product
Phase 3 Cohort Group 2	Placebo	0 µg	0 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and up to 60-month Extension Period	Placebo

Total Number of Intervention Groups/Arms	Phase 2 Cohort Base Period - 4 treatment groups Phase 2 Cohort Extension Period - 3 treatment groups Phase 3 Cohort Base and Extension Periods - 2 treatment groups
Duration of Participation	Each participant will take part in the trial from the time the participant provides documented informed consent through the final contact. Participants eligible for enrollment in the Phase 2 Cohort Extension Period will be required to provide documented informed consent for that study period. Phase 2 Cohort: After a screening period of up to 28 days, each eligible participant will be randomized to receive assigned double-blind study intervention for 12 weeks in the Base Period. The participants who complete the Base Period and provide documented informed consent will be re-randomized to continue treatment in an ~40-month Extension Period. The participants who discontinue study intervention or complete the Base Period before Amendment 01 is approved and the Extension Period becomes available are not eligible to enroll in the Extension Period. Phase 3 Cohort: After a screening period of up to 28 days, each eligible participant will be randomized to receive assigned double-blind study intervention for 12 weeks in the Base Period and then will continue treatment in an Extension Period of up to 5 years. A telephone follow-up visit will occur 14 days after the last study visit, for adverse event monitoring.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes

Study governance considerations are outlined in Appendix 1. The Data Monitoring Committee for this study is external to the Sponsor.

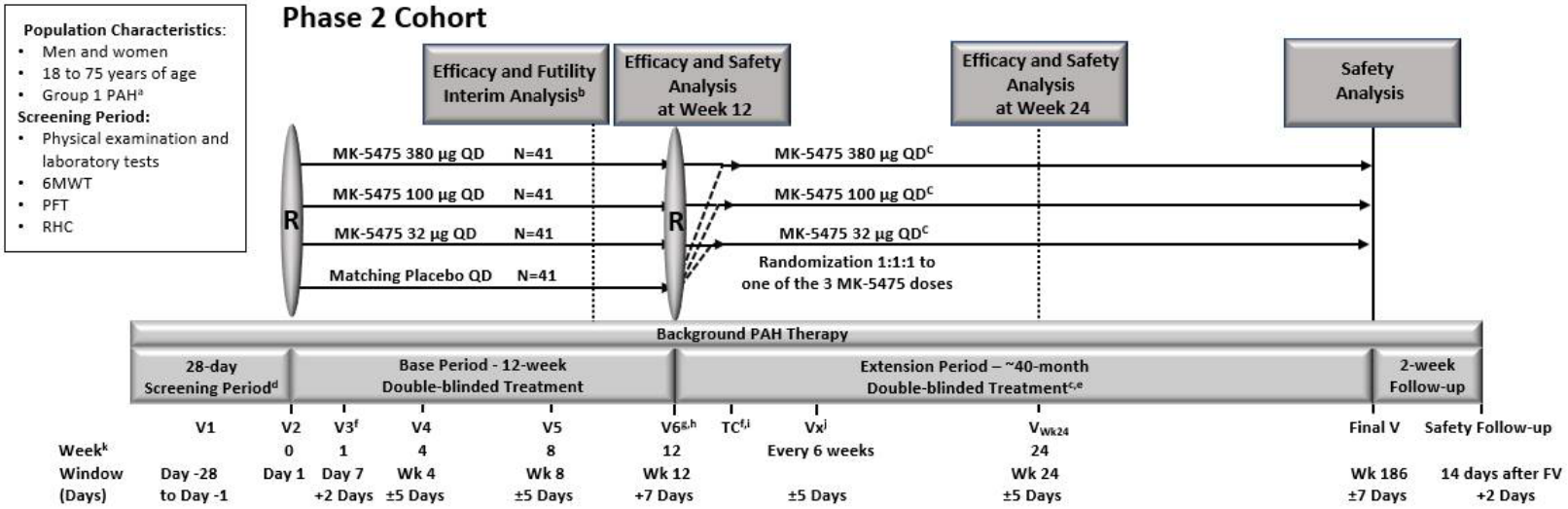
Study Accepts Healthy Participants: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design for Phase 2 Cohort is depicted in Figure 1. The study design for Phase 3 Cohort is depicted in Figure 2.

Figure 1 Study Design – Phase 2 Cohort



6MWT=6-minute walk test; CRF=Case Report Form; FV=Final Visit; PAH=pulmonary arterial hypertension; PFT=pulmonary function tests; QD=once daily; R=randomization; RHC=right heart catheterization; TC=telephone contact; V=visit; V_{Wk24}=Visit at Week 24; Wk=Week.

[a] The diagnosis of PAH should be confirmed by RHC.

[b] An interim analysis for efficacy and futility (nonbinding) is planned when CCI [redacted] have completed or discontinued Phase 2 Cohort Base Period.

[c] The participants who received MK-5475 during the Base Period will initially receive the same MK-5475 doses in the Extension Period. The participants who received matching placebo during the Base Period will initially be randomized 1:1:1 to receive 1 of 3 MK-5475 doses (380 µg, 100 µg, or 32 µg). After selection of the MK-5475 dose for Phase 3, the 3 MK-5475 dose groups in the Phase 2 Cohort Extension Period will be collapsed into a single dose group for the remainder of the Phase 2 Cohort Extension Period (Section 4.1). Participants will be reassigned to the selected single dose group at their next scheduled visit.

[d] Screening procedures will be performed over multiple days and should be performed in order (See Study Operations Manual). Data collected during the 28-day screening period will be registered as Visit 1 in the CRF.

[e] The participants who complete the Base Period and provide documented informed consent for the Extension Period may be enrolled. The participants who complete the Base Period before Amendment **01** approval by the study site are not eligible.

[f] Visit 3 and TC are telephone visits.

[g] Visit 6 procedures may be performed over multiple days.

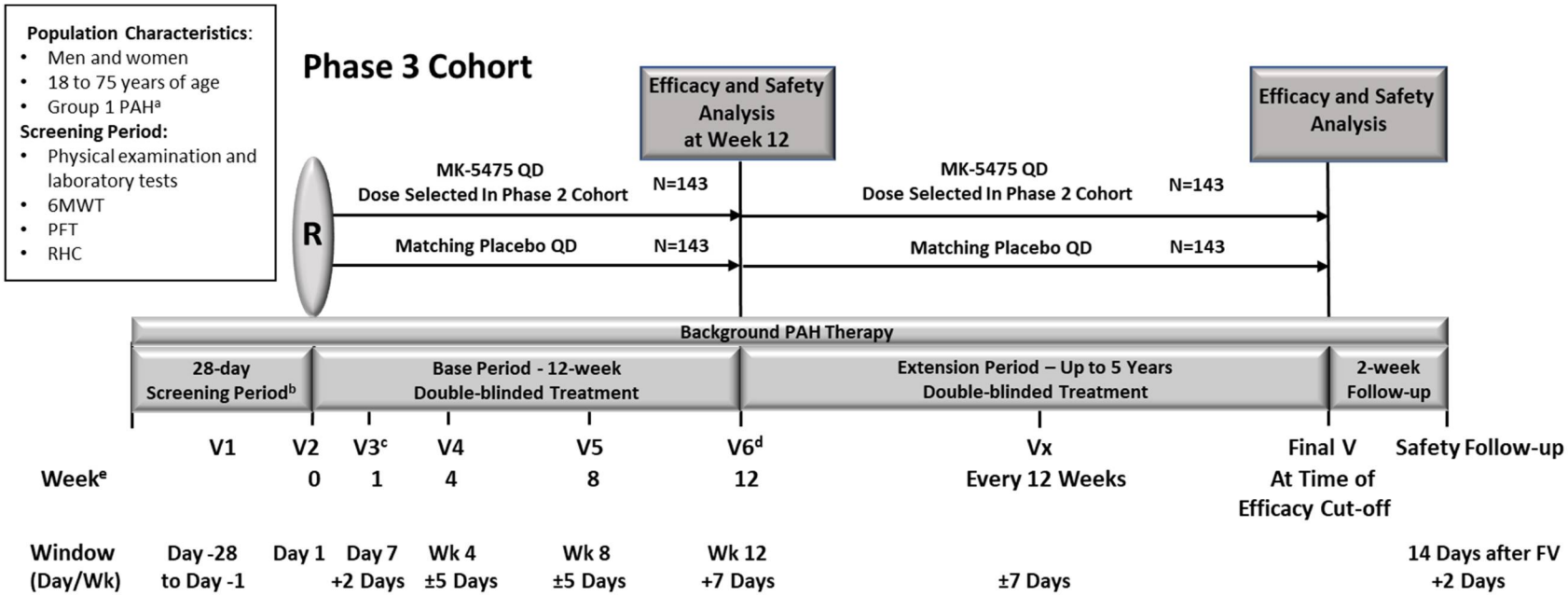
[h] Visit 6 is the last visit for the Base Period and the Baseline Visit for the Extension Period.

[i] For participants who complete the Base Period and enroll in the Extension Period, TC occurs the day after Visit 6 (+2 days). For participants who complete the Base Period but do not continue in the Extension Period, TC occurs 14 days after V6 (+2 Days).

[j] Study visits in the Extension Period will occur every 6 weeks until Final Visit. For participants already enrolled in the Extension Period, the transition to an every 6-week visit frequency will occur at Week 24 or at the next visit that falls on a 12-week interval (eg, Week 36, 48, 60, and every 12 weeks thereafter through study completion).

[k] The weeks are numbered beginning at Randomization (V2).

Figure 2 Study Design – Phase 3 Cohort



6MWT=6-minute walk test; CRF=Case Report Form; PAH=pulmonary arterial hypertension; PFT=pulmonary function tests; QD=once daily; R=randomization; RHC=right heart catheterization; V=visit; Wk=Week.

[a] The diagnosis of PAH should be confirmed by RHC.
[b] Screening procedures will be performed over multiple days and should be performed in order (See Study Operations Manual). Data collected during the 28-day screening period will be registered as Visit 1 in the CRF.
[c] Visit 3 is a telephone visit.
[d] Visit 6 procedures may be performed over multiple days.
[e] The weeks are numbered beginning at Randomization (V2).

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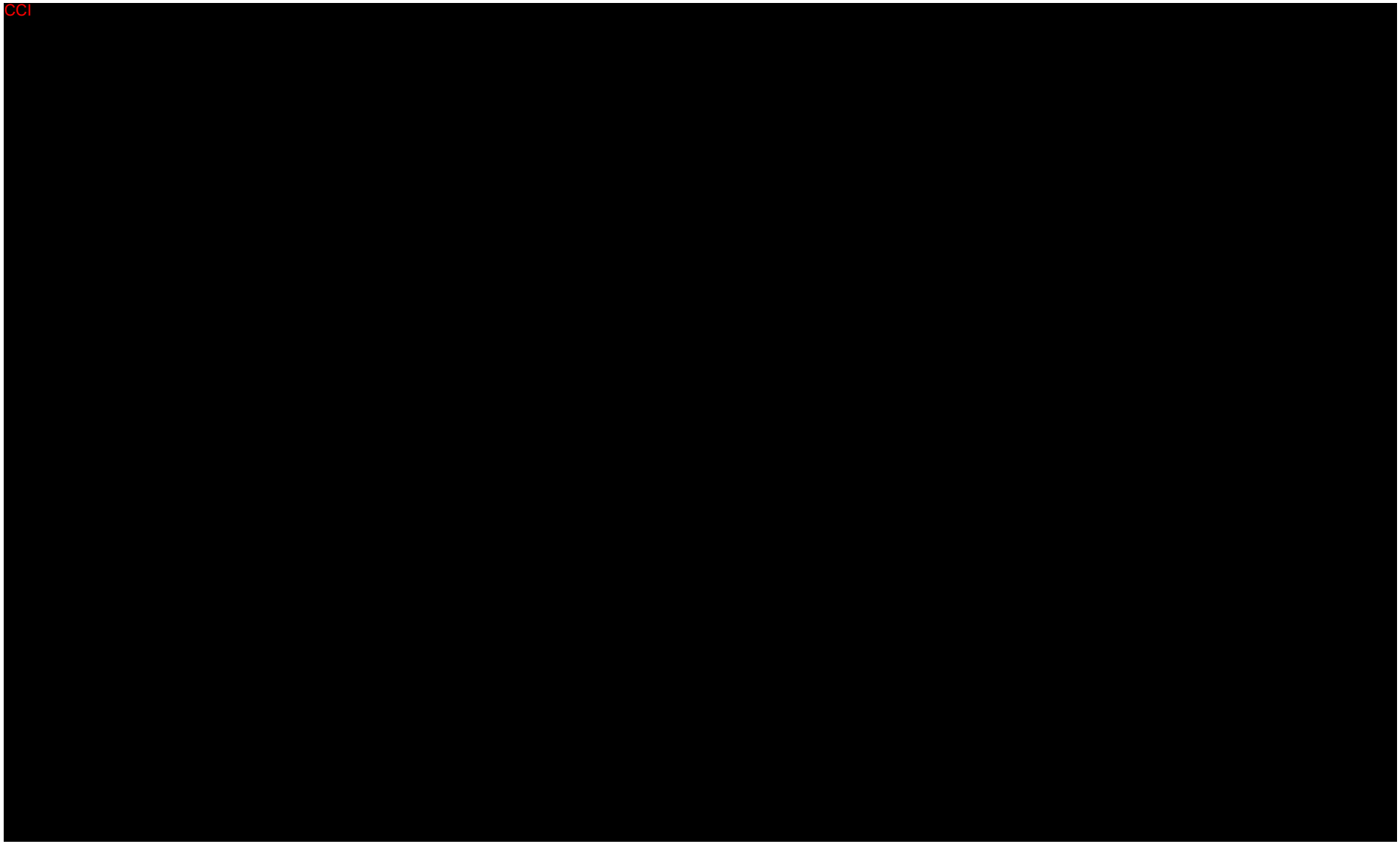

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2 INTRODUCTION

MK-5475 is a small-molecule stimulator of sGC, formulated as a dry powder for inhaled delivery, which is being developed for the treatment of PAH.

2.1 Study Rationale

PAH defines a group of rare, progressive conditions characterized by increased vascular resistance in the pulmonary arterial circulation, related to pre-capillary disease. Despite substantial progress in PAH management, increased awareness, and multiple PAH-specific therapies, the long-term prognosis for PAH patients remains poor and the disease can progress to right-sided heart failure and death.

Localized/inhaled delivery of the sGC stimulator MK-5475 is anticipated to provide benefit in PAH patients by selectively reducing PVR and pulmonary arterial pressure via sGC/cGMP-mediated pulmonary vasodilation, without lowering systemic vascular resistance or BP. Inhalation results in MK-5475 delivery to the deepest segments of the lung airways (respiratory bronchioles and alveoli). MK-5475 has properties suitable for dry powder formulation and delivery and demonstrates pulmonary-selective blood pressure reduction following inhalation dosing in an animal model of PAH and participants with PAH. Inhaled delivery of MK-5475 is thus expected to have sGC-based effects on endpoints associated with PAH, while minimizing systemic sGC pharmacology.

The purpose of this multicenter, randomized, placebo-controlled, double-blind Phase 2/3 operationally seamless adaptive study is to evaluate the efficacy, safety, and tolerability of MK-5475 in participants with PAH. This study will be carried out in 2 parts. The first part is a Phase 2 dose selection cohort which includes a 12-week Base Period followed by a blinded treatment Extension Period, to further inform on the safety and tolerability of MK-5475. Initially, responses to the 3 different doses of MK-5475, compared to placebo, will be assessed in the Phase 2 Cohort Base Period. After selection of the MK-5475 dose for Phase 3, the 3 MK-5475 dose groups in the Phase 2 Cohort Extension Period will be collapsed into a single dose group for the remainder of the Phase 2 Cohort Extension Period. The treatment dose with the best efficacy and safety profile in the Phase 2 Cohort Base Period will be evaluated in the subsequent Phase 3 confirmatory cohort.

The design is operationally seamless adaptive; of the 3 doses studied in the Phase 2 Cohort, a single dose of interest will be evaluated in the Phase 3 Cohort. In the Phase 3 Cohort of this operationally seamless adaptive Phase 2/3 study, the 12-week Base Period will be followed by a blinded treatment Extension Period, to further inform on the safety and efficacy of MK-5475 in this population.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-5475.

Pulmonary hypertension is a chronic disorder of the pulmonary circulation characterized by increased PVR, ultimately leading to right ventricular failure and death. The Updated

Clinical Classification of Pulmonary Hypertension (Nice, 2018) [Simonneau, G., et al 2019] classifies the numerous conditions that are known to lead to, or to be associated with, the development of PH into 5 groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and therapeutic approach. PAH, or Group 1 PH, may occur in the absence of a demonstrable cause or known triggering factor (idiopathic PAH, Group 1.1), in the context of familial history of PAH or a gene mutation known to be associated with PAH (heritable PAH, Group 1.2), as the result of the use of drugs and toxins (Group 1.3), or associated with various conditions including connective tissue diseases, HIV infection, portal hypertension, and congenital heart disease (Group 1.4). PAH in long-term responders to calcium channel blockers (Group 1.5), PAH with venous/capillary involvement (Group 1.6), and persistent PH of the newborn (Group 1.7) are less frequent pre-capillary PH forms, also included in Group 1, but with a distinct clinical presentation, prognosis, and treatment.

The epidemiology of PAH displays some variation, probably related to selection biases. The incidence of adult PAH is estimated to be 2.3 cases per million in the United States [Frost, A. E., et al 2011]. European registry data revealed an estimated incidence of PAH ranging from 2.4 to 7.6 cases per million [Swinnen, K., et al 2019] [Frost, A. E., et al 2011]. Estimated PAH prevalence rate ranges from 6.6 to 291 per million in the US [Kirson, N. Y., et al 2011] [Dubroff, J., et al 2020] [Fenstad, E. R., et al 2019] [Frost, A. E., et al 2011] and from 6.6 to 52 per million in 4 European countries (France, Scotland, United Kingdom, and Germany) [Humbert, M., et al 2006] [Peacock, A. J., et al 2007] [Ling, Y., et al 2012] [Hoeper, M. M., et al 2016]. Both old and contemporary registries have shown that PAH predominantly affects females. The NIH cohort noted that females were 1.8 times more likely to be affected by PAH relative to their male counterparts. Both the REVEAL and the French registry found the female: male ratio to be 3.6:1 and 1.9:1, respectively [Frost, A. E., et al 2011] [Humbert, M., et al 2006].

2.2.1 Pharmaceutical and Therapeutic Background

PAH is caused by pulmonary arterial constriction and obstruction associated with proliferative vascular remodeling, formation of plexiform lesions and in situ thrombosis. The pathophysiology of PAH involves multiple pathways, which are influenced by many overlapping secondary messenger systems. Expression of the vasoconstrictor endothelin is increased while production of vasodilators, such as prostacyclin and NO, is decreased. Therapies for PAH have sought to achieve vasodilation in the pulmonary arterial circulation by targeting these 3 specific pathways (the endothelin pathway, the prostacyclin pathway and the NO pathway), thus decreasing elevated PVR and lessening right ventricular afterload.

There are 2 currently approved PAH treatment options which focus on the NO pathway: PDE5 inhibitors and the oral sGC stimulator, riociguat. In healthy individuals, endothelial cell-derived NO acts on smooth muscle cells to induce vasodilation by increasing production of the second messenger cGMP via stimulation of sGC. In PAH, the NO-sGC-cGMP pathway is downregulated because of endothelial dysfunction leading to reduced NO bioavailability and subsequent relative sGC and cGMP deficiency. PDE5 inhibitors act to decrease the degradation of cGMP, whereas the sGC stimulator riociguat acts to increase the formation of cGMP; both lead to pulmonary vasodilation. However, in addition to pulmonary artery vasodilation, the sGC stimulator riociguat also induces systemic vasodilation, which

can result in systemic hypotension and hypotension-related events, poorly tolerated by PAH patients. Due to activity within the same pathway and increased risk of hypotension, the concomitant use of riociguat and PDE5 inhibitors is contraindicated.

The limitations of nonselective vasodilation in the pulmonary and systemic arteries extends to most other commonly prescribed therapies for PAH, such as ERAs and prostacyclin-based therapies, which have vasodilatory properties and are administered either orally or parenterally. Due to mechanism-based systemic side effects and concerns of hypotension, these medications require careful monitoring and dose titration, and their potential to reduce PVR in PAH patients may not be fully realized. Based on the current high morbidity and mortality rates for PAH patients and based on the side effect and titration profiles of current available PAH-specific medication, there is a high unmet medical need for new PAH therapies.

Inhaled administration of pulmonary vasodilators represents an attractive alternative to oral or parenteral drug therapy, due to direct delivery to the desired site of action, potentially increasing pulmonary circulation selectivity and diminishing systemic side effects, such as hypotension. MK-5475 is a small-molecule stimulator of sGC, which has been formulated as a dry powder for inhaled delivery. An inhaled dry-powder sGC stimulator is hypothesized to avoid most of the side effects associated with systemically administered vasodilators and to allow coadministration of MK-5475 with other PAH medications, including PDE5 inhibitors. Compared with nebulization, inhalation of dry powder microparticles is faster and more efficient because of the much higher respirable fraction and minimal extrapulmonary drug loss. Dry powder inhalers are also convenient and easy to use.

2.2.2 Preclinical and Clinical Studies

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2.2.3 Information on Other Study-related Therapy

Not applicable.

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 product.

Potential participants will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, participant management and PAH-specific background therapy will take into account the local standard of care.

By delivering this compound via inhalation, decreased systemic exposure will enable therapeutic effect at the site of action while minimizing the potential for adverse effects, such as hypotension due to excessive systemic arterial vasodilation.

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

This study will be carried out in 2 parts, a Phase 2 dose selection cohort and a Phase 3 confirmatory cohort. Each cohort includes a Base Period and an Extension Period.

In men and women aged 18 to 75 years (inclusive) with pulmonary arterial hypertension (PAH):

Primary Objectives	**Primary Endpoints**
Phase 2 Cohort – to evaluate the effect of MK-5475 versus placebo on the pulmonary vascular resistance (PVR) at Week 12. Hypothesis: at least one MK-5475 dose is superior to placebo in reducing PVR from baseline at Week 12.	PVR (centrally assessed)
Phase 3 Cohort – to evaluate the effect of MK-5475 versus placebo on 6-minute walk distance (6MWD) at Week 12. Hypothesis: MK-5475 is superior to placebo in increasing 6MWD from baseline at Week 12.	6MWD
Secondary Objectives	**Secondary Endpoints**
Phase 2 Cohort - to evaluate the effect of MK-5475 versus placebo on 6MWD at Week 12.	6MWD
Phase 2 Cohort - to evaluate the effect of MK-5475 versus placebo on hemodynamic parameters other than PVR at Week 12.	-Mean right arterial pressure (mRAP) -Cardiac index -Stroke volume index (SVI)
Phase 3 Cohort – to evaluate the effect of MK-5475 versus placebo on 6MWD at Week 24.	6MWD
Phase 3 Cohort - to evaluate the effect of MK-5475 versus placebo on the WHO functional PAH class at Week 12.	WHO functional class

Phase 2 and Phase 3 Cohorts (independently) – to evaluate the safety and tolerability of MK-5475.	-Adverse Events (AEs) -Discontinuation of study intervention due to AEs

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4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, placebo-controlled, parallel-group, double-blind Phase 2/3 operationally seamless adaptive study to evaluate the efficacy, safety, and tolerability of inhaled MK-5475 in participants with PAH. This study will be conducted in conformance with GCP principles and will be carried out in 2 parts: a Phase 2 dose selection cohort and a Phase 3 confirmatory cohort, each including a 12-week Base Period and an Extension Period.

Participants in both cohorts of this Phase 2/3 study will be adults with PAH (Groups 1.1 to 1.4), as defined in the Updated Clinical Classification of Pulmonary Hypertension (Nice, 2018) [Simonneau, G., et al 2019]. The PAH diagnosis must have been established using the updated scientific guidelines [Frost, A., et al 2019] and confirmed by a diagnostic RHC performed at any time prior to Screening. Participants will not be eligible for the study if they have been diagnosed with PH associated with left heart disease (Group 2 PH), lung disease (Group 3 PH), pulmonary artery obstructions (Group 4 PH) or PH with unclear and/or multifactorial mechanisms (Group 5 PH). All participants will continue to receive their PAH-specific background therapy during the course of the study.

For both cohorts, during the 28-day screening period (Visit 1), participant study eligibility will be assessed based on the demographic, disease diagnostic, hemodynamic, functional, echocardiographic, pulmonary function, and prior/concomitant therapy I/E criteria outlined in Sections 5.1 and 5.2. Consented participants will complete all Visit 1 procedures, as detailed in the SoAs.

Participants meeting all study entry eligibility criteria at Screening may be considered for randomization after Sponsor concurrence on key I/E criteria (See Section 8.11.2). Eligibility for study participation will be reassessed by the investigator at Randomization (Visit 2) to determine if participants continue to meet the I/E criteria and if, between Screening and Randomization, they experienced events that would exclude them for participating in the study, eg, acutely decompensated right heart failure or changes in PAH-specific therapy. Participants who have completed or prematurely discontinued the Phase 2 Cohort are not eligible to participate in the Phase 3 Cohort.

At Visit 2, participants who meet study eligibility criteria will enter the double-blind treatment period, as described below for each cohort. CCI [redacted]

Phase 2 Cohort

In the Phase 2 Cohort Base Period, 3 doses of MK-5475 (380 µg, 100 µg, and 32 µg) will be compared to placebo. The efficacy, safety, and tolerability of each MK-5475 dose will be assessed when all participants in the Phase 2 Cohort Base Period have completed or discontinued the 12-week treatment period. An IA for efficacy and futility (nonbinding) is

planned when approximately 120 participants have completed or discontinued the Phase 2 Cohort Base Period. The Phase 2 Cohort Base Period may stop at the IA and a dose for the Phase 3 Cohort may be selected at that time OR the study may be stopped early for futility (Section 9.7).

The primary objective of the Phase 2 Cohort Base Period is to evaluate the effect of MK-5475 versus placebo on PVR in participants with PAH at Week 12. Of the 3 MK-5475 doses studied, the dose (380 µg, 100 µg, or 32 µg) with the best efficacy and safety profile in the Base Period of this cohort will be selected for evaluation in the subsequent Phase 3 confirmatory cohort, alongside a placebo control group.

Participants who remain on study intervention and complete the Visit 6/Week 12 assessments (***including RHC***) may enroll in the ~40-month blinded Extension Period if they satisfy the SpO_2 and seated BP study eligibility criteria (Section 5.2) at Week 12 and provide documented informed consent. Participants who discontinue study intervention or complete the Phase 2 Cohort Base Period before Amendment 01 is approved and the Extension Period becomes available will not be eligible to enroll in the Extension Period.

The objective of the Phase 2 Cohort Extension Period is to evaluate the longer-term safety and tolerability of the 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) in this participant population.

To supplement the routine blinded trial monitoring outlined in this study, an external DMC will monitor the interim data (Section 9.7).

This Phase 2/3 study may be stopped if analysis of the data collected either at the time of the IA or at the end of the Phase 2 Cohort Base Period shows that none of the MK-5475 doses has a desirable efficacy and safety profile.

Participants will take part in the Phase 2 Cohort Base Period for approximately 16 weeks, including a screening period of up to 4 weeks and a 12-week double-blind treatment period. Approximately 164 eligible participants will be randomized in a 1:1:1:1 ratio to MK-5475 380 µg, MK-5475 100 µg, MK-5475 32 µg, and placebo. Participants will be instructed to inhale 1 dose per day, in the morning, for 84 consecutive days. At the end of the 12-week treatment period, pulmonary vascular hemodynamics will be assessed via RHC, following the same procedures as for the baseline measurements. In the Extension Period, the participants who received placebo during the Base Period will initially be assigned randomly in a 1:1:1 ratio to once-daily dosing with 1 of the 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) and will be given new randomization numbers. The participants who received MK-5475 during the Base Period will initially receive the same MK-5475 doses in the Extension Period and will be assigned new randomization numbers, to maintain study blinding.

After selection of the MK-5475 dose for Phase 3, the 3 MK-5475 dose groups in the Phase 2 Cohort Extension Period will be collapsed into a single dose group for the remainder of the Phase 2 Cohort Extension Period.

Phase 3 Cohort

In both the Base and the Extension Period of the Phase 3 Cohort, the MK-5475 dose (either 380 µg, 100 µg, or 32 µg) selected in the Phase 2 Cohort Base Period will be compared to placebo. The primary objective for the Base Period of Phase 3 Cohort is to evaluate the effect of MK-5475 versus placebo on 6MWD in participants with PAH at Week 12. The Base Period will be followed by a double-blind Extension Period, to further inform on the efficacy, safety, and tolerability of MK-5475 in this participant population.

In the Phase 3 Cohort Base Period, participants will take part in the study for approximately 16 weeks, including a screening period of up to 4 weeks and a 12-week double-blind treatment period. Approximately 286 eligible participants will be randomized in a 1:1 ratio to MK-5475 and placebo. Participants will be instructed to inhale 1 dose per day, in the morning, for 84 consecutive days. 6MWD will be measured, using the same procedure as for the baseline measurement, every 4 weeks and at the end of Phase 3 Cohort Base Period. All participants will continue treatment in an Extension Period until a requisite number of clinical worsening events are observed in the Phase 3 Cohort and a second Phase 3 study. The second Phase 3 study will be described in a separate protocol. A separate integrated analysis plan will be written, providing more details. A CAC, whose members are blinded to the study group assignments, will review all reported clinical events and adjudicate the clinical events related to clinical worsening (See Appendix 1).

In both Phase 2 and Phase 3 Cohorts, additional hemodynamic parameters, changes in symptoms, biomarkers, and participant self-rated quality-of-life questionnaire scores will be used to evaluate response to treatment throughout the study.

Selected members of the Sponsor study team and management will be unblinded to results from Phase 2 Cohort Base Period and Phase 3 Cohort Base Period, to evaluate the efficacy and safety profile of MK-5475 (Section 9.7). For the Phase 2 Cohort Extension Period and Phase 3 Cohort Extension Period, separate blinded Sponsor study teams will monitor the ongoing study.

For each cohort, the double-blind treatment period concludes with a final visit. All participants will complete a telephone follow-up visit 14 days (+ 2 days) after the final visit, for AE monitoring.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in Section 10.3.4. Regular safety assessments will be performed during the study (Section 8.3.9).

To supplement the routine trial monitoring outlined in this study, an external DMC will monitor interim data (Section 9.7).

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

This operationally seamless adaptive Phase 2/3 study is being conducted to evaluate the efficacy, safety, and tolerability of MK-5475 for the treatment of PAH, when added to PAH-specific background therapy. The conduct of this study is supported by evidence from preclinical and clinical studies, in which MK-5475 appeared to be safe and well tolerated, and in which proof of concept has been established - single doses of MK-5475 can effectively reduce PVR, without inducing systemic hypotension in this patient population.

The operationally seamless adaptive design, by combining into a single study objectives which otherwise would have been evaluated in 2 separate studies, will reduce the development timelines while using the same operational infrastructure. The study team will select a dose for the Phase 3 Cohort after reviewing all safety and efficacy information collected in the Phase 2 Cohort Base Period. Given the severity of the disease and the unmet medical need, this study design allows expedited clinical drug development and accelerated timeline for potential registration and patient access, while ensuring study integrity [Food and Drug Administration 2019].

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Pulmonary Vascular Hemodynamics

PAH is characterized by increased vascular resistance in the pulmonary arterial circulation. Hemodynamic measures, such as pulmonary arterial pressure, pulmonary vascular resistance, right atrial pressure, and cardiac index, are the cornerstones of diagnosis and risk stratification in PAH and play an important role during early drug development, to elucidate the mechanism of action and to define the dose-response relationship. Several studies have evaluated the prognostic utility of hemodynamic variables after PAH-specific treatment initiation [Weatherald, J., et al 2018] [Tiede, H., et al 2013]. Invasive assessment of pulmonary vascular hemodynamics is a reliable indicator of treatment efficacy and reduction in PVR induced by PAH-specific therapies was shown to correlate with improved exercise capacity and improved clinical outcomes, supporting the use of PVR as the primary or secondary endpoint in Phase 2 studies of investigational PAH therapies as a signal for efficacy [Savarese, G., et al 2013]. The variables used for the calculation of PVR, as well as other hemodynamic variables, are obtained during RHC. The percent change from baseline in PVR at Week 12 will be used as the primary efficacy analysis for the Phase 2 Cohort Base Period.

6-Minute Walk Distance

Whereas hemodynamic measures play an important role during the early development of the drug, to elucidate the mechanism of action and to define the dose-response relationship in Phase 2 studies, Phase 3 efficacy study objectives focus on improving exercise capacity, ameliorating symptoms, reducing PAH-related morbidity, and improving QoL. Furthermore,

the use of an invasive hemodynamic measurement endpoint, acceptable in a smaller Phase 2 study, would be challenging in a larger sample Phase 3 study.

The 6MWT is a submaximal exercise test during which the distance walked (6MWD), oxygen saturation, systemic BP, heart rate, and the degree of dyspnea and fatigue (Borg CR10 Scale) are evaluated. The 6MWT provides an indirect estimate of aerobic capacity and correlates with pulmonary vascular hemodynamics. In particular, 6MWD is directly correlated with cardiac index increase and inversely correlated with PVR decrease [Savarese, G., et al 2013]. The use of the change in 6MWD as a primary endpoint in clinical trials is based on findings from studies which demonstrated that increases in 6MWD are associated with improved clinical outcomes among patients with PAH. A clinically meaningful 6MWD increase of 30 to 50 meters is considered predictive of better long-term prognosis and reflects positively in patient-important outcomes, such as HRQoL [Mathai, S. C., et al 2012] [Divers, C., et al 2017]. Change in 6MWD at Week 12 will be the primary efficacy endpoint of the Base Period of the Phase 3 Cohort. The change in 6MWD will be a secondary efficacy endpoint for the Phase 2 Cohort Base Period at Week 12 and for the Extension Period of Phase 3 Cohort at Week 24, and an exploratory endpoint for the Phase 2 Cohort Extension Period at Week 24.

Time to Clinical Worsening

TTCW is a composite endpoint of morbidity and mortality in a time-to-event analysis [Sitbon, O., et al 2015] [Pulido, T., et al 2013] [Galie, N., et al 2015]. The components of this composite endpoint include death, PAH-related hospitalization, and disease progression.

CCI

[redacted]

WHO Functional Class

The WHO classification of functional status is a measure of disease severity, based on a patient's description of their level of functioning and symptoms of disease in relation to their everyday activity. Patients are assigned 1 of 4 WHO-FC, dependent on limits of physical activity. As WHO-FC increases from I to IV, limits of physical activity increase. WHO-FC is a predictor of survival, both before and during treatment [Waxman, A. B. 2015], and remains an important part of the ongoing assessment of patients with PAH. Improvement in WHO-FC predicts survival independently of PAH cause or time of diagnosis. Furthermore, changes in

6MWD correlate with WHO-FC; increases in 6MWD are observed for those who show improvement in WHO-FC and decreases in 6MWD are observed for those who show worsening of WHO-FC [Divers, C., et al 2017]. As such, the effect of MK-5475 on WHO-FC will be assessed throughout both Phase 2 and Phase 3 Cohorts.

NT-proBNP

The most widely studied biomarker in PAH is brain (B-type) natriuretic peptide, secreted by ventricular cardiomyocytes in response to stretching. Serum levels of its N-terminal fragment (NT-proBNP) have been correlated with right ventricular function in PAH and high plasma levels of NT-proBNP with additional serial increases have a strong independent association with mortality [Lewis, R. A., et al 2020]. As such, the effect of MK-5475 on NT-proBNP serum level will be assessed during the Phase 2 Cohort up to Week 24 and throughout the Phase 3 Cohort.

4.2.1.2 Patient-Reported Outcomes

Physical/functional, emotional and social aspects of HRQoL are negatively impacted by PAH. The clinical definition of disease severity, including invasive and noninvasive measurements, does not capture the extensive realm of physical, emotional and psychosocial issues which affect PAH patients. PAH-targeted therapies produce a variable benefit in HRQoL, and some measures of HRQoL may also correlate with survival prognosis. The effect of treatment on PROs will be evaluated using a disease-specific QoL questionnaire, the LPH questionnaire. Interpretation of the magnitude of change in the LPH questionnaire (total and physical dimension) scores will be based on clinically meaningful thresholds estimated using the PGI-S and PGI-C questions. The PROs will be assessed during the Phase 2 Cohort Base Period and throughout the Phase 3 Cohort.

Living With Pulmonary Hypertension (LPH) Questionnaire

A 21-item, disease-specific tool, the LPH questionnaire will assess the impact of PAH on HRQoL. Adapted from the Minnesota Living with Heart Failure Questionnaire for use in patients with PAH, the LPH questionnaire has demonstrated strong content and psychometric validity [Bonner, N., et al 2013]. Participants are asked to recall how their PAH impacted their life during the past week. It takes approximately 5 minutes to complete. Response options are on a 6-point Likert-type scale ranging from 0 ‘No’ to 5 ’Very much’. A total (overall) score is calculated by summing the responses to all questions. A physical dimension score and an emotional dimension score can also be calculated [Bonner, N., et al 2013]. A higher score indicates that the participants are more affected by their medical condition (ie, have worse QoL). The total (overall) and physical dimension scores will be the key PRO endpoints in the study, as they have shown to be more responsive to change over time compared to the emotional score [Bonner, N., et al 2013].

Patient Global Impression of Change (PGI-C) and Severity (PGI-S)

Considering that minimally important difference thresholds indicating clinically significant changes or differences using anchor-based approaches for the LPH questionnaire have not yet been established, PGI-C and PGI-S questionnaires will be used to validate clinically

meaningful thresholds for the total and physical dimension scores from the LPH questionnaire in the study population.

The PGI-C will include 2 single-item questionnaires for assessing overall change in the disease and disease-related physical limitations, respectively, compared with the start of treatment. Each PGI-C questionnaire contains one question (1a) asking the participant to assess the degree of change compared to the start of the treatment using the following response options: “much better”, “a little better”, “no change”, “a little worse”, or “much worse”. A subsequent question (1b) then asks the participant to indicate whether he/she feels the degree of change (improvement or worsening) reported is important or not (yes/no).

The PGI-S will include 2 single-item questionnaires for assessing the current severity of disease and disease-related physical limitations, respectively, using the following response options: “None”, “Mild”, “Moderate”, “Severe”, or “Very severe.”

It is anticipated to take approximately 4 minutes to answer all PGI-C and PGI-S questions. Data from these questions will be used to provide anchors for estimating minimally important differences in the total and physical dimension scores from the LPH questionnaire.

4.2.1.3 Safety Endpoints

The safety data for MK-5475 to date is described in the IB. General safety and tolerability will be evaluated by clinical review of relevant parameters, including AEs, physical examinations, vital signs (ie, pulse rate, BP, temperature, arterial oxygen saturation, respiratory rate), PFTs, 12-lead ECG, laboratory safety tests (blood chemistry, hematology, anticoagulation tests, urinalysis, and urine pregnancy testing for all WOCBPs) at prespecified time points.

AEs associated with symptomatic hypotension, pulmonary hemorrhage, and hemoptysis are prespecified safety topics of interest (See Section 9.6.2.1).

All procedures will be conducted at the time points specified in the SoA. AEs will be recorded according to Section 8.4 and assessed as defined in Section 10.3.4.

4.2.1.4 Pharmacokinetic Endpoints

MK-5475 is an inhaled drug being developed for the management of PAH. As with any inhaled compound, PK exposures are primarily determined by lung burden, which cannot be directly measured. Therefore, the exploratory PK endpoints for this study will consist of assessments of systemic $AUC_{0\text{-}24}$ and C_{max}. Acknowledging the limitations of these data, they will be used for PK modeling to determine systemic exposures and to explore their relationship with pharmacodynamic endpoints and systemic hemodynamic measurements. PK samples will be collected from all participants as described in the SoA (Section 1.3) and Section 8.6.1.

4.2.1.5 Pharmacodynamic Endpoints

Reduction in PVR is being employed as the primary pharmacodynamic endpoint in the Phase 2 Cohort Base Period. This measurement directly reflects disease severity and response to therapy, as it incorporates measurements of pulmonary vasoconstriction (pulmonary artery pressure) and cardiac performance (cardiac output), in the context of a well-established relationship between PVR and the clinical endpoint of 6MWD.

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

The placebo control group is an essential arm in this study, as it supports the evaluation of the safety and efficacy of MK-5475 in adult participants with PAH. The efficacy profile of a

new agent is best characterized by comparison to placebo. Similarly, the safety profile of any drug is best characterized versus placebo, to facilitate an unbiased assessment of safety and tolerability. Participants receiving placebo during the study will continue to receive their background PAH-specific therapy.

4.3 Justification for Dose

Inhaled administration of pulmonary vasodilators represents an attractive alternative to oral or parenteral therapy, due to direct delivery to the desired site of action, potentially increasing pulmonary circulation selectivity and diminishing systemic side effects, such as hypotension. Inhaled MK-5475 has been evaluated in 5 completed and 3 ongoing Phase 1 clinical studies. Based on data from these studies, inhaled MK-5475 is generally well tolerated when administered as single or multiple inhaled doses of up to 380 µg in healthy adult participants, and when administered as a single inhaled dose of up to 480 µg in adult participants with PAH.

CCI [redacted]

The 3 dose levels are selected to provide data to characterize the exposure-response relationship that will inform dose selection for the Phase 3 Cohort of this study and future studies. CCI [redacted]

CCI [redacted]

The proposed doses will be administered once per day; the regimens were selected based on the following considerations:

- Data from Study PN002 at single nominal doses of 120, 240, and 360 µg in 23 PAH participants with RHC, showing mean peak reduction in PVR from baseline of approximately 26%, with no clear relationship between the magnitude of PVR reduction and the evaluated doses.

- Data from Study PN002 at single nominal doses of 120, 240, and 360 µg in 23 PAH participants with functional respiratory imaging, showing maximal pulmonary blood volume increase from baseline at 8 hours postdose of approximately 5%, with generally no clear relationship between pulmonary blood volume change and the evaluated doses, except that significant pulmonary blood volume increase was observed at 24 hours postdose only with the 360 µg dose.

- Based on in vitro data, MK-5475 dissociates slowly in the MK-5475-sGC complex, with an estimated CCI for the complex. In addition, a CCI

- Based on data from Study PN002 across dose levels evaluated with RHC (up to 360 µg), there was no evidence of decreasing systolic BP or increasing heart rate with increasing plasma MK-5475 concentration, supporting that a minimal systemic hemodynamic effect is expected following inhaled MK-5475 administration at doses up to 360 µg.

- Data from Study PN008 showed that MK-5475 plasma exposure following administration using the single-actuation inhaler at 380 µg and 100 µg was generally within the predefined PK comparability bounds of the multiple-actuation Phase 1 inhaler at the 360 (6 x 60) µg dose and the 120 (2 x 60) µg dose, respectively.

Based on all the considerations, the top dose selected for the Phase 2 Cohort of this study is 380 µg. A low dose of 32 µg is selected for evaluation in the Phase 2 Cohort, to expand the exposure-response dataset that can be used to inform dose selection for the Phase 3 Cohort and for future studies and to define a minimally efficacious dose. The 32 µg inhaler formulated for the Phase 2/3 study is the lowest feasible strength that can be developed using a conventional formulation. The mid dose of 100 µg is selected for evaluation in the Phase 2 Cohort based on minimal overlap of plasma exposures from that at the high dose at 380 µg and the low dose at 32 µg.

Participant response to the 3 different doses of MK-5475 (32 µg, 100 µg, and 380 µg) will be assessed in the Phase 2 Cohort Base Period. Of these, the treatment dose that shows the best efficacy, as assessed by pulmonary vascular hemodynamics, no evidence of clinically meaningful systemic hypotension, and overall favorable safety profile will be selected for the subsequent Phase 3 Cohort.

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.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

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.

Early study termination of both the Phase 2 and/or Phase 3 cohorts may be the result of the Sponsor's plan to modify or discontinue the development of MK-5475 in PAH.

5 STUDY POPULATION

Adult participants with PAH will be enrolled in this study. All I/E criteria apply to both Phase 2 and Phase 3 Cohorts, except where specified.

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. Has the following PAH groups, as defined by the Updated Clinical Classification of Pulmonary Hypertension (Nice, 2018) [Simonneau, G., et al 2019]:
   a. Group 1.1 Idiopathic PAH
   b. Group 1.2 Heritable PAH
   c. Group 1.3 Drug and toxin-induced PAH
   d. Group 1.4 PAH associated with:
      - Connective tissue disease
      - HIV infection
      - Simple repaired congenital systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) with persistent PH ≥1 year after surgical repair and with no clinically significant residual shunt.
2. Has a diagnosis of PAH performed as standard of care, per scientific guidelines, and documented by historical RHC at any time prior to Screening; if participant is postsurgical repair of systemic-to-pulmonary shunt, diagnostic RHC must have been performed at least 1 year after surgery.
3. Has an eligibility RHC, meeting all the following criteria:
   - mean pulmonary artery pressure (mPAP) ≥25 mmHg
   - PVR of ≥3 Wood units
   - PCWP or LVEDP ≤15 mmHg.

   For the Phase 2 Cohort, the eligibility RHC should be performed during Screening and will be centrally reviewed. A participant with RHC performed [CCI redacted] prior to Visit 1/Screening may have the RHC results submitted for central review and, if deemed

adequate, the RHC may count as baseline. In each case, the RHC should be performed after at [redacted].

For the Phase 3 Cohort, an RHC performed [redacted] prior to Visit 1/Screening may count for eligibility assessment. An RHC will be performed during Screening if an RHC performed [redacted] prior to Visit 1/Screening is not available.

4. Has WHO-FC symptoms Class II to IV.
5. Has two 6MWD measurements between 150 and 500 meters, 1 at Screening and 1 at Randomization. The relative difference between the 2 measurements (ie, absolute difference/mean) must be ≤15%. If the relative difference between the two 6MWD measurements is >15%, the Randomization 6MWT may be repeated after at least 4 hours. If the relative difference between the 2 Randomization 6MWD measurements is ≤15%, the participant can be randomized and the last 6MWD will be considered the baseline value.
6. Has stable concomitant background PAH-specific therapy [redacted] with any of the following agents:
    - an ERA and/or
    - a PDE5i and/or
    - an oral prostacyclin analogue or oral prostacyclin receptor agonist (eg, oral beraprost, oral treprostinil, oral selexipag), an intravenous prostacyclin analogue (eg, IV treprostinil, IV epoprostenol, IV iloprost) or a subcutaneous prostacyclin analogue (eg, SC treprostinil).
7. If on vasodilators other than PAH-specific therapy (including calcium channel blockers or L-arginine supplementation), has stable concomitant use (no change in dose for at least [redacted] to and over the duration of Screening).
8. If on calcium channel blockers, a participant from Groups 1.1, 1.2, and 1.3 must have a history of being a nonresponder to acute pulmonary vasoreactivity testing.
9. If on anticoagulants, has stable concomitant use (the same dosage of direct oral anticoagulants and in the same therapeutic range for vitamin K antagonists) for at [redacted] to and over the duration of Screening.

Demographics

10. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent.
11. Has a BMI between 18.5 kg/m^2 and 40 kg/m^2.
12. Is willing to comply with scheduled visits, treatment plan, laboratory tests, and/or other study procedures and study restrictions (see Section 5.3 for a complete summary of study restrictions).
13. Agrees to allowing site contact via phone or email for follow-up purposes.

Male Participants

14. There are no contraception requirements for male participants.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and:
  - Uses an acceptable contraceptive method, 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 14 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 WOCBPs 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 (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) 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 8.3.7.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a WOCBP with an early undetected pregnancy.

Informed Consent

16. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. A supplemental documented informed consent/assent is required for participation in the Phase 2 Cohort Extension Period. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

17. Sponsor concurrence on key criteria must be obtained before the participant is randomized into the study.

Notes:

- Procedures performed as standard of care for PAH (clinical assessments, diagnostic investigations) prior to and during Screening may be used to determine eligibility.

- The investigator must provide the required supporting documentation (eg, specific information about a participant's medical history and prior hemodynamic diagnosis of PAH) to the Sponsor, to support participant's eligibility for participation in the study.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has Group 2 PH, Group 3 PH (including PH associated with idiopathic interstitial pneumonia), Group 4 PH, or Group 5 PH according to the Updated Clinical Classification of Pulmonary Hypertension (Nice, 2018) [Simonneau, G., et al 2019].
2. Has Group 1.5 PAH, long-term responders to calcium channel blockers, defined by sustained clinical improvement to WHO-FC I or II and sustained hemodynamic improvement after at least 1 year on CCBs only.
3. Has Group 1.6 PAH, with overt features of venous/capillary (PVOD/PCH) involvement.
4. For participants with Group 1.4 HIV-associated PAH, has any of the following within 90 days prior to and for the duration of Screening:
    - concomitant active opportunistic infections;
    - plasma HIV-1 RNA ≥50 copies/mL or CD4+ T-cell count <200/mm^3;
    - changes in antiretroviral regimen.
5. Has evidence of more-than-mild obstructive lung disease on PFT at Screening with FEV1/FVC <70% and FEV1 <60% of predicted value after bronchodilator administration.
6. Has evidence of more-than-mild parenchymal lung disease based on medical history and chest imaging (eg, high-resolution CT), and/or restrictive lung disease with Total Lung Capacity (TLC) <60% of predicted on PFT at Screening.
7. Has evidence of more-than-mild OSA that is untreated. Participants with well-controlled, treated OSA are eligible.
8. Has evidence or history of left heart disease, including any of the following:
    - left ventricular ejection fraction (LVEF) ≤45%;

- moderate or severe left-sided valvular disease (aortic or mitral valve stenosis or regurgitation);
- Grade 3 and 4 left ventricular diastolic function on echocardiographic evaluation.

A historical transthoracic Doppler echocardiogram performed [redacted] prior to Screening is acceptable to demonstrate echocardiographic eligibility criteria. If a historical echocardiogram is not available, a transthoracic Doppler echocardiogram will be performed during Screening.

9. Has 3 or more of the following risk factors for heart failure with preserved ejection fraction:
   - BMI >30 kg/m^2;
   - history of essential systemic hypertension;
   - diabetes mellitus of any type;
   - history of coronary artery disease established by any of the following: history of stable angina, history of myocardial infarction, previous or planned percutaneous coronary intervention or coronary artery bypass graft, angiographic evidence of significant coronary artery disease (>70% stenosis in more than 1 vessel), positive stress test.
10. Has oxygen saturation measured by pulse oximetry (SpO_2) <90%, despite supplemental oxygen therapy. In case the accuracy of oxygen saturation measurement by pulse oximetry is unreliable, arterial blood gas sampling (SaO2) should be performed.
11. Had clinically unstable or acutely decompensated right heart failure within 30 days prior to and over the duration of Screening including, but not limited to, hospitalization or emergency room visit for acute decompensated heart failure.
12. Has seated systolic BP >160 mmHg or <90 mmHg or seated diastolic BP >100 mmHg.
13. Has significant chronic renal insufficiency, as defined by eGFR <30 mL/min/1.73 m^2 (calculated using the MDRD equation) or by ongoing dialytic support.
14. Has evidence of chronic liver disease (ie, Child-Pugh B or C), portal hypertension, cirrhosis, or hepatic laboratory abnormalities (ALT or AST ≥3 times the ULN or total bilirubin ≥2 x ULN).
15. Is included in a cardiopulmonary rehabilitation program initiated within 90 days prior to Screening or is planning to initiate cardiopulmonary rehabilitation during the study.
16. Has acute or chronic impairment(s) (other than dyspnea), limiting the ability to perform 6MWT.
17. Is a current smoker or currently uses electronic cigarettes (vapes).
18. Is unable to correctly use the DPI prior to randomization due to, but not limited to, cognitive impairment or physical limitations.

19. Has other severe acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or that would confound study analysis or impair study participation or cooperation.
20. Has a history of cancer (malignancy). Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated, with appropriate follow-up, and therefore unlikely to recur for the duration of the study, in the opinion of the investigator (eg, malignancies which have been successfully treated ≥5 years prior to Screening).
21. Has a known hypersensitivity to any of the ingredients or excipients of the IMP.
22. At the time of signing the informed consent, is a user of illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence.
23. Has a known psychiatric or any other cognitive disorder that would, in the opinion of the investigator, interfere with the participant's ability to cooperate with the requirements of the study.
24. Is a WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study intervention (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

25. Has used intravenous inotropes including, but not limited to levosimendan, dopamine, dobutamine, epinephrine, norepinephrine, noradrenaline or milrinone within 30 days prior to and over the duration of Screening.
26. Has concomitant use of inhaled prostacyclin analogues (eg, inhaled iloprost, inhaled epoprostenol or inhaled treprostinil), inhaled NO, or oral sGC modulators (eg, riociguat, vericiguat), or has used these medications within 90 days prior to and over the duration of Screening.

Prior/Concurrent Clinical Study Experience

27. Has participated in another investigational study CCI [redacted] prior to Screening. This window will be derived from the date of the last dose of study medication taken in the previous study. Participants enrolled in observational studies may be included and will be reviewed on a case-by-case basis for approval by the Sponsor.
28. For Phase 2 Cohort Extension Period: has not completed Visit 6/Week 12 study assessments, as listed in the SoA.
29. For Phase 2 Cohort Extension Period: has discontinued study intervention or completed the Phase 2 Cohort Base Period before Amendment 01 was approved and the Extension Period became available.
30. For Phase 3 Cohort enrollment: is currently participating in, has prematurely discontinued, or has completed the Phase 2 Cohort.

Other Exclusions

31. 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.

5.3 Lifestyle Considerations

No restrictions are required.

5.3.1 Caffeine, Alcohol, and Tobacco Restrictions

No caffeine or alcohol restrictions are required. Use of tobacco products will not be allowed for the duration of the study. Tobacco use will be assessed as indicated in the SoA (Section 1.3).

5.3.2 Activity Restrictions

Participants will be advised to abstain from strenuous exercise before each study visit requiring blood collection for clinical laboratory tests, as NT-proBNP may be affected by recent exercise. Similarly, NT-proBNP plasma samples must be collected prior to the 6MWT.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized 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 as required. 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 are outlined in Table 2.

Table 2 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
Phase 2 Cohort Group 1	Experimental	MK-5475	Drug	Powder	380 µg	380 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and for ~40 months Extension Period	Test Product	IMP	Sponsor
Phase 2 Cohort Group 2	Experimental	MK-5475	Drug	Powder	100 µg	100 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and for ~40 months Extension Period	Test Product	IMP	Sponsor
Phase 2 Cohort Group 3	Experimental	MK-5475	Drug	Powder	32 µg	32 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and for ~40 months Extension Period	Test Product	IMP	Sponsor
Phase 2 Cohort Group 4	Placebo Comparator	Placebo	Drug	Powder	0 µg	0 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period	Placebo	IMP	Sponsor
Phase 2 Cohort Group 4a (before Phase 3 dose selection)	Experimental	MK-5475	Drug	Powder	380 µg	380 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product	IMP	Sponsor
Phase 2 Cohort Group 4b (before Phase 3 dose selection)	Experimental	MK-5475	Drug	Powder	100 µg	100 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product	IMP	Sponsor
Phase 2 Cohort Group 4c (before Phase 3 dose selection)	Experimental	MK-5475	Drug	Powder	32 µg	32 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product	IMP	Sponsor

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
Phase 2 Cohort Group 4a, 4b, & 4c (after Phase 3 dose selection)	Experimental	MK-5475	Drug	Powder	380 µg OR 100 µg OR 32 µg	380 µg OR 100 µg OR 32 µg	Inhalation	Oral inhalation once daily for ~40 months Extension Period	Test Product	IMP	Sponsor
Phase 3 Cohort Group 1	Experimental	MK-5475	Drug	Powder	380 µg OR 100 µg OR 32 µg	380 µg OR 100 µg OR 32 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and up to 60-month Extension Period	Test Product	IMP	Sponsor
Phase 3 Cohort Group 2	Placebo Comparator	Placebo	Drug	Powder	0 µg	0 µg	Inhalation	Oral inhalation once daily for 12 weeks Base Period and up to 60-month Extension Period	Placebo	IMP	Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.
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.

All supplies indicated in Table 2 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.

All placebos were created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. 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.

Study intervention may be dispensed via home delivery to the participant if allowed per local guidelines. Home delivery should only be used in exceptional circumstances (eg, DPI malfunction) and after consultation with the Sponsor. Only authorized site staff are permitted to organize the shipment of the study intervention from the site to the participant. Refer to the Study Operations Manual for procedures to ensure participant data privacy, ensure temperature control, manage temperature excursions, maintain full traceability, return of used and unused study intervention, and preserve the study blind.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. This study has 2 parts, a Phase 2 dose selection cohort and a Phase 3 confirmatory cohort. There are 4 study intervention arms in the Phase 2 Cohort Base Period, 3 study intervention arms in the Phase 2 Cohort Extension Period, and 2 study intervention arms in the Phase 3 Cohort. Participants in the Phase 2 Cohort Base Period will be assigned randomly in a 1:1:1:1 ratio to 1 of 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) or a matching placebo study intervention, respectively. In the Phase 2 Cohort Extension Period, the participants who received placebo during the Base Period will initially be assigned randomly in a 1:1:1 ratio to 1 of the 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) and will be given new randomization numbers. The participants who received MK-5475 during the Base Period will initially receive the same MK-5475 doses in the Extension Period and will be assigned new randomization numbers, to maintain study blinding.

After selection of the MK-5475 dose for Phase 3, the 3 MK-5475 dose groups in the Phase 2 Cohort Extension Period will be collapsed into a single dose group for the remainder of the Phase 2 Cohort Extension Period.

Participants in the Phase 3 Cohort will be assigned randomly in a 1:1 ratio to the MK-5475 dose selected in the Phase 2 Cohort Base Period or matching placebo study intervention.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. WHO-FC at the time of randomization (Class II or Class III/IV).

CCI [redacted]

6.3.3 Blinding

CCI [redacted]

CCI [redacted]

Selected members of the Sponsor study team and management will be unblinded to data analysis results from the Phase 2 Cohort Base Period and the Phase 3 Cohort Base Period, to evaluate the efficacy and safety profile of MK-5475. For the Phase 2 Cohort Extension Period and the Phase 3 Cohort Extension Period, separate blinded Sponsor study teams will monitor the ongoing study (Section 9.7). Individuals directly involved with study conduct will not be unblinded.

Blinding to intervention assignment will be maintained at all investigational sites. For both Phase 2 Cohort Base Period and Phase 3 Cohort Base Period, the data analysis results will not be shared with the investigators before the completion of each respective cohort of the study, inclusive of each cohort's Extension Period.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment for 3 consecutive days OR compliance ≤90% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Records of study intervention compliance for each participant will be kept during the study. The investigator or qualified designees will review study intervention compliance during each site visit and at the completion of the study.

Participants are expected to self-administer an inhaled dose every morning and record each administration (ie, date and time) in their medication diary. Compliance assessments will be based on participant reporting (medication diary), corroborated with inspection of the returned DPIs during the site visits. Data in the medication diary will be documented in the source documents and the eCRF. Compliance calculations will be defined in the sSAP. Issues with compliance should be discussed with the participant and addressed as deemed appropriate by the investigator.

A record of the number of MK-5475 or placebo DPIs dispensed to and used by each participant must be maintained and reconciled with study intervention and compliance records. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Intervention start and stop dates, including dates for intervention delays will also be recorded in the eCRF.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. 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 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 OTC 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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Listed below are specific examples of prohibited concomitant therapy:

- Any inhaled prostacyclin or prostacyclin analogue (eg, inhaled iloprost, inhaled epoprostenol, or inhaled treprostinil)
- Any sGC stimulators (eg, riociguat, vericiguat)
- Inhaled NO
- Inhaled nitrates (eg, amyl nitrite)

Note: A medication should not be stopped for the purpose of meeting study inclusion criteria. The decision to stop/interrupt medication is based on investigator's judgment.

Long-term chronic oxygen therapy use is allowed. Oxygen should be given at the standard flow rate used at home at each assessment throughout the study, including the administration of 6MWT. Note: the 6MWT should be performed with the same oxygen equipment used at home.

6.5.1 Rescue Medications and Supportive Care

CRUs will be staffed with medically trained personnel with appropriate access to full-service acute care hospitals to facilitate rapid institution of medical intervention.

6.6 Dose Modification

Participants will be randomized to a fixed-dose regimen of MK-5475 or matching placebo for the duration of Phase 2 Cohort Base Period (380 µg, 100 µg, 32 µg, or placebo) and Phase 3 Cohort (the MK-5475 dose selected in the Phase 2 Cohort Base Period or placebo). In the Phase 2 Cohort Extension Period, the participants who received placebo during the Base Period will initially be assigned randomly in a 1:1:1 ratio to 1 of the 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) and will be given new randomization numbers. Participants who received MK-5475 during the Base Period will initially receive the same

MK-5475 doses in the Extension Period and will be assigned new randomization numbers, to maintain the study blinding.

After selection of the MK-5475 dose for Phase 3, the 3 MK-5475 dose groups in the Phase 2 Cohort Extension Period will be collapsed into a single dose group for the remainder of the Phase 2 Cohort Extension Period.

No other dose modifications are permitted.

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

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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 8.11.5 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's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a change in medical condition, change in medical treatment 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 pregnancy.
- The participant fails to comply with the dosing, evaluations, or other requirements of the study, despite investigator's repeated efforts to reinforce compliance.
- An individual participant reports an SAE considered related to the study intervention by the investigator.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

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 specific details regarding withdrawal from FBR, 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 providing documented informed consent 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.
- Clinic in-person visit may be replaced by telephone, video, or home visit using site staff or a nursing service, if circumstances do not support an in-person site visit and after consultation with the Sponsor .
- The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 500 mL (**Table 11**, **Table 12**).
- 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 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

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.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all his/her questions, and obtain documented informed consent. before performing any procedure related to FBR. A copy of the informed consent. will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All I/E criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study. The Sponsor will review participant's key I/E criteria prior to randomization into the study. The investigator will make the final decision to include a participant in 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 randomization, site personnel will add the treatment/randomization number to the participant

identification card. For the Phase 2 Cohort Extension Period, each participant who completes the Base Period, satisfies the eligibility criteria, and provides documented informed consent will be given a new participant identification card with their new Extension Period treatment/randomization number.

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

Participants' medical history, including medical conditions, diagnostic results, allergies, and relevant physical examination findings, will be obtained by the investigator or qualified designee. The site must provide the required supporting documentation (specific information about a participant's medical history and prior hemodynamic diagnosis of PAH) to support participant's eligibility for participation in the study.

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 90 days before starting the study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication taken by the participant during the study on the appropriate eCRF (See Sections 1.3 and 6.5).

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number for the cohort for which they are screened, that will be used to identify the participant for all procedures that occur prior to randomization in that cohort. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.2.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number, in a numerical sequence specific for each cohort (Section 8.11.3), identifies the participant for all procedures occurring within the cohort after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

In the Phase 2 Cohort, each participant who completes the Base Period and provides documented informed consent for the Extension Period will be assigned a new treatment/randomization number for the Extension Period.

In the Phase 3 Cohort, a single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

The first dose of study intervention will be administered at the study site at Visit 2 . Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately the same time each day.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered once daily, in the morning, at approximately the same time throughout the duration of the study.

8.1.8.2 Dry Powder Inhaler Use Training

Participants will be trained by site staff on the proper use of the DPI.

At Visit 1/Screening

1. Participants will receive training from the site staff and will review instructions for DPI use.

2. Participants will be expected to administer a placebo dose under the guidance of the site staff.

3. Participants unable to correctly use the DPI (after instruction by the site staff) at this visit due to, but not limited to, physical limitations or cognitive impairment, are not eligible for study enrollment.

At Visit 2/Randomization

1. Site staff will review the process for DPI use with the participant.

2. The site will document that retraining occurred.

3. Participants will administer the double-blind study intervention (MK-5475 or matching placebo) in the presence of the site staff.

At Visit 3/Day 7 (+ 2days) – Telephone visit

The site staff will contact the participant to assess whether the participant is experiencing DPI performance issues. If the participant is experiencing DPI performance issues, site staff will re-review the process for DPI use with the participant and/or caregiver. An unscheduled visit will occur if the issues cannot be addressed via telephone.

8.1.8.3 Witnessed Dosing

Administration of study intervention will be witnessed by the investigator and/or qualified study staff at the randomization visit.

8.1.8.4 Dispense Double-blind Study Intervention

For both cohorts, the double-blind study intervention for the Base Period (MK-5475 or matching placebo) will be dispensed to participants at Visit 2/Day 1, Visit 4/Week 4, and Visit 5/Week 8. Study intervention for the Extension Period of Phase 2 Cohort (MK-5475 380 µg, 100 µg, or 32 µg) will be dispensed starting at Visit 6 and every 6 weeks thereafter, until the end of the Extension Period. For participants already enrolled in the Phase 2 Cohort Extension Period, the transition to an every 6-week visit frequency will occur at Week 24 or at the next visit that falls on a 12-week interval (eg, Week 36, 48, 60. and every 12 weeks thereafter through study completion). Study intervention for the Extension Period of Phase 3 Cohort (MK-5475 or matching placebo) will be dispensed starting at Visit 6 and every 12 weeks thereafter, until the end of the Extension Period.

Defective DPIs will be replaced by the site as needed. Refer to the Study Operations Manual for further details.

8.1.8.5 Dispense/Review Participant Dosing Diary

Participants will receive paper-based dosing diaries as specified in the SoA (Section 1.3) to document administering the study intervention and to include any comments related to the DPI use. Participants should bring their completed diary to all study visits. Site personnel should review the diaries at each study visit to monitor compliance and review for any potential AEs from the comments entered.

8.1.8.6 Investigational Product Compliance and Accountability

Adherence to study intervention will be assessed by participant report during the double-blind treatment period as described in the SoA (Section 1.3). Every effort will be made to maintain adherence as close to 100% as possible. Interruptions from the protocol-specified treatment plan for 3 consecutive days or compliance ≤90% (defined as 3 or more missed doses of study intervention within 30 days, between scheduled study visits) requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Refer to Section 6.4 for further details on study intervention compliance.

8.1.8.7 Telephone Contact Between Study Visits

Unscheduled telephone contact between study visits may occur as needed. Unscheduled visit(s) may be performed as needed, or if the participant requires retraining on study intervention administration.

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 (including vital status assessment at the end of the study) as outlined in the SoA and Section 8.11.5, to minimize missing outcome data.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final visit for that study period 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 and additional Visit Requirements (refer to SoA, Section 1.3).

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically

qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

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.

All measuring instruments used for hemodynamic measurements must be calibrated according to the hospital standards and/or manufacturer's instructions. Additional details are provided in the RHC Guidance Document.

The spirometer is to be calibrated according to ATS/ERS technical standards [Graham, B. L., et al 2019] and the device manual, on the days when spirometry is performed. It is preferred that the calibration equipment used to calibrate the spirometer be subjected to a validated calibration, according to manufacturer's specifications.

8.2 Efficacy Assessments

Refer to the SoAs for the planned time points of these assessments.

8.2.1 Right Heart Catheterization

Pulmonary vascular hemodynamic measurements are necessary to confirm study participants' eligibility in the Phase 2 and Phase 3 Cohorts and for primary and secondary endpoint analyses in Phase 2 Cohort (Section 1.3). RHC using a pulmonary artery floating catheter (eg, Swan-Ganz catheter) will be performed for pulmonary vascular hemodynamic assessment, if not available within the required time frame for both cohorts (Section 5.1).

For Phase 2 Cohort, the Week 12 RHC will be performed within 4 to 8 hours after the last morning dose of study intervention. Participants who withdraw early from the study will be encouraged to complete the RHC at the Week 12 visit.

Both RHC procedures will include complete hemodynamic profile, cardiac output, arterial oxygen saturation (SaO_2, %), mixed venous oxygen saturation (SvO_2, %), hemoglobin, systemic BP (noninvasive), heart rate, and body weight. If, despite all efforts, PCWP is deemed unreliable, left heart catheterization must be performed to measure LVEDP. Standards for RHC performance and invasive pressure measurement are described in the RHC Guidance Document. To guarantee standardized conditions for RHC and hemodynamic measurements across participating study centers, investigators must follow the principles defined in the RHC Guidance Document.

All RHC measurements should be recorded on source documents and entered into the respective eCRF. RHC pressure tracings will be labeled in accordance with the blinding process described in the RHC Guidance Document and submitted for central review.

8.2.2 6-Minute Walk Test

The 6MWT (including Borg CR10 Scale rating) will be performed at Screening, Randomization, Week 12, and Week 24 in the Phase 2 Cohort, and at all site visits in the Phase 3 Cohort.

For study enrollment, the Screening and the Randomization 6MWD must be between 150 and 500 meters, with the 2 values within ± 15% of each other. If the relative difference between the two 6MWD measurements is >15%, the Randomization 6MWT may be repeated after at least 4 hours. If the relative difference between the 2 Randomization 6MWD measurements is ≤15%, the participant can be randomized and the last 6MWT (including Borg Scale assessment) will be considered the baseline test.

The 6MWT will be performed in accordance with the official European Respiratory Society/American Thoracic Society technical standard for field walking tests in chronic respiratory disease[Holland, A. E., et al 2014]. Technicians performing the test will be trained according to these published procedures [Holland, A. E., et al 2014]. Participants will refrain from physical exercise for a minimum of 2 hours prior to testing. The 6MWT will be performed preferably at approximately the same time of day at each visit, to minimize

intraday variability, and after the NT-proBNP blood sample is obtained. Long-term chronic oxygen therapy use is allowed during 6MWT. Oxygen should be kept at the standard flow rate and with the same equipment used at home. Sites will be provided with detailed instructions in the Study Operations Manual.

8.2.3 WHO Functional Class

The WHO-FC will be assessed at every site visit in the Phase 2 Cohort Base Period, every 12 weeks in the Phase 2 Cohort Extension Period, and throughout the Phase 3 Cohort. Participants will be assigned 1 of 4 functional classes, according to the modified WHO classification of functional status of patients with pulmonary hypertension [Stuart, R. 1998]:

Class I – Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or near syncope.

Class II – Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or near syncope.

Class III – Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or near syncope.

Class IV – Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by any physical activity.

PAH participants who have experienced a syncopal episode should be assigned to WHO-FC IV.

8.2.4 NT-proBNP

Blood samples for assessment of NT-proBNP will be collected as specified in the SoA for Phase 2 Cohort (at baseline [Visit 2], Week 12, and Week 24) and in the SoA for Phase 3 Cohort (at baseline [Visit 2], Visit 6 [Week 12], and every other visit thereafter [every 24 weeks]). As NT-proBNP may be affected by recent exercise, participants will be advised to abstain from exercise before each study visit requiring blood collection for clinical laboratory tests. Similarly, NT-proBNP plasma samples must be taken prior to the 6MWT. This sample should be collected with the participant in the same position at each visit (eg, sitting or semi-recumbent).

8.2.5 Patient-reported Outcomes

All PRO questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: LPH, PGI-S (physical limitations), PGI-S (overall), PGI-C (physical limitations) and PGI-C (overall). The questionnaires should be administered according to the SoAs (Section 1.3). It is best practice and strongly

recommended that ePROs are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. To that extent, *the PRO administration should be the first procedure performed during each site visit*. If the visit is expected to extend over multiple days (Visit 2/Randomization and/or Visit 6), the PROs will be administered as the first procedure on the first day of that visit.

If a participant discontinues the study intervention or withdraws consent during the Base Period of either cohort, Visit 6/Week 12 PROs will be administered. If a Phase 3 Cohort participant prematurely discontinues study intervention and agrees to be followed for the remaining study duration, he/she will be asked to complete the PROs up to the final visit, according to the SoA (Section 1.3.2). If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed. In the eventuality that electronic administration of the PROs is not available, study teams can use the paper back-up process, if allowed per the Site Monitoring Plan (see Study Operations Manual).

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[redacted]

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,

including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8 (**Table 11**, **Table 12**).

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

8.3.1 Physical Examinations

Complete and directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard and as outlined in the SoAs (Section 1.3). Height and weight will be measured and recorded. The complete physical examinations will, at a minimum, include assessments of general appearance, skin, lymphatic system, eyes, ears, nose, throat, CV system, respiratory system, abdomen/gastrointestinal system, musculoskeletal system, and neurological system. The directed physical examinations will, at a minimum, include assessment of the cardiovascular and respiratory systems. Other body systems may be evaluated with either type of examination. Abnormalities considered clinically significant should be reported as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses. A physical examination (complete or directed) may be performed at any unscheduled visit if deemed necessary by the investigator or medically qualified designee.

8.3.2 Body Weight

Body weight (kg) will be measured using a standardized scale at each of the predefined time points outlined in SoAs (Section 1.3). Participant will be weighed wearing light clothing and no shoes. Body weight should be reported with precision to 1 decimal place (eg, 0.1 kg).

8.3.3 Vital Signs

Oral, axillar, tympanic, or temporal artery temperature, pulse rate, pulse oximetry, respiratory rate, and systolic and diastolic BP will be assessed. The same method should be used for all measurements across visits.

BP and pulse measurements will be assessed in seated position with an automated device. Manual techniques will be used only if an automated device is not available.

Vital signs will be measured in a sitting position after 5 minutes of rest.

Detailed information regarding BP and heart rate monitoring is contained in the Study Operations Manual. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs or ECIs.

8.3.4 Pulmonary Function Testing and DLCO

Pulmonary function testing and single-breath carbon monoxide uptake should be performed in accordance with the technical standards established by the ATS/ERS [Miller, M. R., et al 2005] [Graham, B. L., et al 2019] [Graham, B. L., et al 2017]. PFT includes spirometry and body plethysmography. Spirometry will only be reassessed after bronchodilation

responsiveness testing in participants who do not meet the PFT inclusion criteria of either FEV1/FVC <70% or FEV1 <60% of predicted value.

FVC, FEV1, FEV1/FVC ratio, FEF25-75, PEF, TLC and DLCO will be recorded at Visit 1/Screening and Visit 6, in both Phase 2 and Phase 3 Cohorts, as outlined in the SoA (Section 1.3). The largest FEV1 and the largest FVC, as well as their ratio (FEV1/FVC), should be reported, even if they were not recorded during the same measurement.

The spirometer is to be calibrated according to the ATS/ERS technical standards and the device manual. Spirometry procedural details not covered by the ATS/ERS technical standards will follow site SOPs and manufacturer's specifications. Spirometry procedural details not covered by the ATS/ERS technical standards document will follow site SOPs and manufacturer's specifications. Every effort should be made to use the same spirometer for each participant and throughout the study.

Report data from each PFT must be available in the source documents.

8.3.5 Electrocardiograms

A standard supine 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position and before the assessment of BP and heart rate as well as before blood collection.

All ECGs performed should be reviewed at the investigative site for participant safety monitoring. The investigator is responsible for retaining all copies of the ECG reports.

8.3.6 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 SoAs (Section 1.3).

- 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 14 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.
- Serum hCG testing will be performed in female participants where a pregnancy is suspected.

8.3.7 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at all site visits, as specified in the SoA (Section 1.3).
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
  - 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.

Refer to Appendix 7 for country-specific requirements.

8.3.8 Vital Status Assessment

Vital status is collected for all participants at the time points specified in the SoA and at the Final Phone Contact. This assessment can also be performed at any point in the trial when vital status is in question, unless the participant has specifically withdrawn consent for further follow-up. The investigator should explore all possible options to contact the participant, per local regulations. The site must document all attempts to contact the participant in source documents.

8.3.9 AE Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs, as specified in the SoAs (Section 1.3), and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period (Section 10.3.4).

The criteria for discontinuation of study intervention for individual participants are in Section 7.1.

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 randomization, must be reported by the investigator, 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 randomization through 14 days 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 Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time 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	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion	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 Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Report if participant has been exposed to any protocol-specified intervention. 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
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Not applicable	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 randomized 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.

Refer to Appendix 7 for country-specific 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

Disease-related events and or disease-related outcomes not qualifying as AEs or SAEs are not applicable to this study.

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. Symptomatic hypotension, defined as a physical finding of systolic BP <90 mmHg or systolic BP decrease of more than 40 mmHg below the participant's baseline which is accompanied by at least 1 symptom, such as presyncope, dizziness, mental status changes, etc. (reported by participant or otherwise witnessed).
2. Pulmonary hemorrhage
3. Hemoptysis
4. Potential DILI events defined as an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon 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).

8.4.8 Medical Device and Drug–Device Combination Products – PQCs/Malfunctions

The method of documenting and reporting of such events (ie, complaints associated with medical devices including PQCs/malfunctions) will occur as below and in Appendix 4.

To fulfill regulatory reporting obligations worldwide, medical device information associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines.

PQCs/malfunctions, including those that involve a participant or any user/associated person, must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

During the course of the study, a participant may provide feedback related to the device or devicelike features of a drug delivery system. This "customer feedback" is defined as a report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark that may suggest an improvement in the functionality or quality of a medical device or devicelike features of a drug delivery system). All reports of customer feedback must be reported to the Sponsor within 14 calendar days of awareness. Sponsor contact information can be found in the Investigator Trial File Binder (or equivalent).

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the AE and the medical device or device constituent of combination product.

8.5 Treatment of Overdose

In this study, an overdose will be defined as any dose of study intervention administered as part of the study exceeding the dose prescribed by the protocol (ie, >1 inhalation/day). It is up to the investigator to decide on the treatment of an overdose, based on the clinical evaluation of the participant, in consultation with the Sponsor.

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

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK will be collaboratively determined by the appropriate departments (Department of Quantitative Pharmacology and Pharmacometrics and the appropriate department within Clinical Research) in the Sponsor's organization. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-5475

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Operations/Laboratory Manual.

PK samples will be collected from all randomized participants according to the PK sampling timelines outlined in the SoA (Section 1.3). At all study visits during the double-blind treatment period where a PK sample will be collected, the participant must ensure that their MK-5475/matching placebo dose aligns with the clinic visit time and PK sample collection. The date and time of the last MK-5475/matching placebo dose taken before PK sample collection will be recorded. The date and time of each PK sample will also be recorded. The PK sampling will occur after the administration of study intervention, as follows:

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For participants who prematurely discontinue study intervention, a PK sample should be collected during the discontinuation visit. For the PK samples collected during the discontinuation visit, the date and time of the last MK-5475/matching placebo dose taken before sample collection, as well as the date and time of PK sample collection will be recorded.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in the Operations/Laboratory Manual.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research will be collected from all participants as specified in the SoA:

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be collected for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled visit, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research
- Serum for future research
- Plasma for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

Not applicable.

8.11 Visit Requirements

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

If a participant misses a scheduled visit and the study site staff are unable to reach the participant, the site will contact the ‘external contact person’ identified by the participant during Screening (see Section 1.3), to collect participant’s vital status (Section 8.3.8).

8.11.1 Scheduling the Visits

For both Phase 2 and Phase 3 Cohorts, the screening RHC (if applicable) will be scheduled in advance at the initial screening visit. For the Phase 2 Cohort, the Visit 6 RHC will be scheduled in advance at Visit 2/Randomization.

During the double-blind treatment period, at the end of each study visit, the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule (Section 1.3). For both Phase 2 and Phase 3 Cohorts, Visit 3/ Day 7 should be scheduled within + 2 days, Visit 4/Week 4 and Visit 5/Week 8 within ± 5 days, and Visit 6/Week 12 within + 7 days. During the Phase 2 Cohort Extension Period, all visits (except Final Visit) should be scheduled within ± 5 days; during the Phase 3 Cohort Extension Period, all visits (except Final Visit) should be scheduled within ± 7 days. If unavoidable, and after consultation with the Sponsor, a visit may be scheduled at a time outside of this recommended range, but the schedule for subsequent visits must be adjusted so that the total duration of the double-blind treatment period is as close as possible to 12 weeks for the Base Period in both cohorts.

Visits should be scheduled relative to the date of Visit 2/ Day 1. If a visit is scheduled at a time other than the protocol designated time, careful consideration must be given to the amount of investigational product the participant has available.

Study sites should update IRT at each scheduled study visit (except screening visits) for purposes of enrollment tracking.

8.11.2 Screening

Over a period of approximately 28 days (Visit 1/Screening), consented potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. The screening period may be extended, under special circumstances (eg, scheduling issues), with the explicit approval of the Sponsor Clinical Director. If a participant fails to meet the study entry criteria during Visit 1/Screening, procedures (***except RHC***) may be repeated once, based on investigator judgment and after consultation with the Sponsor. Participants may only be rescreened once. Unless otherwise indicated, all screening procedures apply for both Phase 2 and Phase 3 Cohort participants.

Participants will be assigned unique screening numbers, specific for each cohort. The Screening procedures will be performed such that the RHC (if required) is performed last, whenever possible. Determination of eligibility will be assessed based on the demographic, disease diagnostic, hemodynamic, functional, echocardiographic, pulmonary function, and prior/concomitant therapy criteria outlined in Sections 5.1 and 5.2. Potential participants will also be assessed for the availability of adequate historical PAH diagnostic data (RHC and echocardiography).

RHC

- For Phase 2 Cohort, participants [redacted] will have the RHC results reviewed by a blinded independent central reviewer.
- For Phase 3 Cohort, participants who have had an RHC performed [redacted] prior to Visit 1/Screening will have the RHC results reviewed by the investigator.

If an adequate historical RHC is not available, an eligibility RHC will be performed during Screening, preferably after the participant has satisfied all other criteria specified in Sections 5.1 and 5.2.

If the results of an adequate RHC do not meet study eligibility criteria, the participant will be screen failed.

If the RHC results meet study eligibility criteria AND all the other entry criteria are met, the participant will progress to Visit 2/Randomization (both cohorts) and the RHC results will count as baseline (Phase 2 Cohort).

Echocardiography

- Participants who had a transthoracic Doppler echocardiogram performed [redacted] prior to Visit 1/Screening will have the test results reviewed by the investigator to demonstrate that related study eligibility criteria are met. If performed outside the 180-day window or not available for review, the procedure will be performed during Screening.

Considering the documented overlapping and multifactorial PH etiologies, accurate PAH differential diagnosis remains a challenge and requires various invasive and noninvasive investigations. Simultaneously, pitfalls in interpretation of pulmonary vascular hemodynamics can also complicate the differentiation of PAH from other PH disorders and contribute to PAH misdiagnosis. The precise identification of PAH clinical and hemodynamic phenotype in the overall PH population is fundamental to safe study conduct, given that pharmacological strategies being developed for treatment of PAH may be deleterious to non-PAH PH patients. As such, a Sponsor Concurrence process is warranted to ensure that key I/E criteria for the study are met and that the selected population accurately reflects the PAH clinical and hemodynamic profile to be studied (see “Sponsor Concurrence Process” section in the Study Operations Manual).

The sites are responsible for entering participant data in the central database. This data will be reviewed by the Sponsor on an ongoing basis. Eligible participants will proceed to Visit 2/Randomization following completion of all screening procedures and Sponsor review and concurrence of key I/E criteria.

After completion of all screening procedures as specified in the SoA (Section 1.3), eligible participants will be provided instruction and be witnessed in the administration of the investigational product using the placebo DPI. Participants will be re-instructed on

appropriate inhalation administration technique as needed. See Section 8.1.8.2 for details. Participants who have completed or prematurely discontinued the Phase 2 Cohort are not eligible to participate in the Phase 3 Cohort.

8.11.3 Randomization

At Visit 2/Randomization (Day 1), eligibility for study participation will be reassessed to determine if participants continue to meet the I/E criteria and if, between Screening and Randomization, they experienced events that would exclude them for participating in the study, eg, acutely decompensated right heart failure or changes in PAH-specific therapy.

Participants who meet all study entry criteria will be randomized as follows:

1. Phase 2 Cohort

Participants in the Phase 2 Cohort Base Period will be assigned randomly in a 1:1:1:1 ratio to 1 of 3 doses of MK-5475 (380 µg, 100 µg, or 32 µg) or a matching placebo, respectively, and will each be assigned a unique, cohort-specific randomization number.

At Visit 6 (Week 12), the participants who complete the Phase 2 Cohort Base Period, Visit 6 assessments (***including RHC***), and provide documented informed consent for the Extension Period will be re-randomized in the Extension Period according to their Base Period treatment assignment and will receive another unique, cohort-specific randomization number. The re-randomization probability is shown in Table 4.

Table 4 Participant Re-randomization Probability in the Phase 2 Cohort Extension Period

Phase 2 Base Period Treatment Group	Phase 2 Extension Period Assigned Treatment Group	Re-randomization Probability
Placebo	MK-5475 32 µg	1/3
Placebo	MK-5475 100 µg	1/3
Placebo	MK-5475 380 µg	1/3
MK-5475 32 µg	MK-5475 32 µg	1
MK-5475 100 µg	MK-5475 100 µg	1
MK-5475 380 µg	MK-5475 380 µg	1

2. Phase 3 Cohort

Participants in Phase 3 Cohort will be assigned randomly in a 1:1 ratio to MK-5475 or matching placebo and will each be assigned a unique, cohort-specific randomization number.

For both cohorts, at Visit 2/Randomization, blood samples for PK analysis should be collected **before** study intervention administration **and after** dosing (Section 8.6.1). Study intervention will be administered by participants as a witnessed dose at the study site.

Visit 2 procedures should preferably be completed in 1 day. In special circumstances (eg, scheduling issues, repeat 6MWT), Visit 2 may be extended to 2 days.

8.11.4 Treatment Period

Visit requirements are outlined in the SoAs (Section 1.3). Specific procedure-related details are provided in Sections 8.1 through 8.9.

At all scheduled site visits from Visit 2/Day 1 onward, the site will dispense (supported by IRT) the appropriate number of DPIs for study intervention administration until the next scheduled site visit.

For both cohorts, Visit 6 (Week 12) is the last visit for the Base Period and the baseline visit for the Extension Period. If necessary, Visit 6 procedures may be performed over multiple days. If the visit is extended over multiple days, the PRO questionnaires will be administered as the first procedure on the first day of the visit.

1. Phase 2 Cohort

Visit 6 is the last visit for the Base Period and the Baseline Visit for the Extension Period. At Visit 6, which may occur over multiple days, the participants will complete the Base Period study procedures (***including RHC***), as scheduled and specified in the SoA, and a reevaluation of SpO_2 and seated systolic BP. If the SpO_2 and seated BP measurements satisfy the study eligibility criteria (Section 5.2), the consented participants will be re-randomized in the Extension Period (Section 8.11.3) on the last day of Visit 6 and will be given new participant ID cards, medication diaries, and study intervention (MK-5475 380 µg, 100 µg, or 32 µg). The first study intervention administration of the Extension Period will be unsupervised, on the day following the last day of Visit 6. Site staff will contact the participants by telephone on that day (+2 days), to assess whether the participants are experiencing any potential AEs. Participants in the Phase 2 Cohort Extension Period will receive study intervention every 6 weeks until Final Visit (Section 8.1.8.4). For participants already enrolled in the Phase 2 Cohort Extension Period, the transition to an every 6-week visit frequency will occur at Week 24 or at the next visit that falls on a 12-week interval (eg, Week 36, 48, 60, and every 12 weeks thereafter through study completion).

2. Phase 3 Cohort

Visit 6 is the last visit for the Base Period and the Baseline Visit for the Extension Period. At Visit 6, the participants will complete the Base Period study procedures as scheduled and specified in the SoA and will be given medication diaries and study intervention (MK-5475 or placebo) for the next 12 weeks. Participants in the Phase 3 Cohort Extension Period will receive study intervention every 12 weeks until Final Visit (Section 8.1.8.4).

Participants in both cohorts will record in their medication diary the date and time of investigational product administration as well as any comments related to the administration experience (eg, device issues). Participants will return their diary and used and unused DPIs at every scheduled site visit.

If, at any time during the study, a participant requires a reassessment of study-related clinical, functional, and/or analytical parameters (eg, 6MWD, WHO-FC), an unscheduled visit may occur. In the event of an unscheduled visit, vital signs, AEs, clinical events, and concomitant medication may be assessed, in addition to the procedure(s) that required reassessment.

Clinic in-person visit may be replaced by telephone, video or home visit using a site staff or a nursing service if circumstances do not support an in-person site visit and after consultation with the Sponsor.

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

All randomized participants should be followed through completion of the study, regardless of premature discontinuation of study intervention, unless the participant withdraws consent from any study follow-up. Participants who discontinue study intervention during the Phase 2 Cohort Base Period should be followed through completion of that study period (Visit 6).

In both Phase 2 and Phase 3 Cohorts, if a participant is discontinued from the study intervention at any time before the completion of the study (or study period, for participants who discontinue during the Phase 2 Cohort Base Period), the participant will complete the Discontinuation Visit procedures at the time of discontinuation and a follow-up visit 14 days (+ 2 days) after the last dose of study intervention, as specified in the SoA (Section 1.3). After the discontinuation of study intervention, the site visits should continue to be performed at time points that correspond to each remaining study visit through the end of the study (or study period, for participants who discontinue during the Phase 2 Cohort Base Period).

- If a participant is discontinued from the study intervention at any time during the Base Period of either cohort, the participant will return to the clinic at Week 12 and will complete all Visit 6 procedures, as scheduled and specified in the SoA (Section 1.3).

- At each post-discontinuation visit (other than Week 12 visit), Phase 2 Cohort participants will have their vital signs (pulse rate, BP, temperature, pulse oximetry, and respiratory rate) recorded and a review of AEs/SAEs. Participants who discontinue study intervention during the Extension Period on or before Week 24 will complete the WHO-FC assessment, the 6MWT, and NT-proBNP measurement, as specified in the SoA (Section 1.3), in addition to the review of AEs/SAEs and recording of their vital signs (pulse rate, BP, temperature, pulse oximetry, and respiratory rate).

- At each post-discontinuation visit (other than Week 12 visit), Phase 3 Cohort participants will complete the WHO-FC assessment and 6MWT, as specified in the SoA (Section 1.3), in addition to the review of AEs/SAEs and recording of their vital signs (pulse rate, BP, temperature, pulse oximetry, and respiratory rate).

- Concomitant therapies specifically prohibited (Section 5.2) while the participant was receiving study intervention are no longer prohibited starting 14 days after discontinuation of study intervention.

For those participants who have discontinued study intervention early and who miss the remaining study visits, sites will be instructed to make efforts to contact them. To enable sites to reach the participants, the participants should provide primary and secondary contact information (eg, home telephone, work telephone, mobile telephone). Sites must document the outcome of the telephone contact(s) to demonstrate diligent efforts have been made.

Additionally, the ICF will explain the importance of continued data collection from participants, including the use of continued contact by telephone.

8.11.6 Final Visit

If applicable, participants will continue study intervention until Week 12 (participants in Phase 2 Cohort Base Period) or until the Final Visit (participants in Phase 2 Cohort Extension Period and in Phase 3 Cohort). For Phase 3 Cohort, the Final Visit will be conducted for all participants when the planned number of clinical worsening events is reached and is announced by the Sponsor. Participants in the Phase 2 Cohort Extension Period and in the Phase 3 Cohort who prematurely discontinue study intervention are required to attend the Final Visit for collection of clinical events and all assessments and procedures outlined in the SoA.

8.11.7 Follow-up Visit

Participants will receive a follow-up telephone call approximately 14 days after the last dose of study intervention (Visit 6/Week 12, for the participants in Phase 2 Cohort Base Period who do not enroll in the Extension Period, or Final Visit, for the participants in Phase 2 Cohort Extension Period and the participants in Phase 3 Cohort) to determine if any AEs have occurred since the last clinic visit.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Other planned analyses (ie, those specific to the analysis of PK data and future biomedical research) are beyond the scope of this document.

In this operationally seamless adaptive Phase 2/3 study, all statistical analyses will be separated to address the primary/secondary/exploratory objectives in the Phase 2 Cohort and the Phase 3 Cohort independently. The dose of MK-5475 used in the Phase 3 Cohort will be determined based on the analysis of data collected in the Phase 2 Cohort Base Period.

9.1 Statistical Analysis Plan Summary

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

Phase 2 Cohort

Study Design Overview	
Treatment Assignment	Base Period: Participants (approximately 41/group) will be randomized in a 1:1:1:1 ratio among 4 treatment groups: 1) MK-5475 380 µg 2) MK-5475 100 µg 3) MK-5475 32 µg 4) placebo matching MK-5475 Extension Period: Participants in the 3 active treatment groups in the Base Period will initially maintain the same treatment assignment in the Extension Period; participants who received placebo during the Base Period will initially be randomized in a 1:1:1 ratio among the 3 treatment groups: 1) MK-5475 380 µg 2) MK-5475 100 µg 3) MK-5475 32 µg After the Phase 3 dose is selected, all participants in the Phase 2 Cohort Extension will receive the selected Phase 3 dose regardless of their randomized treatment group.
Analysis Populations	Efficacy: FAS Safety: APaT

Primary Endpoint	Percent Change from baseline in PVR at Week 12
Key Secondary Endpoints	N/A
Statistical Methods for Key Efficacy Analyses	The differences (each MK-5475 dose minus placebo) in percent change from baseline and the associated 95% CIs and *p*-values will be provided based on a robust regression model. Missing PVR observations at Week 12 from participants in all treatment groups will be imputed based on the observed PVR observations at Week 12 from the placebo group.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences (each MK-5475 dose minus placebo) in the percentage of participants with events, these analyses will be performed using the M&N method.
Interim Analyses	One interim analysis is planned when CCI [redacted] have completed or discontinued the Phase 2 Cohort Base Period. The purpose of the IA is to allow an early stop for Phase 2 Cohort Base Period for efficacy (including selection of the Phase 3 dose) or to stop the study for futility. Results will be reviewed by an eDMC. The primary analysis of efficacy data from the Phase 2 Cohort will occur when all participants in this cohort have completed (or discontinued prior to the end of) the Base Period. Although the Phase 2 Cohort can continue in the study (in the Extension Period), the Base Period analysis is not considered an interim analysis.
Multiplicity	There are 3 treatment group comparisons that may be tested to address the primary hypothesis. Testing will be done in a sequential manner in descending order of MK-5475 randomized dose group, stopping at the point statistical significance is not achieved.
Sample Size and Power	The planned sample size is approximately 164 participants. For the percent change from baseline in PVR at Week 12, the study has 85% power to demonstrate that MK-5475 380 µg is superior to placebo group at an overall one-sided 2.5% alpha level.

Phase 3 Cohort

Study Design Overview	
Treatment Assignment	Participants (approximately 143/group) will be randomized in a 1:1 ratio between 2 treatment groups: 1) MK-5475 2) placebo matching MK-5475
Analysis Populations	Efficacy: FAS Safety: APaT
Primary Endpoint	Change from baseline in 6MWD at Week 12
Key Secondary Endpoints	N/A
Statistical Methods for Key Efficacy Analyses	The difference (MK-5475 minus placebo) in change from baseline and the associated 95% CI and *p*-value will be provided based on a robust regression model. Missing 6MWD observations at Week 12 from participants in both treatment groups will be imputed based on the observed 6MWD observations at Week 12 from the placebo group.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences (MK-5475 minus placebo) in the percentage of participants with events, these analyses will be performed using the M&N method.
Interim Analyses	No interim analyses are planned. (The primary analysis of efficacy data from the Phase 3 Cohort will occur when all participants in this cohort have completed [or discontinued prior to the end of] the Base Period. Although the Phase 3 Cohort will continue in the study [in the Extension Period], the Base Period analysis is not considered an interim analysis.)
Multiplicity	As there is a single hypothesis test involving a single endpoint and a single between-treatment comparison, no multiplicity adjustment is required.
Sample Size and Power	The planned sample size is approximately 286 participants. For the change from baseline in 6MWD at Week 12, the study has 90% power to demonstrate that MK-5475 is superior to placebo group at a one-sided 2.5% alpha level.

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 (both cohorts, Base and Extension Periods) will be conducted as a double-blind study under in-house blinding procedures. At the end of each Base Period of the study, a copy of the database will be frozen after medical/scientific review has been completed and data from the Base Period have been declared final and complete. The study team will be unblinded to perform and review the full analysis of data from the Base Period as well as author a CSR. A separate, blinded Sponsor team (ie, blinded to participant-level treatment

assignment) will then be assigned to continue the conduct of each Extension Period. All personnel who are unblinded for each Base Period data analysis will be excluded from any future data review at the individual participant level. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed and data have been declared final and complete.

Results of this study will be presented in 4 separate reports based on DBLs:

1. At the end of the Phase 2 Base Period for Phase 2 Cohort primary analysis
2. At the end of the Phase 2 Extension Period for the Phase 2 Cohort final analysis
3. At the end of the Phase 3 Base Period for the Phase 3 Cohort primary analysis
4. At the end of the Phase 3 Extension Period for the Phase 3 Cohort final analysis

The Sponsor will generate the randomized allocation schedules for study intervention assignment for this protocol, and the randomization will be implemented in the interactive voice response system.

Blinding issues related to the analyses to be conducted while the study is still ongoing are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypothesis of the Phase 2 Cohort and Phase 3 Cohort are stated in Section 3 separately.

9.4 Analysis Endpoints

9.4.1 Phase 2 Cohort Efficacy Endpoints

Primary Efficacy Endpoint

- Mean percent change from baseline in PVR at Week 12

Secondary Efficacy Endpoints

- Mean change from baseline in 6MWD at Week 12
- Mean change from baseline in selected hemodynamic parameters at Week 12
    - mRAP
    - Cardiac index
    - SVI

CCI

[redacted]

9.4.2 Phase 3 Cohort Efficacy Endpoints

Primary Efficacy Endpoint

- Mean change from baseline in 6MWD at Week 12

Secondary Efficacy Endpoint

- Mean change from baseline in 6MWD at Week 24
- Proportion of participants whose WHO-FC is not worse at Week 12 relative to baseline

CCI

[redacted]

9.4.3 Safety Endpoints

Safety parameters are described in Section 4.2.1.3

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, vital signs, laboratory safety tests and pulmonary function tests.

9.4.4 Derivations of Efficacy Endpoints

Computational details for selected efficacy endpoints in Sections 9.4.1 and 9.4.2 are provided below:

- $PVR = \frac{PAPmean - PCWP}{CO}\ (Wood\ Unit)$
- $Cardiac\ Index = \frac{CO}{BSA}\ (L/min/m^2)$
- $SVI = \frac{Stroke\ volume}{Body\ surface\ area}\ (mL/m^2)$
- PAH-related mortality TTCW is defined as the time from randomization to the first occurrence of PAH-related death, PAH-related hospitalization, or disease progression.
- All-cause mortality TTCW is defined as the time from randomization to the first occurrence of all-cause death, PAH-related hospitalization, or disease progression.
- LPH physical dimension score = sum of scores from the questions 2, 3, 4, 5, 6, 7, 12, 13 in the LPH questionnaire (each scored 0 to 5 allowing a score in the range of 0 to 40) [Bonner, N., et al 2013].
- LPH total score = sum of all scores from the 21 questions in the LPH questionnaire (each scored 0 to 5 allowing a total score in the range of 0 to 105) [Bonner, N., et al 2013].

9.5 Analysis Populations

Although the analyses of the Phase 2 Cohort and Phase 3 Cohort will be performed separately, the definitions of analysis populations are the same for both cohorts.

9.5.1 Efficacy Analysis Population

The FAS population will serve as the primary population for all efficacy analyses. All randomized participants in the respective cohort who receive at least 1 dose of study treatment will serve as the basis for this population. For PVR and 6MWD, inclusion in the FAS population also requires having a baseline observation. For other efficacy endpoints except TTCW, inclusion in the FAS population requires having at least 1 observation (baseline or post-baseline). Participants will be included in the treatment group to which they are randomized.

9.5.2 Safety Analysis Population

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

be the same for analyses of both the Base and Extension Periods. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal *p*-values for secondary endpoints may be provided as an assessment of strength of evidence without intent to make inferential claims. All statistical tests will be conducted at the α=0.025 (one-sided) level.

For analysis purposes, the baseline assessment is considered the one closest to but before or on the day of randomization (Day 1).

9.6.1 Statistical Methods for Efficacy Analyses

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

Efficacy analyses of the Phase 2 Cohort and the Phase 3 Cohort will be performed separately. The analyses at the end of the Extension Period will include data collected in both the Base and Extension Period of each study cohort. No statistical comparisons will be made for either Extension Period.

9.6.1.1 Phase 2 Cohort

In the Phase 2 Cohort, efficacy endpoints will be collected during the Base and Extension Periods. For the Base Period, the analysis timepoint of interest is Week 12. For the Extension Period, the analysis timepoint of interest is Week 24. Summary statistics will be provided for every planned data collection timepoint described in the SoA (Section 1.3).

Primary Endpoint

Following the ICH E9 (R1) guidance [European Medicines Agency 2020], The primary estimand for the primary objective used for the Phase 2 Cohort contains 5 attributes:

- The treatment condition of interest is MK-5475 or matching placebo with stable concomitant PAH-specific therapy, as defined in Section 5.1.

- The population of participants targeted by the clinical question are male/female participants with PAH between the ages of 18 and 75 years (inclusive).
- The variable to address the clinical question is PVR at Week 12.
- The following are intercurrent events, along with the approaches to handle them:
    - Death: hypothetical strategy to evaluate PVR at Week 12 as though death would not occur.
    - Treatment discontinuation: treatment policy strategy seeking to use every participant's actual Week 12 value, regardless of whether they are still taking study medication.

      The approach to handling missing data for these intercurrent events is described below.
- The population-level summary is mean percent change from baseline in PVR at Week 12.

For this estimand, the primary approach will use a robust regression method to address the primary hypothesis. Robust regression method will be used because percent change from baseline in PVR is not expected to follow a normal distribution, based on other Phase 2 clinical trials which have used non-parametric methods for analyzing PVR [Simonneau, G., et al 2012] [Ghofrani, H. A., et al 2010]. The robust regression model will include terms for treatment and WHO-FC (Class II and Class III/IV). Missing PVR observations at Week 12 from participants in all treatment groups will be imputed following a PMM. Missing data due to death will be imputed as the worst outcome among all observed data. Missing data due to treatment discontinuation will be imputed based on the observed PVR observations at Week 12 from the placebo group referred as J2R (detailed below). If there are missing Week 12 data for other reasons, J2R will also be used. The randomization seed for imputations will be 5475007.

The difference (MK-5475 minus placebo) in percent change from baseline and the associated 95% CI and *p*-value will be provided. A *p*-value for the comparison of MK-5475 versus placebo <0.025 (one-sided) will be considered statistically significant contingent upon the multiplicity strategy (Section 9.8).

The following steps will be taken to perform the primary analysis, including imputation for missing data. Percent change from baseline in PVR at Week 12 is the response variable:

1. Define imputation model for different missingness patterns:
    a. Obtain the worst outcome among all observed data.
    b. Within the placebo group, for participants with both baseline and Week 12 data, fit an ANCOVA model including terms for treatment and WHO-FC (Class II and Class III/IV).

2. Impute missing data for different missingness patterns:

    a. Death: for participants (in both treatment groups) who died before Week 12, the worst outcome among all observed data will be used to impute the missing Week 12 values.

    b. Reasons other than death: For participants (in both treatment groups) missing the response variable, the fitted model in Step 1 will be used to impute the missing values.

3. Robust regression based on a Huber-type M estimator [Huber, P. J. 1973] will be performed for the imputed dataset. The model will include terms for treatment and WHO-FC (Class II and Class III/IV).

4. Steps 2 and 3 will be repeated 50 times to create 50 complete datasets and 50 sets of parameter estimates.

5. The final parameter estimate for the mean percent change will be the average of the 50 parameter estimates for the mean percent change from Step 4.

6. Steps 1 through 5 will be repeated 200 times based on bootstrap resampling. The resulting standard error for the mean percent change will be the standard error of the resulting parameter estimates obtained in the 200 bootstrap resampled datasets. The CI and *p*-value will be derived from a normal distribution based on the final parameter estimate and its standard error.

Two sensitivity analyses for percent change from baseline in PVR will be performed to assess the impact of missing data imputation. Within the same PMM structure in the primary analysis, for missing data due to reasons other than death, 1 analysis will use a tipping point approach and the other analysis will use an approach referred to as washout imputation.

In the tipping point approach, missing values due to reasons other than death will be imputed based on the first step in the primary analysis with a positive adjustment Δ added for the MK-5475 group. The inference will be carried out for a range of values of Δ. The smallest value of Δ that renders the significant result into a non-significant result will be the tipping point value, which provides a measure of robustness of the primary result.

In the washout imputation approach, missing values due to reasons other than death in the MK-5475 group will be imputed from a normal distribution with the expected value set to the baseline value in the MK-5475 group and standard deviation computed based on the root mean squared error from the ANCOVA model described in the primary analysis. Missing values in the placebo group will be imputed in the same way as in the primary analysis.

Secondary Endpoint

The primary approach for addressing the mean change from baseline in 6MWD at Week 12 will use the same robust regression method described above for the primary endpoint. Summary statistics will be provided for other selected hemodynamic parameters listed in

Section 9.4.1. Table 5 summarizes the analysis strategy for efficacy endpoints in the Phase 2 Cohort.

Table 5 Analysis Strategy for Primary and Secondary Efficacy Endpoints in the Phase 2 Cohort

Endpoint	Type	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Percent Change from baseline in PVR at Week 12	P Sen Sen	RR RR RR	FAS FAS FAS	PMM-J2R PMM-Tipping point PMM-Washout
Secondary Endpoints				
Change from baseline in 6MWD at Week 12	P	RR	FAS	PMM-J2R
Change from baseline in selected hemodynamic parameters at Week 12	P	SS	FAS	N/A

6MWD=6-minute walk distance; FAS=full analysis set; J2R=jump-to-reference; N/A=not applicable; P=Primary; PMM=pattern mixture model; PVR=pulmonary vascular resistance; RR=robust regression; Sen=Sensitivity; SS=summary statistics.

9.6.1.2 Phase 3 Cohort

In the Phase 3 Cohort, efficacy endpoints will be collected during the Base and Extension Periods. For the Base Period, the analysis timepoint of interest is Week 12. For the Extension Period, the analysis timepoint of interest is Week 24. Summary statistics will be provided for every planned data collection timepoint described in the SoA (Section 1.3).

Primary Endpoint

The primary estimand for the primary objective used for the Phase 3 Cohort contains 5 attributes:

- The treatment condition of interest is MK-5475 or matching placebo on background stable concomitant PAH-specific therapy, as defined in Section 5.1.
- The population of participants targeted by the clinical question are male/female participants with PAH between the ages of 18 and 75 years (inclusive).
- The variable to address the clinical question is 6MWD at Week 12.
- The following are intercurrent events, along with the approaches to handle them:
    - Death: hypothetical strategy to evaluate 6MWD at Week 12 as though death would not occur.

- Treatment discontinuation: treatment policy strategy seeking to use every participant's actual Week 12 value, regardless of whether they are still taking study medication.

  The approach to handling missing data for these intercurrent events is described below.

- The population-level summary is mean change from baseline in 6MWD at Week 12.

For this estimand, the primary approach will use a robust regression method to address the primary hypothesis. Robust regression method will be used because change from baseline in 6MWD is not expected to follow a normal distribution, based on other Phase 3 clinical trials which have used non-parametric methods for analyzing 6MWD [Rubin, L. J., et al 2002] [Rubin, L. J., et al 2015]. The robust regression model will include a term for treatment and WHO-FC (Class II and Class III/IV). Missing 6MWD observations at Week 12 from participants in all treatment groups will be imputed following a PMM. Missing data due to death will be imputed based on the worst outcome among all observed data. Missing data due to treatment discontinuation will be imputed based on the observed 6MWD observations at Week 12 from the placebo group referred as J2R (detailed below). If there are missing Week 12 data for other reasons, J2R will also be used. The randomization seed for imputations will be 5475007.

The difference in change from baseline and the associated 95% CI and *p*-value will be provided (MK-5475 minus placebo). A *p*-value for the comparison of MK-5475 versus placebo <0.025 (one-sided) will be considered statistically significant.

The following steps will be taken to perform the primary analysis, including imputation for missing data. Percent change from baseline in 6MWD at Week 12 is the response variable:

1. Define imputation model for different missingness patterns:

   a. Obtain the worst outcome among all observed data.

   b. Within the placebo group, for participants with both baseline and Week 12 endpoint, an MMRM model including terms for treatment and WHO-FC (Class II and Class III/IV) will be fit.

2. The same procedure in Steps 2 through 6 described in Section 9.6.1.1 will be used for analysis.

Two sensitivity analyses of the estimand for change from baseline in 6MWD will be performed to assess the impact of missing data imputation. Within the same PMM structure in the primary analysis, for missing data due to reasons other than death, 1 analysis will use a tipping point approach and the other analysis will use an approach referred to as washout imputation. The analysis approaches are the same as in the 2 sensitivity analyses described in Section 9.6.1.1 except the missing data due to reasons other than death will be imputed by the MMRM model in the primary analysis.

As a supplemental analysis, the primary analysis will be repeated, excluding participants who participated in the Phase 2 Cohort.

Secondary Endpoint

The primary approach for addressing the mean change from baseline in 6MWD at Week 24 will use the same robust regression method in Section 9.6.1.1. Summary statistics will be provided for the proportion of participants whose WHO-FC is not worse at Week 12 relative to baseline. Table 6 summarizes the analysis strategy for efficacy endpoints in the Phase 3 Cohort.

Table 6 Analysis Strategy for Primary and Secondary Efficacy Endpoints in the Phase 3 Cohort

Endpoint	Type	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Change from baseline in 6MWD at Week 12	P Sen Sen	RR RR RR	FAS FAS FAS	PMM-J2R PMM-Tipping point PMM-Washout
Secondary Endpoints				
Change from baseline in 6MWD at Week 24	P	RR	FAS	PMM-J2R
Proportion of participants whose WHO functional class does not worsen at Week 12 relative to baseline.	P	SS	FAS	N/A

6MWD=6-minute walk distance; FAS=full analysis set; J2R=jump-to-reference; N/A=not applicable; P=Primary; PMM=pattern mixture model; RR=robust regression; Sen=Sensitivity; SS=summary statistics; WHO=World Health Organization.

9.6.2 Analysis Methods for Safety Analyses

Safety analyses of the Phase 2 Cohort and the Phase 3 Cohort will be performed separately. The analysis methods for safety analyses are the same for both cohorts. The analyses at the end of the Extension Period will include data collected in both the Base and Extension Period of each study cohort.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, PFTs, and ECG measurements. Except where noted otherwise, the same analyses will be performed at the end of the Base Period and at the end of the Extension Period.

The Treatment Period will include all data from randomization up to 14 days after the last dose of study medication. All safety endpoints will be analyzed for the time frame consisting of the treatment period + 14-day post-treatment follow-up, except SAEs. For SAEs, the analysis will include all post-treatment follow-up.

AEs will be coded using the standard MedDRA and grouped according to SOC.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, drug-related AE, SAE, and drug-related SAE, as well as who discontinued from study intervention due to an AE and who had an AE resulting in death. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with these events will be provided.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with specific AEs will be provided for AEs that occur in at least 4 participants in any treatment group. This threshold for the numbers of events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when fewer participants per group have events and thus would add little to the interpretation of potentially meaningful differences.

Point estimates and 95% CIs will be provided for the percentage of participants with safety parameters that meet predefined limits of change based on the same criteria used above for the specific AEs.

CIs for between-treatment group differences will be provided using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985]. These CIs will not be adjusted for multiplicity and should be regarded only as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Rainfall plots with point estimates and 95% CIs will be displayed for AEs that occur in at least 4 participants in any treatment group.

Assessment of Safety Topics of Interest

Safety topics of interest include AEs of symptomatic hypotension, pulmonary hemorrhage, and hemoptysis. The safety topics of special interest will be summarized by treatment group of the number and percentage of participants. Point estimates and 95% CIs for between-group differences will be provided based on the criteria described above for specific AEs.

A summary of the analysis strategy for safety parameters is provided in Table 7.

Table 7 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI[a]	Graphical Display[a]
Overall Safety Assessment	Any AE	X	X	
	Any serious AE	X	X	
	Any drug-related AE	X	X	
	Any serious and drug-related AE	X	X	
	Discontinuation due to AE	X	X	
	Death	X	X	
	SOCs, PDLCs (incidence ≥4 of participants in any treatment groups)	X	X	
	Specific AEs (incidence ≥4 of participants in any treatment groups)	X	X	X
	Specific AEs, SOCs, PDLCs (incidence <4 of participants in any treatment groups)	X		
	Change from Baseline results (laboratory tests, ECGs, vital signs)	X		
Safety Topics of Special Interest	Symptomatic hypotension Pulmonary hemorrhage Hemoptysis	X	X	X

AE=adverse event; CI=confidence interval; ECGs=electrocardiograms; PDLC=predefined limit of change; SOC=system organ class; X=results will be provided.

[a] 95% between-group CI and graphical display will not be provided for the analysis of the Phase 2 Cohort Extension Period.

9.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed separately for each cohort by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

For analysis purposes, the baseline assessment is considered the one closest to but before or on the day of randomization (Day 1).

9.7 Interim Analyses

Analyses of data to be performed while the study is in progress are described below.

CCI

The O'Brien–Fleming alpha-spending function [Lan, K. K. G. and DeMets, D. L. 1983] will be used for the efficacy IA to assess the superiority of MK-5475 versus placebo. The spending function can be expressed as

$$\alpha(t) = 2 - 2\Phi\left(\frac{Z_{\alpha/2}}{\sqrt{t}}\right)$$

where 't' denotes the percentage of information included at the IA, and 'Φ' denotes the standard normal cumulative distribution function.

With this alpha spending approach, the cumulative significance level will be approximately CCI (one-sided) at the IA and CCI at the final analysis of the Phase 2 Cohort Base Period, respectively. This testing approach controls the one-sided alpha between the efficacy IA and final analysis at 0.025. The operating characteristics for the interim efficacy analysis are shown in Table 8.

Table 8 Power to Demonstrate Superiority of MK-5475 vs placebo on the Primary Endpoint of % Change in PVR in Phase 2 Cohort Base Period at the Interim Analysis

Analysis timepoint	Cumulative α Spent (one-sided)	Power (%) for Various True Effect Sizes				
		-30%	-35%	-40%	-45%	-50%
CCI CCI	CCI	59.5	75.0	86.7	93.9	97.6
IA=interim analysis; PVR=pulmonary vascular resistance.						

CCI

CCI [redacted]

CCI [redacted]

Study enrollment will not be paused while the IA is being conducted. Blinding to treatment assignment will be maintained at all investigational sites. Participant-level unblinding will be restricted to an internal unblinded statistician and a scientific programmer performing the IA. Treatment-level results and/or participant-level data from the IA will be provided by the unblinded statistician to the eDMC. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the IA, if required, to act on the recommendations of the eDMC. The processes by which recommendations and decisions are reached and communicated will be documented in the DMC charter. Before final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IA. The results of the IA will not be shared with the investigators before completion of the Phase 2 Cohort.

Phase 2 Cohort Base Period

If the IA is cancelled, at the end of the Phase 2 Cohort Base Period, selected members of the Sponsor study team and management will be unblinded to comprehensive results from the Phase 2 Cohort Base Period to evaluate the efficacy and safety profile of MK-5475 for selecting a dose for the Phase 3 Cohort. The MCP-Mod method [Center for Drug Evaluation and Research 2015] may be used to support the finding of a suitable dose for Phase 3 Cohort. Details will be described in the sSAP. This study may stop if analysis of the data collected at the end of the Phase 2 Cohort Base Period shows that none of the MK-5475 doses has a desirable efficacy and safety profile.

Phase 3 Cohort Base Period

The analysis at the end of Phase 3 Cohort Base Period represents the final analysis for Phase 3 Cohort Base Period. At the end of the Phase 3 Cohort Base Period, selected members of the Sponsor study team and management will be unblinded to comprehensive Base Period results from the Phase 3 Cohort, for preparing a CSR and regulatory submissions. For the Extension Period of Phase 3 Cohort, a separate blinded Sponsor study team will monitor the ongoing study. Individuals directly involved with study conduct will not be unblinded.

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this study, an external DMC will monitor the interim data. The DMC will not be involved in the dose selection decision. More details are described in Section 10.1.4.3.

9.8 Multiplicity

Multiplicity for the Phase 2 Cohort and the Phase 3 Cohort will be considered separately in this operationally seamless adaptive design study.

Phase 2 Cohort

For the Phase 2 Cohort Base Period, there are 3 treatment group comparisons that may be tested to address the primary hypothesis. Testing will be done in a sequential manner in descending order of MK-5475 randomized dose group, stopping at the point statistical significance is not achieved.

The multiplicity strategy strongly controls the Type I error at 2.5% (one-sided) to address the primary hypothesis.

Phase 3 Cohort

As there is a single hypothesis involving a single comparison, no multiplicity control is required in the Phase 3 Cohort.

9.9 Sample Size and Power Calculations

Sample size and power calculations for the Phase 2 Cohort and the Phase 3 Cohort have been performed separately in this operationally seamless adaptive design study.

9.9.1 Efficacy

Phase 2 Cohort

The study design assumptions are based on results from other Phase 2 clinical trials in the literature for PAH participants with similar design. In the Phase 2 study assessing selexipag, the observed mean percent change from baseline PVR was 33% with standard deviation 0.34,

and the overall study completion rate was 91% [Simonneau, G., et al 2012]. Comparable results were reported in a Phase 2 study assessing riociguat [Ghofrani, H. A., et al 2010].

Through 12 weeks post-randomization, drop-out is expected to be approximately 10% in each treatment group. However, based on the approach to missing data, all randomized participants per group are expected to be included in the primary analysis and are the basis for sample size and power calculations, accounting for imputation of missing data.

Power and sample size are based on the percent change from baseline in PVR at Week 12. Assuming the true percent change from baseline in PVR at Week 12 is -30% for each MK-5475 dose versus 0% for placebo, the assumed percent change from baseline in PVR at Week 12 using J2R to impute missing data would be 27% for each MK-5475 dose versus 0% for placebo. The assumed standard deviation of the difference of percent change from baseline in PVR at Week 12 between each MK-5475 and placebo is 0.4. Under these assumed percent change and standard deviation, a sample size of 41/group provides more than 85% power (approximately 86.4%) to demonstrate superiority for each of the MK-5475 treatment comparisons using a one-sided alpha=0.025.

With respect to the secondary endpoint of change from baseline in 6MWD at Week 12, a sample size of 41/group will provide a half-width of the 95% CI to be 30 meters, assuming the standard deviation of the change from baseline in 6MWD is 70.

Phase 3 Cohort

The study design assumptions are based on results from Phase 3 PAH clinical studies in the literature with similar design [Ghofrani, H. A., et al 2013] [Galie, N., et al 2008] [Galie, N., et al 2005] [Rubin, L. J., et al 2002]. A clinically relevant increase in 6MWD (>30 meters) correlates with improved clinical outcomes in PAH (Section 4.2.1.1).

Through 12 weeks post-randomization, drop-out is expected to be approximately 10% in each treatment group. However, based on the approach to missing data, all randomized participants per group are expected to be included in the primary analysis and are the basis for sample size and power calculations, accounting for imputation of missing data.

Power and sample size are based on the change from baseline in 6MWD at Week 12. Assuming the true change from baseline in 6MWD at Week 12 is 30 meters for MK-5475 versus 0 meters for placebo, the assumed change from baseline in 6MWD at Week 12 using J2R to impute missing data would be 27 meters for MK-5475 versus 0 meters for placebo. The assumed standard deviation of the difference of change from baseline in 6MWD at Week 12 between each MK-5475 and placebo is 70 meters. Under these assumed change and standard deviation, a sample size of 143/group provides 90% power to demonstrate superiority for each of the MK-5475 treatment comparisons using a one-sided alpha=0.025.

9.10 Subgroup Analyses

Analyses of the Phase 2 Cohort and the Phase 3 Cohort will be performed separately. The subgroups analyzed will be the same for both cohorts, except PVR at baseline.

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of each subgroup. The following are examples of classification variables (the subgroup categories will be defined in the sSAP and other subgroups may be defined and described in the sSAP):

- Age
- Sex
- PAH subtypes
- Number of background PAH-specific therapies
- Type of background PAH-specific therapy
- 6MWD at baseline
- PVR at baseline (Phase 2 Cohort only)

9.11 Compliance (Medication Adherence)

Analyses for the Phase 2 Cohort and the Phase 3 Cohort will be performed separately. The approach to summarizing compliance will be the same for both cohorts. Analysis details will be provided in the sSAP.

9.12 Extent of Exposure

Analyses of the Phase 2 Cohort and the Phase 3 Cohort will be performed separately. The approach to summarizing exposure will be the same for both cohorts.

The extent of exposure will be summarized as duration of treatment in terms of number of puffs. Dose interruption will be summarized. Summary statistics will be provided on the extent of exposure for the APaT population. Further detail will be provided in the sSAP.

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 his/her 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 his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee may be composed of some or all of the following members:

- Sponsor personnel,
- Investigators participating in the study, and
- Consulting therapeutic-area experts and clinical trialists.

The Steering Committee will provide guidance on the operational aspects of the study, evaluate recommendations from the DMC, and make recommendations to the EOC.

Specific details regarding responsibilities and governance of the Steering Committee will be described in a separate charter.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.4 Clinical Adjudication Committee (CAC)

A CAC will evaluate the following events (including events from participants who continue to be followed after discontinuation of double-blinded study intervention) for the purposes of confirming them according to the criteria in Section 8.2.6, as well as evaluating the presence of confounding factors.

TTCW composite endpoint components:

- PAH-related mortality TTCW:
    1. PAH-related death
    2. PAH-related hospitalization
    3. Disease progression as assessed by WHO-FC, 6MWD, and need for additional treatment.
- All-cause mortality TTCW:
    1. All-cause death
    2. PAH-related hospitalization
    3. Disease progression as assessed by WHO-FC, 6MWD, and need for additional treatment

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

Specific details regarding endpoint definitions can be found in the CAC Charter.

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.

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.

Previous medical records or transfer records including, but not limited to, echocardiogram results, pulmonary function test results, and RHC results will be retained in the participant's source document at the study site.

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

The tests detailed in Table 10 will be performed by the central laboratory, with the exception of routine urinalysis, pregnancy testing, and screening laboratory tests, which will be performed by the local laboratory.

- Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for I/E of participants are detailed in Sections 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 10 Protocol-required Laboratory Assessments

Laboratory Assessments			
Hematology	**Chemistry**	**Other Tests**	**Routine Urinalysis**

• Hemoglobin
• Hematocrit
• RBC count
• RBC indices:
  • MCV
  • MCH
  • %Reticulocytes
• Platelet count
• WBC count with differential:
  • Neutrophils
  • Lymphocytes
  • Monocytes
  • Eosinophils
  • Basophils
• **Coagulation tests:**
  • PT
  • aPTT
  • INR
	• NT-proBNP[a]
	• BUN
	• Serum creatinine[b] and eGFR
	• Uric acid
	• Sodium
	• Potassium
	• Chloride
	• Calcium
	• PG
	• ALP
	• ALT/SGPT
	• AST/SGOT
	• Albumin
	• Total protein
	• Total bilirubin
	• Direct (conjugated) bilirubin
	• Indirect (unconjugated) bilirubin
		• Highly sensitive urine hCG pregnancy test, for WOCBP only
		• β-hCG pregnancy test (serum), as needed for WOCBP only
		• FSH (as needed, to confirm postmenopausal state)
			By dipstick:
			• Blood
			• Glucose
			• Protein
			• pH
			• Ketones
			• Bilirubin
			• Urobilinogen
			• Nitrite
			• Leukocyte esterase
			• Specific gravity
			• Microscopic examination (if blood or protein abnormal results are noted)

6MWT=6-minute walk test; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; INR=International Normalized Ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MDRD=Modification of Diet in Renal Disease; NT-proBNP=N-terminal pro b-type natriuretic peptide; PG=plasma glucose; PT=prothrombin time; RBC=red blood cells; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cells; WOCBP=women of childbearing potential;			

Laboratory Assessments			
Hematology	**Chemistry**	**Other Tests**	**Routine Urinalysis**
NOTES: All study-required laboratory assessments will be performed by a central laboratory, with the exception of routine urinalysis, pregnancy testing and the Screening laboratory assessments. a. Blood samples for NT-proBNP should be obtained prior to the 6MWT. As NT-proBNP may be affected by recent exercise, participants should be advised to abstain from exercise before each study visit requiring blood collection for clinical laboratory tests. b. eGFR to be calculated using the MDRD formula.			

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

NT-proBNP results will not be reported to investigative sites until the study has been unblinded.

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."

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

- 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

The recording and follow-up procedures described in this protocol apply to the drug-device combination product intended to be used by a study participant according to the study protocol. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Combination Product – A product comprised of 2 or more regulated components (ie, a drug and a device; a biologic and device; a biologic and a drug; or a drug, a device, and a biologic). Combination products can be single entity, copackaged, or colabeled.

Complaint – Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. This would include PQC, AE, and customer feedback.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part – A drug, device, or biological product that is part of a combination product.

Customer Feedback – A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark that may suggest an improvement in the functionality or quality of a medical device, or device like features of a drug delivery system).

Malfunction – The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device – Any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap,
- investigation, replacement, or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

PQC – Any communication that describes a potential defect related to the identity, strength, quality, purity, or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Injury – An injury or illness that:

1. Is life-threatening,
2. Results in permanent impairment of a body function or permanent damage to a body structure, or
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions

Recording

When a complaint including PQC/malfunction occurs it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug-device combination product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

Assessing Causality

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

The investigator will use clinical judgment to determine the relationship.

Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and 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.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female 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, Mullerian 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 female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females 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[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b,c] • IUS[b,d] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the WOCBP 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.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner 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.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[e] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] Penile/external condoms must be used in addition to the WOCBP's hormonal contraception [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [d] IUS is a progestin releasing IUD [e] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[e]

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

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.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

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

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

10.7.1 Argentina-specific Requirements

Section 1.3 Schedule of Activities, Section 8.3.7 Pregnancy Testing

Pregnancy testing must be performed monthly during treatment as well as at the end of study intervention.

10.7.2 France-specific Requirements

Section 8.4.4 Regulatory Reporting Requirements for SAE

According to the French regulations regarding the timeline of safety data reporting for SAE and AESI:

- The investigator must notify the Sponsor of all SAEs immediately without exceeding 24 hours.
- In the event of premature termination of the trial for safety reasons, the Sponsor will inform the ANSM and the CPP without delay within a maximum period of 15 days.

10.8 Appendix 8: Approximate Blood Volume Tables

Table 11 Phase 2 Cohort Approximate Blood Volumes Drawn/Collected by Trial Visit and by Sample Types

	Phase 2 Cohort Base Period						**Phase 2 Cohort Extension Period**			**Early DC**	**Follow-up**
Phase 2 Cohort/ Trial Visit	Screening Visit	Rand/ Visit 2/ Day 1	Visit 3/ Day 7	Visit 4/ Week 4	Visit 5/ Week 8	Visit 6/ Week 12	TC 1 Day After Visit 6	Visit X Every 6 Weeks	Final Visit	DC Visit	14 days After Final Visit
Approximate Blood Volume (mL)											
NT-proBNP		3				3		3[a]		3[b]	
Serum β-Human Chorionic Gonadotropin (β-hCG) (WOCBP only)	If required, included with the Chemistry Sample										
Serum Follicle-Stimulating Hormone (FSH) (WOCBP only)	If required, included with the Chemistry Sample										
Hematology		2		2	2	2		2[d]	2	2	
PT/INR, aPTT		3		3	3	3		3[d]	3	3	
Chemistry		3		3	3	3		3[d]	3	3	
Screening CBC Local laboratory	2										
Screening Chemistry (including eGFR, ALT, AST, ALP and bilirubin) Local laboratory	3										
Pharmacokinetic Samples		6+6[c]		6	6	6		6[d]	6	6	
Blood for Planned Genetic Analysis		9									
Blood (Serum) for FBR		10				10					
Blood (Plasma) for FBR		10				10					
Expected Total (mL)	5	52[c]		14	14	37		17[a,d]	14	17[b]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; CBC=complete blood count test; DC=discontinuation; eGFR=estimated glomerular filtration rate (calculated using MDRD equation); FBR=future biomedical research; FSH=follicle-stimulating hormone; INR=International Normalized Ratio; MDRD=Modification of Diet in Renal Disease; mL=milliliters; NT-proBNP=N-terminal pro b-type natriuretic peptide; PT=prothrombin time; Rand=randomization; TC=telephone contact; WOCBP=women of childbearing potential.

[a] Sample collected only at Week 24.

[b] Sample collected during the DC Visit only if the DC occurs prior to Week 24.

[c] One sample collected predose, one sample collected postdose (See Sec. 8.6.1).

[d] Sample collected every 12 weeks until Final Visit.

Table 12 Phase 3 Cohort Approximate Blood Volumes Drawn/Collected by Trial Visit and by Sample Types

	Phase 3 Cohort Base Period						**Phase 3 Cohort Ext Period**		**Early DC**	Follow-up
Phase 3 Cohort/ Trial Visit	Screening Visit	Rand/ Visit 2/ Day 1	Visit 3/ Day 7	Visit 4/ Week 4	Visit 5/ Week 8	Visit 6/ Week 12	Visit X/ Every 12 weeks	Final Visit/	DC Visit	14 days post-FV
Approximate Blood Volume (mL)										
NT-proBNP		3				3	3[a]	3	3	-
Serum β-Human Chorionic Gonadotropin (β-hCG) (WOCBP only)	If required, included with the Chemistry Sample									-
Serum Follicle-Stimulating Hormone (FSH) (WOCBP only)	If required, included with the Chemistry Sample									
Hematology	-	2	-	2	2	2	2	2	2	-
PT/INR, aPTT		3		3	3	3	3	3	3	
Chemistry	-	3	-	3	3	3	3	3	3	-
Screening CBC Local laboratory	2									-
Screening Chemistry (including eGFR, ALT, AST, ALP and bilirubin) Local laboratory	3									-
Pharmacokinetic Samples		6 + 6[b]		6	6	6	6[a]	6	6	-
Blood for Planned Genetic Analysis/		9								-
Blood (Serum) for FBR		10				10				
Blood (Plasma) for FBR		10				10				
Expected Total (mL)	5	52[b]		14	14	37	17[a]	17	17	-

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; CBC=complete blood count test; DC=discontinuation; eGFR=estimated glomerular filtration rate (calculated using MDRD equation); Ext=Extension; FBR=future biomedical research; FSH=follicle-stimulating hormone; FV=Final Visit; INR=International Normalized Ratio; MDRD=Modification of Diet in Renal Disease; mL=milliliters; NT-proBNP=N-terminal pro b-type natriuretic peptide; PT=prothrombin time; Rand=randomization; WOCBP=women of childbearing potential.

[a] Starting at Week 24, will be collected at every other visit until the Final Visit

[b] One sample collected predose, one sample collected postdose (See Sec. 8.6.1).

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency for the Safety of Medicines and Health Products)
APaT	All Participants as Treated
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the curve
AUC_{0-24}	area under the curve over 24 hours
BMI	body mass index
BNP	brain natriuretic peptide, B-type natriuretic peptide
BP	blood pressure
CAC	Clinical Adjudication Committee
CCB	calcium channel blocker(s)
CD4+	cluster of differentiation 4 positive
cGMP	cyclic guanosine monophosphate
CI	confidence interval
C_{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPP	Comités de Protection des Personnes (Committees of Protection of Persons)
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography

Abbreviation	Expanded Term
CTFG	Clinical Trial Facilitation Group
CV	cardiovascular
D	day
DBL	database lock
DDI	drug-drug interaction
DLCO	diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPI	dry powder inhaler
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	Electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
ERA	endothelin receptor antagonist
ERS	European Respiratory Society
EU CT	European Union Clinical Trial
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEF25-75	forced expiratory flow at 25% to 75% of FVC
FEV1	forced expiratory volume in 1 second
FMF	Final Market Formulation
FRI	functional respiratory imaging

Abbreviation	Expanded Term
FSH	follicle-stimulating hormone
FSR	first site ready
FVC	forced vital capacity
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
I/E	inclusion/exclusion
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
J2R	jump-to-reference
JRCT	Japan Registry of Clinical Trials
LAM	lactation amenorrhea method
LPH	Living with Pulmonary Hypertension questionnaire
LVEDP	left ventricular end diastolic pressure
MAD	multiple ascending dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures

Abbreviation	Expanded Term
M&N	Miettinen and Nurminen
mRAP	mean right arterial pressure
NCT	National Clinical Trial
NIH	National Institutes of Health
NO	nitric oxide
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal fragment of prohormone B-type natriuretic peptide
OSA	obstructive sleep apnea
OTC	over-the-counter
PAH	pulmonary arterial hypertension
PBV	pulmonary blood volume
PCH	pulmonary capillary hemangiomatosis
PCWP	pulmonary capillary wedge pressure
PDE5	phosphodiesterase type 5
PDE5i	phosphodiesterase type 5 inhibitor
PDLC	predefined limit of change
PEF	peak expiratory flow
PFT	pulmonary function tests
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PH	pulmonary hypertension
PK	pharmacokinetic(s)
PMM	pattern mixture model
PN	protocol number
PQC	product quality complaint(s)
PRO	patient-reported outcome
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
QoL	quality of life
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management

Abbreviation	Expanded Term
RHC	right heart catheterization
RNA	ribonucleic acid
SAD	single ascending doses
SAE	serious adverse event
SAP	Statistical Analysis Plan
SaO2	arterial oxygen saturation
SC	subcutaneous
sGC	soluble guanylate cyclase
SoA	schedule of activities
SOC	system organ class
SOPs	standard operating procedures
SpO2	oxygen saturation measured by pulse oximetry
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
SVI	stroke volume index
SvO_2	mixed venous oxygen saturation
t1/2	terminal half-life
T cells	T-type lymphocytes
TLC	total lung capacity
T_{max}	time to maximum plasma concentration
TTCW	time to clinical worsening
ULN	upper limit of normal
UTN	Universal Trial Number
VA	alveolar volume
WHO	World Health Organization
WHO-FC	World Health Organization functional class
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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