Official Protocol Title:	A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Dose MK-5475 in Participants with Pulmonary Hypertension Associated with COPD
NCT number:	NCT04370873
Document Date:	24-Sep-2021

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Dose MK-5475 in Participants with Pulmonary Hypertension Associated with COPD

Protocol Number: 006-05

Compound Number: MK-5475

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	146752
EudraCT	2020-000488-22

Approval Date: 24 September 2021

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
MK-5475-006-05	24-SEP-2021	Part 3 added. The purpose of this amendment is to allow enrollment of participants unwilling or unable to undergo RHC and to increase the sample size for FRI and CPET to allow more robust statistical analyses of these 2 PD assessments. Part 3 eliminates RHC.
MK-5475-006-04	14-SEP-2021	Country Specific: Hepatitis B surface antigen exclusion criteria updated by making it less restrictive. This will allow participants with stable chronic hepatitis B to participate in the study. No additional risk to these participants will be incurred, as their disease is stable and those with significant liver disease would still be excluded.
MK-5475-006-03	04-JUN-2021	Exercise exclusion criteria removed to improve screening and enrollment.
MK-5475-006-02	01-FEB-2021	Changes to multiple inclusion and exclusion criteria to improve screening and enrollment
MK-5475-006-01	11-SEP-2020	Dosing of MK-5475 in Part 2 of the study will be with the For Market Formulation (FMF) which has a potency of 380µg and will be used in later phase trials
Original Protocol	13-MAR-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

Part 3 added. Part 3 allows for enrollment of an additional 15 participants, who will have pharmacodynamic measurements done at baseline and then again after 4 weeks of dosing with MK-5475. Measurements will include FRI and CPET testing but will not include RHC. The purpose is to increase the sample size for FRI and CPET to allow more robust statistical analyses, while allowing enrollment of participants who are unwilling or unable to undergo RHC.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Objectives Table, Estimated Duration, Number of Participants, and Intervention Groups updated.	Updated to reflect objectives that apply to addition of Part 3. Estimated duration and number of participants adjusted to account for Part 3. To define Intervention groups that will apply to Part 3.
1.2 Schema	Part 3 Schema added	To provide a diagram of the Part 3 design which eliminates RHC.
1.3 Schedule of Activities	Part 3 study procedures table added HR and BP timing updated to within 15 minutes before and after 6 -minute walk test.	To provide list of procedures that apply only to Part 3. To provide clarification as to timing of measurements related to 6-minute walk test.

Section # and Name	Description of Change	Brief Rationale
2.1 Study Rationale	Changed to a 3-Part study, updated PVR data from PN 002. Added age range and rationale for Part 3	Reflects addition of Part 3. To provide most current results of PVR from PN 002. Increased age range since invasive RHC procedure will not be performed in Part 3.
2.2 Background	Updated name of drug delivery device to dry powder inhaler (DPI). Moved protocol 002 and 004 narratives to completed studies section. Added high level summary of PN006 safety results for Part 2, to date. Added protocol summary for PN 007 to Ongoing Studies Section.	Name change to DPI as per internal decision. To provide most current program and safety data.
3.0 Hypothesis, Objectives and Endpoints	Updated objectives that will also be applied to Part 3.	To reflect addition of Part 3.
4.1 Overall Study Design	Part 3 study design added, which includes removal of RHC procedure, sample size for Part 3 and randomization ratio.	To enhance patient recruitment by eliminating RHC, while bolstering dataset for FRI and CPET.
4.2 Scientific Rationale for Study Design	Rationale for Part 3 added.	To eliminate the need for RHC and to provide a more robust dataset for PD analysis associated with FRI and CPET, if needed.
4.3.3 Rationale for Dose and Dose Interval	Updated to include Part 3.	To reflect addition of Part 3.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Criteria #4: Age range for Part 3 adjusted to upper age of 85. Criteria #14 indicates echo applies to parts 1 and 2 only. Part 3 participants require historical RHC.	To enhance enrollment in Part 3. To ensure participants have confirmed PH diagnosis.
5.2 Exclusion Criteria	Criteria #s 7, 10, 17 and 18 updated to include Part 3. Criteria # 6: A positive hepatitis B surface antigen will be permitted provided it is not an acute infection.	To reflect addition of Part 3. To expand pool to include chronic hepatitis B patients that would otherwise be good PH-COPD candidates for enrollment into the trial.
5.3 Lifestyle Considerations	Part 3 included for dietary, caffeine and alcohol restrictions.	To reflect addition of Part 3.
6.1 Study Interventions Administered	Part 3 added to Study Interventions Table	To reflect addition of Part 3.
6.3 Blinding	Part 3 sample allocation schedule added.	To describe sample allocation based on sample size and treatment group for Part 3.
6.4 Study Intervention Compliance	Device name changed to DPI.	Per internal decision in device name description.
6.6 Dose Modification (Escalation/Titration/Other)	Preliminary Part 2 PD data will be used to trigger the start of Part 3. Part 2 and 3 may run in parallel, if needed	To allow for continued assessment of CPET and FRI measures depending on outcome of preliminary review of PD data from Part 2.
8.1.8 Study Intervention Administration	Updated to include Part 3 and dosing window expanded to +/- 2 hours.	To reflect addition of Part 3. To provide more flexibility for dosing.

Section # and Name	Description of Change	Brief Rationale
8.1.11 Domiciling	Updated to include Part 3.	To reflect addition of Part 3.
8.3.1 Physical Examinations	Updated to include Part 3.	To reflect addition of Part 3.
8.6.1 Blood Collection for Plasma MK-5475	Updated to indicate that PK samples done at time of RHC applies only in Part 2.	To ensure appropriate draw of PK samples in Part 2.
8.7 Pharmacodynamics	Updated to indicate RHC applies to Part 2 only.	RHC will not be performed in Part 3.
8.7.2 CT Scan for Functional Respiratory Imaging	Updated to include Part 3.	To reflect addition of Part 3.
8.7.3 Cardiopulmonary Exercise Testing	Updated to include Part 3. Baseline CPET interval extended to 10 weeks from Day 1 in the event the participant is not randomized within 35 days of Day 1.	To reflect addition of Part 3. To enable rescreening of participants that had baseline CPET performed but were not randomized within 35 days of Visit 1.
8.11.2 Treatment Period	Description of Part 3 Treatment Period was added.	To reflect addition of Part 3.
8.11.5 Critical Procedures Based on Study Objectives	Updated for the addition of Part 3. Time windows associated with RHC apply to Part 2 only. FRI defined as critical procedure in Part 3.	To reflect addition of Part 3. To define RHC applies only to Part 2.
9.1 Statistical Analysis Plan Summary	Added that Part 3 will be part of secondary and exploratory analysis.	Updated to account for the inclusion of Part 3.

Section # and Name	Description of Change	Brief Rationale
9.4 Analysis Endpoints	Secondary and Exploratory Analysis endpoints updated to include Part 3	Updated to account for the inclusion of Part 3.
9.6 Statistical Methods	Updated to include Part 3.	Updated to account for the inclusion of Part 3.
9.7 Interim Analysis	Part 2 CPET and FRI data will be analyzed to determine adequate sample size timing for triggering Part 3	A more robust dataset for FRI and CPET may or may not be needed depending on outcome preliminary analysis. This will determine timing to trigger Part 3.
10.8 Appendix 8 Blood Volume Table	Blood Volume Table for Part 3 added Hepatitis B DNA sample, if needed, has been added to blood volume table	Blood volume requirements differ for Part 3 due to elimination of RHC. To confirm Hepatitis B is chronic.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Dose MK-5475 in Participants with Pulmonary Hypertension Associated with COPD

Short Title: MK-5475 PH-COPD Study

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

This study is to be conducted in male and female participants diagnosed with PH-COPD.

Primary Objectives	Primary Endpoints
- Objective: To assess the safety and tolerability of MK-5475 in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease following 7 and 28 days of dosing. (Parts 1, 2 and 3)	- Safety and tolerability will be evaluated during clinical assessments that include vital signs, safety laboratory testing, physical examinations, ECG readings, and review of adverse events (AEs). (Parts 1, 2 and 3)
- Objective: To assess the effect of MK-5475 on pulmonary vascular resistance following 28 days of dosing in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease. (Part 2) - Hypothesis: MK-5475 reduces mean pulmonary vascular resistance following 28 days of dosing in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease when compared to placebo. A true mean difference (MK-5475-placebo) of 15% is considered clinically meaningful. (Part 2)	- Percent change from baseline for PVR of MK-5475/placebo on Day 28 in Part 2.

Secondary Objectives	Secondary Endpoints
- To obtain preliminary plasma pharmacokinetic data of MK -5475 (e.g AUC0-24, AUC0-inf, Cmax, Tmax, terminal half-life, accumulation ratio) in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease (Parts 1, 2 and 3)	- AUC0-inf, AUC0-24, Cmax, C24, Tmax, apparent terminal half-life, accumulation ratio
- To assess the effect of multiple inhaled doses of MK-5475 on pulmonary blood volume in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease (Parts2 and 3)	- Percent change from baseline for PBV of MK-5475/placebo on Day 28 in Parts 2 and 3.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Pulmonary Hypertension
Population	Participants with pulmonary hypertension associated with COPD
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 12 to 21 months 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 24-48 participants will be allocated/randomized such that evaluable participants complete the study as described in Section 9.5.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Inter-vention Group Part</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="3">Part 1</td><td>MK-5475</td><td>360 µg</td><td>Once Daily</td><td>Inhalation</td><td>Days 1-7[a]</td><td>Experimental</td></tr>
<tr><td>Pbo</td><td>0 µg</td><td>Once Daily</td><td>Inhalation</td><td>Days 1-7</td><td>Pbo control</td></tr>
<tr><td>Pbo</td><td>0 µg</td><td>Once</td><td>Inhalation</td><td>Screening 2</td><td>Training</td></tr>
<tr><td rowspan="3">Parts 2 and 3</td><td>MK-5475</td><td>380 µg[b]</td><td>Once Daily</td><td>Inhalation</td><td>Days 1-28</td><td>Experimental</td></tr>
<tr><td>Pbo</td><td>0 µg</td><td>Once Daily</td><td>Inhalation</td><td>Days 1-28</td><td>Pbo control</td></tr>
<tr><td>Pbo</td><td>0 µg</td><td>Once</td><td>Inhalation</td><td>Screening 2</td><td>Training</td></tr>
</table>
Abbreviations: Pbo = Placebo, µg = micrograms
[a] Following review of PK and safety data, a second 7 days of dosing may be initiated A dose of up to 360 µg up to twice a day may be administered based on PK data in this population.
[b] Dose strength may be adjusted downwards, if indicated.
</td></tr>
<tr><td>Total Number</td><td>4</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 10 to 16 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 5 weeks, each participant in Part 1 will be receiving assigned intervention for approximately 7 to 14 days and each participant in Parts 2 and 3 will be receiving assigned intervention for approximately 27 to 32 days. Participants in Part 1 may participate in Part 2 or 3 upon SPONSOR agreement. Participants in Part 2 may not participate in Part 3. After the end of treatment, each participant will be followed for 14 days.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 13.

1.2 Schema

A high-level study design is depicted in Figure 1, Figure 2 and Figure 3. Refer to SOA (Section 1.3) for full details.

Figure 1 Part 1 Study Design

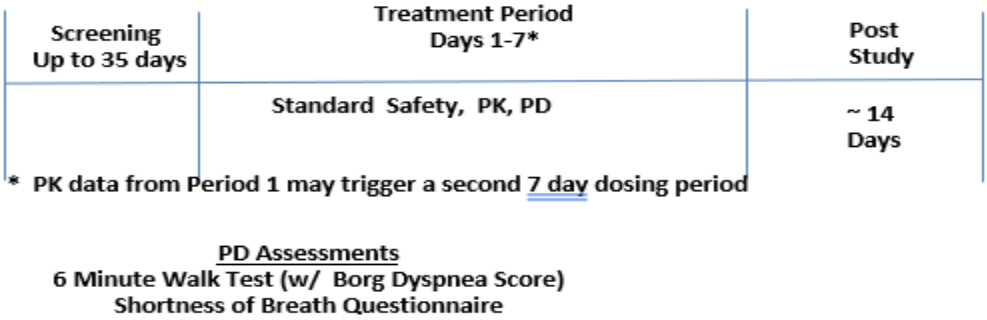


Figure 2 Part 2 Study Design

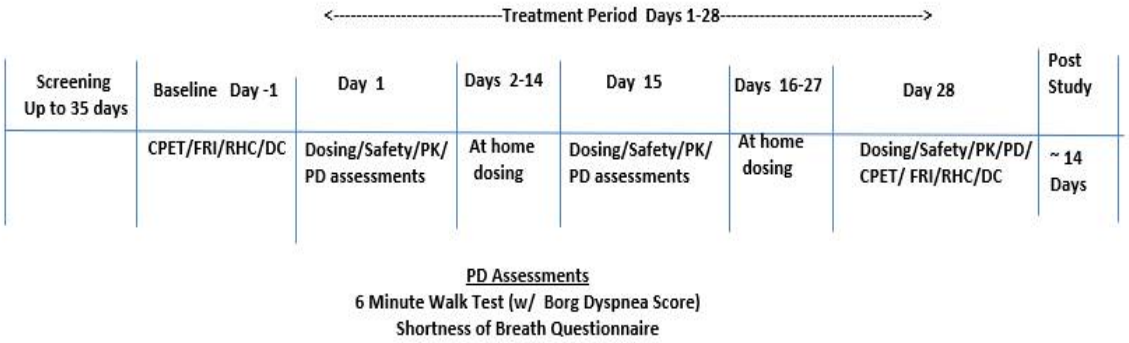
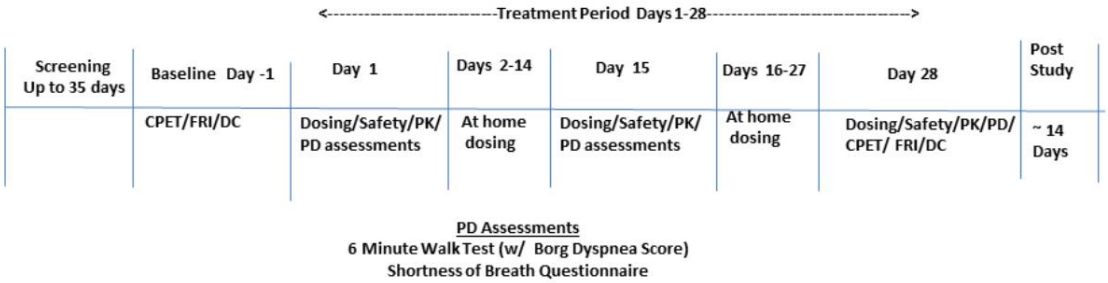


Figure 3 Part 3 Study Design



1.3 Schedule of Activities

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days prerandomization	Screening 2 ≤ 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.
Administrative Procedures													
Informed Consent	X												
Informed Consent for Future Biomedical Research (optional)	X												
Participant Identification Card	X												
Inclusion/Exclusion Criteria	X	X	X										
Medical History	X	X	X										
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		X	
Assignment of Screening Number	X												
Assignment of Treatment/Randomization Number			X										
MK-5475/Placebo Witness Dosing				X	X	X	X	X	X	X			
Domiciling			X	X						X			See Section 8.1.11 for domiciling details
Standard Meals				X						X			Days 1 and 7: Meals 4 and 10 hrs postdose. Snacks at 7 and 13 hrs postdose. See Section 5.3.1 additional meal details

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days prerandomization	Screening 2 ≤ 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.
Inhaler Training/placebo administration		X											Preferably done at Screening 2 but, may be done at screening 1 if within 7 days of Predose Day 1. Retraining may occur during dosing period, at discretion of investigator
Training with Spirometry Device		X											Training will be done for each participant at one occasion for site spirometry measures
Inspiratory Flow Meter Assessment		X	X		X	X	X	X	X	X			Preferably done at Screening 2 but, may be done at screening 1 if within 7 days of Day 1. Days 1-7: Predose First daily dose only
Safety Procedures													
Full physical examination	X		X							X		X	Day 1: Predose Day 7: 24 hr post dose. See Section 8.3.1 for PE procedure: See Section 8.11.5 for timing window.
Height	X												See Section 8.3.1 for height and weight procedures
Weight	X											X	

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 <= 35 days prerandomization	Screening 2 <= 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.
Heart Rate (HR), Blood Pressure (BP)	X		X	X	X	X	X	X	X	X		X	Days 1: Predose and 3 hrs post dose Days 2 -6: Predose Day 7: Predose, 1, 3 and 24 hrs post dose. Take before and after 6MWT on Days 1 and 7. See operations manual for 6MWT. See Section 8.3.2 for all vital sign procedures. See Section 8.11.5 for timing window.
Orthostatic Vital Signs	X		X				X			X			Days 1 and 4: Predose Day 7: Predose and 24 hrs postdose
Respiratory Rate (RR)	X		X	X	X	X	X	X	X	X		X	Day 1: Predose and 3 hrs postdose Days 2 -6: Predose Day 7: Predose and 24hrs postdose
Body Temperature	X		X							X		X	Day 1: Predose Day 7: 24 hrs postdose

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days prerandomization	Screening 2 ≤ 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.
12-lead ECG	X		X	X			X			X		X	Day 1: Predose and 3 hrs postdose Day 4: Predose Day 7: Predose, 3 and 24 hrs postdose See Section 8.3.3 for all appropriate ECG procedures. See Section 8.11.5 for timing window.
Echocardiogram (if needed)	X												Follow site SOP for assessment
High Resolution CT Scan (if needed)	X												Follow site SOP for CT procedure
PFTs	X		X							X			Day1: Predose Day 7: Predose and 24 hr postdose. See Section 8.7.4 for parameters to be performed at screening and during intervention period. See Section 8.11.5 for timing window.
Serum (β-hCG; WOCBP only)	X											X	
Urine Pregnancy Test (WOCBP only)			X										
Serum FSH - (WONCBP only)	X												

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days prerandomization	Screening 2 ≤ 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.
HIV, hepatitis B and C screen (per site SOP)	X												
UDS or BDS (per site SOP)	X		X										Screening and D1 predose UDS or BDS is mandatory, any additional UDS or BDS are conducted per site SOP
ABGs			X							X			On room air, if tolerated by participant. Follow site SOP for ABG procedure. Day 1: Predose Day 7: 24 hrs postdose
Oxygen Saturation (Pulse Oximetry)	X		X		X		X			X			On room air, if tolerated by participant. Day 1: Predose Day 2: Predose Day 4: Predose Day 7: Predose and 24 hrs postdose. Before and after 6MWT
Hematology	X		X							X		X	Day 1: Predose Day 7: 24 hrs postdose See Appendix 2 for laboratory test details
Urinalysis	X		X							X		X	
Chemistry	X		X							X		X	
PT/ aPTT	X		X							X		X	
AE/SAE review	X	X	X	X	X	X	X	X	X	X		X	See all sections under 8.4
AE/SAE review via contact												X	Contact 14 days post Day 7 to assess for AEs

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days prerandomization	Screening 2 ≤ 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.
Pharmacokinetics													
Blood for Plasma MK-5475 and or Metabolites Assay			X	X	X	X	X	X	X	X			Days 1: Predose, 5 min, 15 min, 0.5, 1, 2, 3, 4 and 8 hrs postdose Day 2 - 6: 1 hr post dose Day 7: Predose, 5 min, 15 min, 0.5, 1, 2, 3, 4. 8 and 24 hrs postdose See operations manual for sample processing details.
Pharmacodynamics													
MMRC Breathlessness Scale	X												
Borg Dyspnea Scale			X							X			Day 1: Predose Day 7: 24 hrs postdose To be performed before and after 6MWT
Shortness of Breath Questionnaire (SOBQ)			X							X			Day 1: Predose Day 7: 24 hrs postdose
6 MWT			X							X			Day 1 Predose Day 7: 24 hrs postdose
Biomarkers													
Blood for Genetic Analysis			X										Collect predose. See sections 8.8 and 8.9

Part 1 (Period 1)													
Study Period:	Screening			Intervention								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 <= 35 days prerandomization	Screening 2 <= 7 days prerandomization	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study[a]	A second 7-day dosing period may be implemented following review of safety and PK data.

[a] Post study visit will occur at the completion of the final dosing period (Period 1 or Period 2, if needed). The decision to move to Period 2, if needed will be communicated through a Protocol Clarification Letter. If Period 2 is not needed, the poststudy visit after Period 1 will occur within approximately 14 days after the decision being communicated.

6 MWT = 6 Minute Walk Test; ABG=Arterial Blood Gas; AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; CT = computed tomography ECG = electrocardiogram; FSH=follicle stimulating hormone; hr= hour; ID=identification; min=minutes; MMRC= Modified Medical Research Council; PE = physical exam; PFT=Pulmonary Function Test; PH = pulmonary hypertension; PK= pharmacokinetic; PT = Prothrombin time; aPTT = activated partial thromboplastin time; SAE=serious adverse event; SOBQ = Shortness of Breath Questionnaire; SOP=standard operating procedure; UDS=Urine Drug Screen; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential

Part 1 (Period 2, if needed)											
Study Period:	Intervention									Post-study	Notes
Scheduled Hour, Day, Week, etc.	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study	
Administrative Procedures											
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X		X	
MK-5475/Placebo Witness Dosing		X	X	X	X	X	X	X			If Period 2 requires twice a day dosing, witness dosing will occur for at least the first dose each day.
MK-5475/placebo at home dosing (second dose only, if needed)			X	X	X	X	X				If there is twice a day dosing and time between first and second is more than 1 hour, home dosing may be appropriate at the discretion of the investigator. In this case, the participant is to bring DPI and dosing diary to CRU for witness dosing and diary review
MK-5475/Placebo and Dose Diary Dispensing (if needed)		X									DPI used for witness dosing will be sent with participant for at home dosing
Domiciling	X	X						X			See Section 8.1.11 for domiciling details
Standard Meals		X						X			Days 1 and 7: Meals 4 and 10 hrs postdose. Snacks at 7 and 13 hrs postdose. See Section 5.3.1 additional meal details
Inspiratory Flow Meter Assessment	X		X	X	X	X	X	X			Days 1-7: Predose First daily dose only

Part 1 (Period 2, if needed)											
Study Period:	Intervention									Post-study	Notes
Scheduled Hour, Day, Week, etc.	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study	
Safety Procedures											
Full physical examination	X							X		X	Day 1: Predose Day 7: 24 hr post dose. See Section 8.3.1 for PE procedure: See Section 8.11.5 for timing window.
Weight										X	
Heart Rate (HR), Blood Pressure (BP)	X	X	X	X	X	X	X	X		X	Days 1: Predose and 3 hrs post dose Days 2 -6: Predose Day 7: Predose, 1, 3 and 24 hrs post dose. Take before and after 6MWT on Days 1 and 7. See operations manual for 6MWT. See Section 8.3.2 for all vital sign procedures. See Section 8.11.5 for timing window.
Orthostatic Vital Signs	X				X			X			Days 1 and 4: Predose Day 7: Predose and 24 hrs postdose
Respiratory Rate (RR)	X	X	X	X	X	X	X	X		X	Day 1: Predose and 3 hrs postdose Days 2 -6: Predose Day 7: Predose and 24hrs postdose
Body Temperature	X							X		X	Day 1: Predose Day 7: 24 hrs postdose

Part 1 (Period 2, if needed)											
Study Period:	Intervention									Post-study	Notes
Scheduled Hour, Day, Week, etc.	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study	
12-lead ECG	X	X			X			X		X	Day 1: Predose and 3 hrs postdose Day 4: Predose Day 7: Predose, 3 and 24 hrs postdose See Section 8.3.3 for all appropriate ECG procedures. See Section 8.11.5 for timing window.
PFTs	X							X			Day1: Predose Day 7: Predose and 24 hr postdose. See Section 8.7.4 for parameters to be performed at screening and during intervention period. See Section 8.11.5 for timing window.
Serum (β-hCG; WOCBP only)										X	
Urine Pregnancy Test (WOCBP only)	X										
UDS or BDS (per site SOP)	X										Screening and D1 predose UDS or BDS is mandatory, any additional UDS or BDS are conducted per site SOP
ABGs	X							X			On room air, if tolerated by participant. Follow site SOP for ABG procedure. Day 1: Predose Day 7: 24 hrs postdose

Part 1 (Period 2, if needed)											
Study Period:	Intervention									Post-study	Notes
Scheduled Hour, Day, Week, etc.	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study	
Oxygen Saturation (Pulse Oximetry)	X		X		X			X			On room air, if tolerated by participant. Day 1: Predose Day 2: Predose Day 4: Predose Day 7: Predose and 24 hrs postdose. Before and after 6MWT
Hematology	X							X		X	Day 1: Predose Day 7: 24 hrs postdose See Appendix 2 for laboratory test details
Urinalysis	X							X		X	
Chemistry	X							X		X	
PT/ aPTT	X							X		X	
AE/SAE review	X	X	X	X	X	X	X	X		X	See all sections under 8.4
Pharmacokinetics											
Blood for Plasma MK-5475 and or Metabolites Assay	X	X	X	X	X	X	X	X			Days 1: Predose, 5 min, 15 min, 0.5, 1, 2, 3, 4 and 8 hrs postdose Day 2 - 6: 1 hr post dose Day 7: Predose, 5 min, 15 min, 0.5, 1, 2, 3, 4. 8 and 24 hrs postdose See operations manual for sample processing details.
Pharmacodynamics											
Borg Dyspnea Scale	X							X			Day 1: Predose Day 7: 24 hrs postdose To be performed before and after 6MWT

Part 1 (Period 2, if needed)											
Study Period:	Intervention									Post-study	Notes
Scheduled Hour, Day, Week, etc.	Predose Day 1	D1	D2	D3	D4	D5	D6	D7		Post-study	
Shortness of Breath Questionnaire (SOBQ)	X							X			Day 1: Predose Day 7: 24 hrs postdose
6 MWT	X							X			Day 1 Predose Day 7: 24 hrs postdose

[a] Post study visit will occur at the completion of the final dosing period (Period 1 or Period 2, if needed).
6 MWT = 6 Minute Walk Test; ABG=Arterial Blood Gas; AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; ECG = electrocardiogram; hr= hour; min=minutes; PE = physical exam; PFT=Pulmonary Function Test; PH = pulmonary hypertension; PK= pharmacokinetic; PT = Prothrombin time; aPTT = activated partial thromboplastin time; SAE=serious adverse event; SOBQ = Shortness of Breath Questionnaire; SOP=standard operating procedure; UDS=Urine Drug Screen; WOCBP = women of childbearing potential;

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Administrative Procedures											
Informed Consent	X										
Informed Consent for Future Biomedical Research (optional)	X										
Inclusion/Exclusion Criteria	X	X	X	X							
Participant Identification Card	X										
Medical History	X	X	X	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	Days 2-14 and 16-27: Conmed review will occur at least 2x/week via phone call. May occur more often at investigator discretion.
Assignment of Screening Number	X										
Assignment of Treatment/Randomization Number				X							
MK-5475/Placebo and Dose Diary Dispensing					X						DPI used for Day 1 witness dosing will be sent with participant for at home dosing
MK-5475/Placebo Witness Dosing					X		X		X		Participant is to bring DPI and dosing diary to CRU for witness dosing and diary review

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
MK-5475/pbo Drug Accountability							X		X		Cross check of dose counter to dose diary to be performed by site staff
Telephone/Virtual Technology Contact for at Home Dosing						X		X			To be performed each day +/- 2 hour of the Day 1 dosing actual time
Inhaler Training/placebo administration		X									Preferably done at Screening 2 but, may be done at screening 1 if within 7 days of Day 1. Retraining may occur during dosing period, at discretion of investigator
Inspiratory Flow Meter Assessment		X		X			X		X		Preferably done at Screening 2 but, may be done at screening 1 if within 7 days of Day 1. Days 1, 15 and 28: Predose
Safety Procedures											
Full physical examination	X									X	See Section 8.3.1 for PE procedure
Targeted physical examination			X						X		Baseline: Prior to the first of 3 PD procedures (RHC, FRI or CPET) Day 28 : Predose Targeted PE consists of CV and respiratory examination.
Height	X										See Section 8.3.1 for height and weight procedures
Weight	X									X	

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Heart Rate (HR), Blood Pressure (BP)	X		X	X	X		X		X	X	Baseline Day: Prior to each of the 3 PD procedures (RHC, FRI and CPET) Day 1: Predose, 1 and 3 hrs postdose. Day 15: Predose Day 28 (D27-32): Predose, 1 and 3 hrs postdose at RHC day Pre-RHC procedure and at least every 5 mins when RHC measures are performed. If FRI is performed on a separate day from RHC, HR/BP will be performed prior to the FRI procedure as well. -Refer to operations manual for timing of HR/BP measures during CPET at baseline and on Day 28 (Day 27-32). -Take before and after 6MWT on Days 1, 15 and 28 (at RHC day). (Taken within 15 minutes of the 6MWT) See operations manual for 6MWT vital sign requirements. See Section 8.3.2 for vital signs procedure. See Section 8.11.5 for timing window

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Orthostatic Vital Signs	X			X			X			X	Days 1 and 15: Predose
Respiratory Rate (RR)	X		X	X	X		X		X	X	Baseline Day: Prior to the first of the 3 PD procedures (RHC, FRI and CPET). Day 1: Predose and 3 hrs postdose Day 15: Predose Day 28 (D27-32): To be done predose on days the 3 PD (RHC, FRI and CPET) measures are performed. Refer to operations manual for timing of additional RR measures during CPET.
Body Temperature	X			X						X	
12-lead ECG	X		X	X	X		X		X	X	Baseline Day: Prior to the first of the 3 PD procedures (RHC, FRI and CPET). Day 1: Predose and 3 hrs postdose Day 15: Predose Day 28: To be done predose on the day RHC is performed.
Echocardiogram (if needed)	X										
High Resolution CT Scan (if needed)	X										Baseline CT scan for FRI may be used for assessment of exclusion criteria

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
PFTs	X		X						X		Baseline and Day 28 PFTs are performed as part of CPET procedure. Under special circumstances, if CPET is not performed, then Baseline and Day 28 PFTs will be done via spirometry. See Section 8.7.4 for PFT details for screening and baseline /intervention periods.
Serum (β-hCG; WOCBP only)	X									X	
Urine Pregnancy Test (WOCBP only)			X						X		
Serum FSH - (WONCBP only)	X										
HIV, hepatitis B and C screen (per site SOP)	X										
UDS or BDS (per site SOP)	X		X								Screening and baseline Day-1 UDS or BDS is mandatory, any additional UDS or BDS are conducted per site SOP
ABGs				X					X		On room air as tolerated. Day 1 and 28 (at RHC day): Predose

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Oxygen Saturation (Pulse Oximetry)	X		X	X	X		X		X		On room, air as tolerated Baseline and Day 28 at least every 5 minutes while RHC is in progress. During CPET assessment Days 1, 15 and 28 (at RHC day): Predose and before and after 6MWT
Hematology	X		X				X		X	X	Days 15 and 28 (at RHC day): Predose See Appendix 2 for laboratory test details. At baseline (prior RHC) and Day 28 (prior RHC), a local lab may also be used in addition to the central lab to assess certain parameters quickly at discretion of investigator. This does not replace the need to collect central lab safety.
Urinalysis	X		X				X		X	X	
Chemistry	X		X				X		X	X	
PT/ INR and aPTT	X		X				X		X	X	
AE/SAE review	X	X	X		X	X	X	X	X	X	Days 2-14 and 16-27: AE/SAE review will occur at least 2x/week via phone call. May occur more often at investigator discretion

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Pharmacokinetics											
Blood for Plasma MK-5475 and or Metabolites Assay					X		X		X		Days 1: Predose, 0.5, 1, 2 and 3 hrs postdose Day 15: 1 hr postdose Day 28: Predose, 0.5, 1, 2 and 3 hrs postdose on the Day RHC is performed. PK sample is also to be drawn prior to start of RHC procedure. If FRI is done on a different day from RHC, then additional PK samples will be drawn prior to start of FRI procedure
Pharmacodynamics											
MMRC Breathlessness Scale	X										
Borg Dyspnea Scale				X			X		X		Days 1, 15: Predose Day 28 (at RHC day): 1hr postdose To be done Pre and post 6MWT
Shortness of Breath Questionnaire (SOBQ)				X			X		X		Days 1, 15: Predose Day 28 (at RHC day): 1 hr postdose
6MWT				X			X		X		Days 1, 15: Predose Day 28 (at RHC day): 1hr postdose
Right Heart Catheterization (RHC) Measurements			X						X		Day 28: 6 to 8 hrs post dose See operations manual and Section 8. 7.1 for details.

Part 2											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Mixed Venous O2 Saturation			X						X		Day 28: 6 to 8 hrs post dose Baseline and Day 28 measures are to be taken during RHC, at least 5 minutes apart. See operations manual and Section 8. 7.1 for details.
CT Scan for Functional Respiratory Imaging (FRI)			X						X		Day 28: 6 to 8 hrs post dose See Section 8.7.2
CPET			X						X		Day 28: 5.5 hrs post dose. See Section 4.1 and 8.7.3
Biomarkers											
Blood for Genetic Analysis				X							Collect predose See sections 8.8 and 8.9
NTproBNP			X						X		Day 28 (at RHC day): Predose See Appendix 2 for details

6MWT = 6 Minute Walk Test; ABG=Arterial Blood Gas; AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; CPET = Cardiopulmonary exercise testing; CT = computed tomography; CV = cardiovascular; DPI = dry powder inhaler; ECG = electrocardiogram; FBR = Future Biomedical Research; FRI = Functional respiratory imaging; FSH=follicle stimulating hormone; ID=identification; MMRC= Modified Medical Research Council; NTproBNP= N-terminal pro-hormone b-type natriuretic peptide; PE= physical exam; PFT=Pulmonary Function Test; PT = Prothrombin time; aPTT = activated partial thromboplastin time; RHC= Right heart catheterization; SAE=serious adverse event; SOBQ = Shortness of Breath Questionnaire; SOP=standard operating procedure; UDS=Urine Drug Screen; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Administrative Procedures											
Informed Consent	X										
Informed Consent for Future Biomedical Research (optional)	X										
Inclusion/Exclusion Criteria	X	X	X	X							
Participant Identification Card	X										
Medical History	X	X	X	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	Days 2-14 and 16-27: Conmed review will occur at least 2x/week via phone call. May occur more often at investigator discretion.
Assignment of Screening Number	X										
Assignment of Treatment/Randomization Number				X							
MK-5475/Placebo and Dose Diary Dispensing					X						DPI used for Day 1 witness dosing will be sent with participant for at home dosing
MK-5475/Placebo Witness Dosing					X		X		X		Participant is to bring DPI and dosing diary to CRU for witness dosing and diary review

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
MK-5475/pbo Drug Accountability							X		X		Cross check of dose counter to dose diary to be performed by site staff
Telephone/Virtual Technology Contact for at Home Dosing						X		X			To be performed each day +/- 2 hours of the Day 1 dosing actual time
Inhaler Training/placebo administration		X									Preferably done at Screening 2 but, may be done at screening 1 if within 7 days of Day 1. Retraining may occur during dosing period, at discretion of investigator
Inspiratory Flow Meter Assessment		X		X			X		X		Preferably done at Screening 2 but, may be done at screening 1 if within 7 days of Day 1. Days 1, 15 and 28: Predose
Safety Procedures											
Full physical examination	X									X	See Section 8.3.1 for PE procedure
Targeted physical examination			X						X		Baseline: Prior to the first of 2 PD procedures (FRI or CPET) Day 28 : Predose Targeted PE consists of CV and respiratory examination.
Height	X										See Section 8.3.1 for height and weight procedures
Weight	X									X	

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Heart Rate (HR), Blood Pressure (BP)	X		X	X	X		X		X	X	Baseline Day: Prior to each of the 2 PD procedures (FRI and CPET) Day 1: Predose, 1 and 3 hrs postdose. Day 15: Predose Day 28 (D27-32): Predose, 1 and 3 hrs postdose HR/BP will be performed prior to the FRI procedure. -Refer to operations manual for timing of HR/BP measures during CPET at baseline and on Day 28 (Day 27-32). -Take before and after 6MWT on Days 1, 15 and 28. (taken within 15 minutes of 6MWT). See operations manual for 6MWT vital sign requirements. See Section 8.3.2 for vital signs procedure. See Section 8.11.5 for timing window

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Orthostatic Vital Signs	X			X			X			X	Days 1 and 15: Predose
Respiratory Rate (RR)	X		X	X	X		X		X	X	Baseline Day: Prior to the first of the 2 PD procedures (FRI and CPET). Day 1: Predose and 3 hrs postdose Day 15: Predose Day 28 (D27-32): To be done predose on days the 2 PD (FRI and CPET) are performed Refer to operations manual for timing of additional RR measures during CPET.
Body Temperature	X			X						X	
12-lead ECG	X		X	X	X		X		X	X	Baseline Day: Prior to the first of the 2 PD procedures (FRI and CPET). Day 1: Predose and 3 hrs postdose Day 15: Predose Day 28: Predose
High Resolution CT Scan (if needed)	X										Baseline CT scan for FRI may be used for assessment of exclusion criteria

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
PFTs	X		X						X		Baseline and Day 28 PFTs are performed as part of CPET procedure. Under special circumstances, if CPET is not performed, then Baseline and Day 28 PFTs will be done via spirometry. See Section 8.7.4 for PFT details for screening and baseline /intervention periods.
Serum (β-hCG; WOCBP only)	X									X	
Urine Pregnancy Test (WOCBP only)			X						X		
Serum FSH - (WONCBP only)	X										
HIV, hepatitis B and C screen (per site SOP)	X										
UDS or BDS (per site SOP)	X		X								Screening and baseline Day-1 UDS or BDS is mandatory, any additional UDS or BDS are conducted per site SOP
ABGs				X					X		On room air as tolerated. Day 1 and 28: Predose

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Oxygen Saturation (Pulse Oximetry)	X		X	X	X		X		X		On room, air as tolerated. During CPET assessment on Days -1 and 28. Days 1, 15 and 28: Predose and also before and after 6MWT
Hematology	X		X				X		X	X	Days 15 and 28: Predose See Appendix 2 for laboratory test details. At baseline and Day 28, a local lab may also be used in addition to the central lab to assess certain parameters quickly at discretion of investigator. This does not replace the need to collect central lab safety.
Urinalysis	X		X				X		X	X	
Chemistry	X		X				X		X	X	
PT/ INR and aPTT	X		X				X		X	X	
AE/SAE review	X	X	X		X	X	X	X	X	X	Days 2-14 and 16-27: AE/SAE review will occur at least 2x/week via phone call. May occur more often at investigator discretion

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
Pharmacokinetics											
Blood for Plasma MK-5475 and or Metabolites Assay					X		X		X		Days 1: Predose, 0.5, 1, 2 and 3 hrs postdose Day 15: 1 hr postdose Day 28: Predose, 0.5, 1, 2 and 3 hrs postdose and Pre- FRI (6-8 hours postdose). If FRI and CPET are done on different days, then PK samples will be drawn prior to the start of both the CPET and FRI.
Pharmacodynamics											
MMRC Breathlessness Scale	X										
Borg Dyspnea Scale				X			X		X		Days 1, 15: Predose Day 28: 1hr postdose To be done Pre and post 6MWT
Shortness of Breath Questionnaire (SOBQ)				X			X		X		Days 1, 15: Predose Day 28: 1 hr postdose
6MWT				X			X		X		Days 1, 15: Predose Day 28: 1hr postdose
CT Scan for Functional Respiratory Imaging (FRI)			X						X		Day 28: 6 to 8 hrs post dose See Section 8.7.2

Part 3											
Study Period	Screening				Intervention					Post-Study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1 ≤ 35 days	Screening 2 ≤ 7 days	Baseline Day -1 (Day -5 to -1)	Predose on Day 1	D1	Days 2-14	D15 (+/- 1 day)	Days 16-27	D28 (D27 to D32)	Post-study	
CPET			X						X		Day 28: 5.5 hrs post dose. See Section 4.1 and 8.7.3
Biomarkers											
Blood for Genetic Analysis				X							Collect predose See sections 8.8 and 8.9
NTproBNP			X						X		Day 28: Predose See Appendix 2 for details

6MWT = 6 Minute Walk Test; ABG=Arterial Blood Gas; AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; CPET = Cardiopulmonary exercise testing; CT = computed tomography; CV = cardiovascular; DPI= dry powder inhaler; ECG = electrocardiogram; FBR = Future Biomedical Research; FRI = Functional respiratory imaging; FSH=follicle stimulating hormone; ID=identification; MMRC= Modified Medical Research Council; NTproBNP= N-terminal pro-hormone b-type natriuretic peptide; PE= physical exam; PFT=Pulmonary Function Test; PT = Prothrombin time; aPTT = activated partial thromboplastin time; SAE=serious adverse event; SOBQ = Shortness of Breath Questionnaire; SOP=standard operating procedure; UDS=Urine Drug Screen; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential

2 INTRODUCTION

2.1 Study Rationale

This is a 3-part, multi-site, multiple-dose trial of MK-5475 in participants with a diagnosis of pulmonary hypertension associated with chronic obstructive pulmonary disease (PH-COPD). MK-5475 has been successfully administered to healthy participants and participants with PAH. The primary objective for this study is to assess MK-5475 in the PH- COPD population by evaluating the safety, pharmacokinetic and pharmacodynamics [including changes in pulmonary vascular resistance (PVR), pulmonary blood volume (PBV) and exercise tolerance].

Currently, there are no specific drug therapies for PH associated with lung diseases. Localized/inhaled delivery of the sGC stimulator MK-5475 is anticipated to provide benefit in the PH-COPD patient population by selectively reducing pulmonary vascular resistance and pulmonary pressure via sGC/cGMP-mediated pulmonary vasodilation.

Data from the PAH study (PN002) has indicated that MK-5475 acutely reduces PVR by a threshold of at least 20% or more in up to 4.5 hours after administration. Since this pharmacodynamic effect is expected to be similar in patients with pulmonary hypertension from other causes, this study for PH-COPD will expand on these results by evaluating the change in PVR after 4 weeks of dosing.

Given patients with PH-COPD tend to be diagnosed in the middle to older adult age range, participants to be enrolled in this study will range in age from 40 to 80 years for Parts 1 and 2. The age range will be from 40 to 85 years for Part 3 given participants will not be required to undergo RHC.

Participants with BMI ≤40 kg/m2 may be included; the ongoing PAH (PN002) study permits the inclusion of participants with BMI ≤35 kg/m2. Given the lack of safety concerns, based on ECG, vital signs, or laboratory safety parameters in the ongoing PAH study (with dosing up to 480 µg), Bridging (PN008) as well as from the FIH and MAD studies, the Sponsor does not consider there to be an increased risk in PH-COPD participants with BMI up to 40 kg/m2. Furthermore, participants with clinically significant co-morbidities will be excluded from participation per exclusion criterion #1 and #2.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

Pulmonary arterial hypertension (PAH) is a serious, often fatal condition that involves increased blood pressure (BP) in the pulmonary arterial circulation, eventually progressing to heart failure and death. A number of therapies for this disease have sought to achieve vasodilation of the pulmonary arterial circulation, thus, relieving the elevated pressure in these blood vessels and lessening the strain on the heart. One pathway that has been

successfully targeted for this purpose is the soluble guanylate cyclase (sGC) pathway. The sGC enzyme is physiologically activated by nitric oxide, which triggers intracellular messenger molecules that result in dilation of blood vessels. The medication riociguat, which is currently approved for treatment of PAH, activates sGC and causes vasodilation. However, this and other therapies for PAH are given systemically, which may result in vasodilation throughout the systemic circulation as well as the pulmonary circulation. This undesirable effect may cause hypotension, limiting the doses of medication that can be given. In addition, systemic administration of pulmonary arterial vasodilators to patients with chronic obstructive pulmonary disease (COPD) may dilate pulmonary blood vessels in diseased areas of lung, causing a mismatch between ventilation and perfusion ("V/Q mismatch") which may cause arterial hypoxemia. This effect has limited the utility of existing medications for treatment of patients with pulmonary hypertension associated with COPD (PH-COPD).

MK-5475 is a small-molecule stimulator of sGC which has been formulated as a dry powder for inhaled delivery with the Sponsor's dry powder inhaler (DPI) device and is being developed for treatment of PAH as well as PH-COPD. By optimizing delivery to the lung, and hence directly to the pulmonary arterial circulation, preclinical models have shown that pulmonary arterial vasodilation can be achieved while limiting systemic exposure. It is also anticipated that MK-5475 will be preferentially deposited in areas of lung that are less damaged by COPD, thereby preserving the relationship between ventilation and perfusion and avoiding V/Q mismatch.

Rats with experimentally-induced pulmonary arterial hypertension were used as the primary pharmacodynamic (PD) model. These experiments showed that MK-5475 successfully reduced pulmonary arterial pressure in rats with minimal to no change in systemic blood pressure, and that inhaled delivery resulted in robust lung exposure to the compound with much lower systemic exposure. Based on the preclinical experiments, the clinical experience with riociguat, and the expectations for pharmacology of an inhaled compound, MK-5475 is expected to achieve therapeutically significant reduction of pulmonary arterial pressure in patients with PAH, with little or no systemic hemodynamic effect.

As with the lead indication, the primary pharmacodynamic effect of MK-5475 in patients with PH-COPD is to induce vasodilation in the pulmonary arterial circulation.

2.2.2 Preclinical and Clinical Studies

Refer to the Investigator's Brochure for detailed preclinical and clinical information on MK-5475. As noted, there were few findings noted in rat studies. In dogs, dose-dependent heart rate and blood pressure changes were noted during systemic intravenous delivery only. In two 1-month dog studies utilizing inhaled delivery, a dose-dependent slight thickening of the bronchial adventitia was noted, and this finding was used to establish the dog NOAEL. The bronchial artery change seen in these dog inhalation toxicology studies at 0.2-0.4 mg/kg/day was not observed in the 3-month dog study.

In the first in human study of 16 healthy male participants (PN001), single dose MK-5475 ranging from 15 to 165 µg was generally well-tolerated. AEs reported were self-limiting and ranged from mild to moderate in intensity. No SAEs or events of clinical interest were

observed. Most frequently reported AEs were headache and oropharyngeal pain. No clinically important findings were observed in vital signs, ECGs, routine lab safety tests, pulmonary function tests and physical exams. Single-dose PK data in PN001 showed that MK-5475 has a median Tmax of 1 hour at doses ranging from 15-165 µg. The geometric mean terminal half-life (t ½) is approximately 2 hours across doses. Plasma exposures (AUC and Cmax) of MK-5475 appeared to show a linear upward trend in relationship to increasing doses. Maximum AUC0-24 observed was 1.47 nM*hr which is approximately three times below the dog NOAEL exposure (4.5 nM*hr). It is expected based on preclinical data and translational PK modeling that steady state will be achieved within 24 hours post the first dose.

PN002: Dosing of MK-5475 in Participants with Pulmonary Hypertension

This 2-part study evaluated the safety, PK and PD [right heart catheterization (RHC) and functional respiratory imaging (FRI)], single-dose MK-5475 ranging from 120 to 480 µg in participants with moderate to severe Group 1 PAH. and was generally well-tolerated. No serious adverse events (SAEs) were reported and no participants discontinued due to an AE. Adverse events (AEs) were mild to moderate in intensity. A total of 52 AEs in 22 of 25 participants were reported. The most frequently reported AEs in 2 or more participants who received MK-5475 were bilirubin increased (1.02 and 2.13 x ULN)(n=2) and hyperkalemia (1.03 to 1.07 x ULN) (n=2) .The most frequently reported nonintervention related AEs reported in 2 or more participants were back pain (n=11) and fatigue(n=2). Refer to the Investigator's Brochure for a full listing of AEs.

Following single inhaled MK-5475 administration, moderate to high inter- and intra-individual variability in AUC and Cmax was observed in PAH participants compared to healthy participants. Geometric mean AUC0-24 in PAH participants ranged from 0.259 to 4.53 nM*hr for the 120 to 480 µg dose levels across study panels/periods. Geometric mean AUC0-24 in PAH participants at 240 µg ranged from 1.04 to 1.71 nM*hr. Geometric mean AUC0-24 in PAH participants at the 300 µg dose level ranged from 2.08 to 2.35 nM*hr across study panels, The geometric mean AUC0-24 at the 360 µg dose level in PAH participants ranged 1.21 to 3.82 nM*hr. Geometric mean AUC0-24 in all study populations thus far has remained below the AUC0-24 corresponding to NOAEL in 1 month tox study in dogs (4.5 nM*hr), except after a single 480 µg dose (AUC0-24=4.53 nM*hr). A total of four PAH participants reached an AUC0-24 higher than the dog NOAEL exposure in at least one of the periods in the study: one dosed at 300 µg (7.25 nM*hr) and three dosed at 360 µg (4.53 to 6.99 nM*hr). The highest individual AUC0-24 at the 360 µg dose level in PAH participants was 6.99 nM*hr which is about 1.6-fold above the NOAEL. Although this was above the 1-month dog NOAEL, the total dose delivered remained below the NOAEL dose of 500 µg. Safety and tolerability profile in participants in whom individual AUC0-24 levels exceeded the NOAEL AUC0-24 appears similar to other participants.

There was a mean percent reduction from baseline for the minimum result over the duration of the RHC procedure of at least 20% for each of the planned doses (120 µg, 240 µg and 360 µg).

The maximum peak effect for increase PBV was seen at 8 hours after dosing of MK-5475.

PN003: MK-5475 MAD Study

This double-blind, randomized, placebo-controlled, multiple-ascending dose study to assess the safety, tolerability and PK of inhaled doses of MK-5475 in healthy male and female participants showed MK-5475 was generally well tolerated for 10 days of multiple dosing ranging from 30 to 165 µg and 5 days of dosing at 240 µg. No SAEs or events of clinical interest were reported. No participants discontinued early from the study. Adverse events were rated mild to moderate by the investigator. All AEs deemed related by the investigator were resolved by discharge from the study. Most frequently reported AEs by 2 or more participants who received MK-5475 were palpitations, abdominal discomfort, diarrhea, fatigue, oral herpes, musculoskeletal chest pain, headache, cough, oropharyngeal pain, throat irritation and contact dermatitis. Refer to the Investigator's Brochure for a full listing of AEs. This study is clinically complete.

In healthy participants, the geometric mean of AUC0-24 were 0.129, 0.424, 0.975, 1.09 and 1.71 nM*hr on Day 1 when the 30, 60, 120, 165 and 240 µg doses were administered. On Day 10 when the 30, 60, 120 and 165 µg doses were administered, the geometric mean of AUC0-24 were 0.218, 0.356, 0.883 and 0.915 nM*hr, respectively. On Day 5 at the 240µg dose, the geometric mean of AUC0-24 was 2.0 nM*hr. The terminal half-life on Day 5 and 10 was approximately 2 hours and is similar to the terminal half-life achieved on Day 1 in the first in human study PN001 (1.88 hours). Cmax was 0.390 nM on Day 1 when the 240µg dose was administered. The Cmax value reached on Day 5 of dosing at 240 µg was 0.435 nM. Following administration of the 240µg dose for 5 consecutive days, the geometric mean AUC0-24 was 2.00 nM*hr which is roughly 2.25 times below the NOAEL (4.5 nM*hr).

PN004: MK5475 Sildenafil DDI Study

This is a randomized, placebo-controlled, crossover, balanced double-blind study of MK-5475/pbo co-administered with open-label sildenafil to assess the safety tolerability and hemodynamic effects during co-administration. This study was conducted in Belgium and is clinically complete. A total of 19 male and female participants were enrolled in the study. No SAEs or events of clinical interest were reported. One participant discontinued early from the study due to flu-like symptoms. Adverse events were rated mild to moderate by the investigator. All AEs deemed related by the investigator were resolved by discharge from the study. Most frequently reported AEs by 2 or more participants which are deemed related to MK-5475 by the investigator include: headache, dizziness, myalgia and hypoesthesia of the feet. A preliminary hemodynamic assessment showed that the effect on semi-recumbent SBP following the coadministration of MK-5475 and sildenafil is similar to that following administration of sildenafil alone

2.2.3 Ongoing Clinical Studies

PN006: MK-5475 PH COPD Study

A total of 9 male and female participants with PH-COPD received and completed 7 days of MK-5475 or placebo in Part 1. No SAEs or ECIs were reported and no participants discontinued due to an AE. A total of 4 AEs were reported in 4 of the 9 participants. The

most common AE was headache (3). Preliminary blinded review of data showed that MK-5475 360 µg or placebo was generally well tolerated based on review of safety assessments. Following once daily inhaled administration of MK-5475 at 360 µg to participants with PH-COPD for 7 days, median time to reach maximum systemic plasma concentrations was 1 hour post dose on Day 1 and Day 7. Geometric mean t1/2 was approximately 2 hours. Geometric mean Cmax and AUC0-24 at 360 µg on Day 1 were 0.830 nM and 3.31 nM*hr, respectively. Geometric mean Cmax and AUC0-24 at 360 µg on Day 7 appeared to be higher than those on Day 1, with an accumulation ratio of approximately 1.2 for Cmax and approximately 1.3 for AUC0-24. AUC 0-24 was slightly less than the NOAEL on Day 7. It is noted that the mean concentrations at 1 hour post dose from Days 2 to 6 were comparable to that on Day 7, suggesting consistent exposures from Days 2 to 7. One participant had a much higher plasma exposure than other participants contributing PK data reported in this memo, with the AUC0-24 value of 10.7 nM*hr on Day 1 and 16.9 nM*hr on Day 7, compared to the projected NOAEL exposure of 4.5 nM*hr. The plasma Cmax and AUC0-24 data excluding results from the participant with very high exposure were generally comparable to that in healthy subjects receiving a single 360 µg and 380 µg MK-5475 dose in PN008.

It was determined that a second period in Part 1 was not needed based on safety and PK from Part 1 of this study.

A total of 8 patients have enrolled in Part 2, to date. No SAEs or ECIs have been reported and no participants have discontinued due to an AE. One drug-related AE of watering eyes has been reported. There was one ECI of accidental overdose reported. One participant took 1 additional dose of study drug on 2 different days. No associated AEs occurred as a result of this ECI. Preliminary blinded review of safety data showed that MK-5475 380 µg or placebo has been generally well tolerated.

PN007: Phase 2/3 Study of MK-5475 in Adults with Pulmonary Arterial Hypertension

This is a multicenter, randomized, placebo-controlled, parallel-group, double-blind Phase 2/3 adaptive study to evaluate the efficacy, safety and tolerability of inhaled MK-5475 in adult participants with PAH. A total of 3 participants have enrolled, to date. One SAE of gastrointestinal bleed was reported in 1 participant. The participant was on warfarin therapy and thus, this AE was determined to be not related to study drug.

PN008: MK-5475 Formulation Bridging Study

This is a randomized, open-label, crossover, balanced study to compare the relative bioavailability of the MK-5475 Phase 1 formulation of 360, 120 µg and 240 µg to FMF of 380, 100 and 195 µg, respectively. A total of 50 male and/or female participants have enrolled and received single-inhaled doses of MK-5475 ranging from 100 to 380 µg in this study. As the study is ongoing, the data presented is preliminary. No SAEs or ECIs have been reported and no participants have discontinued due to an AE. A total of 10 non-serious AEs have been reported in 9 participants. All AEs were rated as mild in intensity. The most common AE reported is headache (3) and macular rash (2). The 2 AEs of macular erythema rash were reported in 2 participants. The one participant developed a rash 24 hours postdose in Period 2. According to the investigator the rash appeared to look like insect bites. The

participant reported having been outdoors a few days prior to the dosing period. The second participant had a medical history of rash and it had worsened during the dosing period. The investigator deemed the AEs of rash as not related to study drug.

In healthy participants, median Tmax was 1-hour post dose following a single-dose inhalation at the 380 µg or 360 µg dose; geometric mean apparent terminal half-life was approximately 2 hours for either dose. Variability in PK parameters for the 380 µg dose using the single-actuation FMF was similar to that for the 360 µg (6 x 60 µg) dose using the Phase 1 formulation. The geometric mean Cmax (0.56 hr*nmol/L) and AUC (2.02 hr*nmol/L) following a single-dose inhalation at the 380 µg dose were lower than those at 360 µg. Cmax and AUC0-inf geometric mean ratio (90% confidence interval) (GMR [90% CI]) for the 380 µg to 360 µg comparison were 0.81 [0.69, 0.95] and 0.78 [0.66, 0.90], respectively. Whereas the Cmax comparison met the predefined comparability bound of 0.67-1.5, the lower 90% CI for AUC0-inf GMR was just below the predefined lower comparability bound.

2.2.4 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 medicine.

By delivering this compound via the inhaled route, 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 is to be conducted in male and female participants diagnosed with PH-COPD.

Objectives	Endpoints
Primary	
• Objective: To assess the safety and tolerability of MK-5475 in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease following 7 and 28 days of dosing. (Parts 1, 2 and 3)	• Safety and tolerability will be evaluated during clinical assessments that include vital signs, safety laboratory testing, physical examinations, ECG readings, and review of adverse events (AEs). (Parts 1, 2 and 3)
• Objective: To assess the effect of MK-5475 on pulmonary vascular resistance following 28 days of dosing in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease. (Part 2) • Hypothesis: MK-5475 reduces mean pulmonary vascular resistance following 28 days of dosing in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease when compared to placebo. A true mean difference (MK-5475-placebo) of 15% is considered clinically meaningful. (Part 2)	• Percent change from baseline for PVR of MK-5475/placebo on Day 28 in Part 2.
Secondary	
• To obtain preliminary plasma pharmacokinetic data of MK -5475 (e.g AUC0-24, AUC0-inf, Cmax, Tmax, terminal half-life, accumulation ratio) in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease (Parts 1, 2 and 3)	• AUC0-inf, AUC0-24, Cmax, C24, Tmax, apparent terminal half-life, accumulation ratio
• To assess the effect of multiple inhaled doses of MK-5475 on pulmonary blood volume in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease (Parts 2 and 3)	• Percent change from baseline for PBV of MK-5475/placebo on Day 28 in Parts 2 and 3.

Objectives	Endpoints
Tertiary/Exploratory	
• To assess the physiologic effects of multiple dose MK-5475 during cardiopulmonary exercise testing (Parts 2 and 3) in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease	• VO2max, exercise capacity, ventilatory efficiency, cardiopulmonary vs. pulmonary limit to exercise and ventilation/perfusion matching
• To explore the relationship of MK-5475 concentration and summarize changes in pulmonary vascular resistance, pulmonary artery pressure, cardiac output/cardiac index, mixed venous oxygen saturation, arterial oxygenation and systemic vascular resistance in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease (Part 2)	• Mean pulmonary artery pressure (mPAP), systemic vascular resistance (SVR), cardiac output (CO)/cardiac index (CI) and mixed venous and arterial oxygenation
• To explore the effects MK-5475 has on 6MWD and level of dyspnea (Parts 1, 2 and 3)	• 6 MWD w/ Borg Dyspnea scale and SOBQ
• To assess the effect of MK-5475 on NTproBNP relative to placebo following 28 days of dosing in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease (Parts 2 and 3)	• Percent change from baseline in NTproBNP levels
• To explore the relationship between genetic variation and response to the treatment(s) administered and mechanisms of disease. Variations across the human genome may be analyzed for association with clinical data collected in this study. (Parts 1, 2 and 3)	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a 3-part, randomized, multi-site study of MK-5475 in participants with PH-COPD. Up to approximately 48 participants will be enrolled.

Part 1 of this study is a double-bind, randomized, placebo-controlled, multiple-dose assessment of safety, tolerability and PK of inhaled MK-5475 in male and female participants diagnosed with PH-COPD. Up to approximately 9 participants will be randomized in a ratio of 6 active (MK-5475 360 µg) and 3 placebo. A minimum of 3 of these participants will fall in the age range of 70 to 80 years. Participants will dose each morning for 7 consecutive days. In Period 1, witness dosing of MK-5475/pbo and scheduled study procedures will occur on all days at the clinical research unit (CRU). Review of available safety and PK data will occur following the 7 days of dosing.

If the PK data from the first 24 hours after Day 1 dosing with 360 ug MK-5475 is substantially lower than observed with patients with PAH, then a second 7-day dosing period will be conducted at a higher dose. Review of a minimum of 4 participants Day 1 PK will be the basis for this decision because prior studies (PN003) demonstrated little to no accumulation with daily dosing. Witness or at home dosing for Period 2 will be dependent on the dosing regimen defined. If needed, in order to ensure 2nd daily dosing adherence and to assess for AEs, at home dosing in combination with telephone contact will occur on all days.

If eligible, participants from Part 1 may continue into Part 2 upon confirmation by the SPONSOR.

Part 2 of this study is a double-bind, randomized, placebo-controlled, multiple-dose assessment of safety, tolerability, PK and PD of inhaled MK-5475 in male and female participants diagnosed with PH-COPD. Up to approximately 24 participants will be randomized with 2:1 ratio of 16 active (MK5475 380 µg) and 8 placebo. Participants will dose each morning for 28 consecutive days. The timing of dosing in Part 2 will be determined following review of PK data from Part 1. PD assessments include PVR by RHC, PBV by FRI with an IV iodinated contrast agent and exercise tolerance via CPET . Baseline PD assessments for PVR, PBV and exercise tolerance will occur a minimum of 1 day but, no more than 5 days prior to dosing on Day 1. At the discretion of the investigator, PD procedures can be completed on the same day or across the 5-day window. Witness dosing of MK-5475/pbo and scheduled study procedures will occur on Days 1, 15 (+/- 1 day) and 28 (+4 days/-1 day) at the CRU. The Day 28 PD assessments for PVR and PBV will occur 6 to 8 hours post dose. To allow flexibility in scheduling of RHC and FRI procedures, dosing may extend to a maximum of 32 days. If the RHC or FRI procedure is scheduled to extend beyond 30 days, participants may be required to return to the CRU to receive a new DPI based on DPI time in use allowances as defined in the study operations manual. Witnessed dosing and the full complement of study procedures scheduled for Day 28 will occur on the day when RHC measures are performed. In order to ensure dosing adherence and to assess for AEs, at home dosing in combination with telephone/virtual technology contact will occur on all other days.

Pharmacodynamic Assessments

In Part 2, pulmonary hemodynamic measurements via RHC will be performed. A minimum of 2 pulmonary hemodynamic measurements taken a minimum of 5 minutes apart, including PVR calculated from data obtained by thermodilution (see manual of operations) will occur at least 1 but, no more than 5 days prior to dosing the first dose of study drug. Values from the 2 consecutive PVR measurements should be within 15% (highest PVR value will define the 15%) of each other to confirm a stable baseline. If the 2 PVR measurements deviate more than 15%, up to 2 additional PVR measurements may be obtained. If a stable baseline cannot be obtained after 4 measurements, the participant will not be eligible to participate in the study. Along with confirming a stable PVR, the following parameters are to be met at baseline RHC in order to continue participation:

1. Mean Pulmonary Arterial Pressure (mPAP) ≥ 25 mmHg. The mean of the mPAP from the 2 individual measures that were used for PVR calculation taken at least 5 minutes apart will serve as the mPAP.

2. PVR ≥ 3.75 Woods units (or ≥ 300 dynes/sec/cm5)

3. Pulmonary Artery Wedge Pressure (PAWP) ≤ 15 mmHg. The mean of the 2 values used to calculate PVR as described above may be used to define the baseline PAWP.

Details on RHC parameters to be performed are noted in the SOA and Section 8.7.1.

Computed tomography (CT) scans with an iodinated contrast agent to assess PBV at baseline and following 28 days of dosing will occur in Part 2 and Part 3. Details on FRI are noted in Section 8.7.2.

A novel CPET procedure to assess exercise tolerance/functional capacity at baseline and following approximately 28 days of dosing will occur in Part 2 and Part 3. Under special circumstances, omission of the CPET procedure will be permitted for the following reasons:

- Technical reasons (e.g. CPET device malfunction)

- Regulatory reasons (e.g. Trade Ministry or Customs denies or delays importation of device)

All participants will be asked to perform the CPET procedure. If a participant is unable to complete the test for the scheduled 3 minutes, documentation of the stop time of the exercise portion of the procedure should be recorded.

Part 3 of this study is a double-bind, randomized, placebo-controlled, multiple-dose assessment of safety, tolerability, PK and PD of inhaled MK-5475 in male and female participants diagnosed with PH-COPD. The timing as to the start of Part 3 will be determined by the Sponsor based on data from Part 2. Specifically, if analysis of incoming RHC, FRI and CPET data suggest that FRI is a reasonable surrogate for some RHC measurements, a larger sample size FRI and CPET will then be useful in order to further explore the

pharmacodynamic properties of this compound on pulmonary blood flow (FRI) and exercise physiology (CPET). Part 3 participants will not undergo RHC procedures as part of this study. Part 2 will continue to enroll participants who will undergo RHC. Up to 15 Part 3 participants will be randomized with a 2:1 ratio active (MK-5475 up to 380 µg): placebo. Participants will dose each morning for 28 consecutive days. PD assessments include PBV by FRI with an IV iodinated contrast agent and exercise tolerance via CPET. Baseline PD assessments for PBV and exercise tolerance will occur a minimum of 1 day but, no more than 5 days prior to dosing on Day 1. At the discretion of the investigator, PD procedures can be completed on the same day or across the 5-day window. Witnessed dosing of MK-5475/pbo and scheduled study procedures will occur on Days 1, 15 (+/- 1 day) and 28 (+4 days/-1 day) at the CRU. The Day 28 PD assessments for PBV will occur 6 to 8 hours post dose. To allow flexibility in scheduling of FRI and CPET procedure, dosing may extend to a maximum of 32 days. If the FRI or CPET procedure is scheduled to extend beyond 30 days, participants may be required to return to the CRU to receive a new DPI based on DPI time in use allowances as defined in the study operations manual. Witnessed dosing and the full complement of study procedures scheduled for Day 28 will occur on the day when the first PD measures (CPET or FRI) are performed. In order to ensure dosing adherence and to assess for AEs, at home dosing in combination with telephone/virtual technology contact will occur on all other days.

Because this is a Phase 1 assessment of MK-5475 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

This study is being conducted to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of MK-5475 after administration of multiple doses to participants with PH-COPD. Preclinical and clinical studies in healthy and PAH participants with this compound support the conduct of this study, given the evidence that the compound appears to be safe, well-tolerated, and has suitable single-dose pharmacokinetics to support an evaluation of multiple dosing in this patient population.

Because this is the first introduction of this compound into participants with PH-COPD, Part 1 of the study is designed to evaluate safety, tolerability, and pharmacokinetics in this population. A smaller group of participants will be administered the dose of 360 µg daily for seven days, with careful observation and monitoring of safety parameters. At the end of this period, safety and PK data will be reviewed to determine whether Part 2 will be triggered. In prior/ongoing studies with this compound, PAH patients have been found to experience lower systemic exposures than healthy participants, presumably based on respiratory impairment associated with their disease. As such, if the PK data from this initial dosing

period is lower than expected, an additional seven-day period of dosing may be repeated in Part 1 at a higher dose, after which the safety and PK data will be reviewed again to determine whether Part 2 should be triggered.

Once the safety, tolerability, and pharmacokinetics have been established in Part 1, pharmacodynamic assessments will be performed in a larger group of participants. The primary assessment for this study, right heart catheterization, is directly related to the ultimately desired clinical efficacy endpoint for this compound and is well-validated in the published literature. In addition, imaging and exercise testing will be used as exploratory measurements to evaluate various aspects of the physiological response to dosing. In Part 3, right heart catheterization will be omitted from the pharmacodynamic assessments, and only FRI and CPET assessments will be conducted. The purpose is to increase the sample size for FRI and CPET to make more robust evaluations of these pharmacodynamic effects. Other endpoints are as noted below.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The Borg Dyspnea Score, UCSD SOBQ and 6-Minute Walk Test (6MWT) are potential endpoints for later clinical studies and will be included to provide preliminary estimates of the impact MK-5475 may have on these parameters.

4.2.1.2 Safety Endpoints

Evaluation of clinically relevant safety parameters will include vital signs, 12-lead ECG, laboratory safety tests (blood and urine chemistry, hematology, anticoagulation tests) at pre-specified timepoints and adverse events throughout the study. Oxygen saturation via pulse oximetry and arterial blood gases will be measured to evaluate the potential for V/Q mismatch. Given this is the first time MK-5475 is being given in the PH-COPD population, these endpoints were chosen to provide a comprehensive evaluation of safety and tolerability of MK-5475.

4.2.1.3 Pharmacokinetic Endpoints

MK-5475 is an inhaled drug being developed for the management of PAH and PH -COPD. As with any inhaled compound, pharmacokinetic exposures are primarily determined by lung burden, which cannot be directly measured. Therefore, the pharmacokinetic end-points for this study will consist of systemic assessments of AUC0-24, AUC0-inf Cmax, C24, Tmax, apparent terminal half-life and accumulation ratio. Acknowledging the limitations of these data, they will be utilized for pharmacokinetic modeling and assessment of the safety margin with regard to systemic exposure.

4.2.1.4 Pharmacodynamic Endpoints

Reduction in PVR is being employed as the primary pharmacodynamic endpoint. 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), and the relationship between PVR and the ultimate clinical endpoint of 6-minute walk distance (6MWD) is well established.

Broadly speaking, FRI imaging will be used because of its potential to inform multiple aspects of clinical development. The primary readout of PBV change will be compared with PVR and will enable estimates of the regional deposition of compound with comparison to regional pharmacodynamic effect within the lung. In COPD, this technique is of particular interest because it will provide data for the presence or magnitude of V/Q mismatch.

Exercise testing (CPET) provides an extensive amount of information on both cardiac and pulmonary function during exercise. This will provide an estimate of whether cardiovascular performance improves relative to pulmonary performance. This will also allow an estimate of the improvement of exercise performance with treatment, which will supplement the other pharmacodynamic measures being performed. Finally, CPET will enable quantitation of the impact of MK-5475 on gas exchange, which will be used to evaluate the potential for V/Q mismatch after multiple dosing.

Assessment of NT pro BNP will be performed. This may provide additional information on disease severity in this population at baseline and Day 28.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 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 absorption, distribution, metabolism, and excretion; 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 multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct future biomedical research on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research 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 future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

One of the primary objectives of this study is to evaluate the safety and tolerability of MK-5475 in this population. The inclusion of a placebo-control will facilitate an unbiased assessment of safety and tolerability. Because this is the first assessment in participants with PH-COPD, they may not receive clinical benefit from MK-5475 thus, an active comparator is not justified.

4.3 Justification for Dose

The methods used in calculating doses and estimated exposures are detailed in Sections 4.3.1 and 4.3.2.

As this is a Phase 1 assessment of MK-5475 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.3.1 Starting Dose for This Study

Because MK-5475 is delivered via the inhaled route, calculations for the human equivalent dose (HED) in the lung are used to set dosing guidelines. As noted in Section 2.2.2, the NOAEL was selected based on the 1-month dog inhaled toxicology study. At the NOAEL dose of 0.02 mg/kg/day, slight bronchial artery thickening was seen in the 1-month study, but was no longer observed in the 3-month study. The HED for the NOAEL dose of 0.02 mg/kg is adjusted for the dog weight of 10 kg and the lung deposition factor of 25% to yield a lung exposure of 50 µg (20 µg /kg * 10 kg *0.25 = 50 µg). This is adjusted for the presumed dog lung size of 100 g to yield an estimated lung burden of 0.5 µg /g. Adjusted for human lung size, with a presumed weight of 1000 g, and assuming 100% deposition in humans, the human delivered dose corresponding to the dog NOAEL would be 500 µg, and the corresponding systemic exposure level would be 4.5 nM*hr AUC 0-24h.

The starting dose for this study will be 360 µg inhaled, delivered once daily for seven days in Part 1. This dose has already been delivered to participants in PN002, and the observed systemic AUC 0-24h at that dose was 1.45 nM*hr. While multiple dosing has not been performed at this dose, in PN003 healthy participants were dosed with multiple doses of 240 µg, with resulting systemic AUC 0-24h of 2.00 nM*hr, higher than that seen at 360 µg in PAH patients. As noted in section 2.2.3, systemic exposures have been consistently higher in

healthy participants compared with patients, likely due to their ability to generate a more robust inhalation. In addition, multiple dose PK has not demonstrated accumulation over time. Therefore, performing multiple dosing at 360 µg daily is justified by the fact that this dose has previously been given in single doses to patients, and that healthy participants have previously been observed to achieve and tolerate higher exposures when given multiple doses of 240 µg.

4.3.2 Maximum Dose/Exposure for This Study

The planned starting dose of 360 µg once daily in Part 1 will be transitioned to a maximum dose of 380 µg inhaled once daily for Part 2 and 3. The Part 2 and 3 dose will utilize a formulation which is intended to deliver the entire dry powder dose in one inhalation, as compared with the formulation used in Part 1 which requires 6 inhalations to deliver 360 µg. The formulation of 380 µg used for Parts 2 and 3 has been shown in a clinical study to have similar PK to the formulation of 360 µg used for Part 1. This dose of 380 µg will be the maximum dose for this study, except in the event that systemic PK in Part 1 is lower than AUC 0-24h of 1.4 nM*hr. In Part 1 of the currently ongoing PN002 in PAH patients, systemic PK levels at the 120 µg dose were found to be substantially lower than expected (based on prior data from healthy participants) and thus the clinical dose was increased. Although lung PK cannot be directly measured, systemic PK is assumed to be a surrogate for lung deposition of compound, and thus far clinical data have shown that systemic PK of MK-5475 is correlated with PVR reduction. Because COPD patients are predisposed to lower ability to generate adequate inspiratory flow, it is anticipated that their systemic PK may again be lower than anticipated due to lower deposition of compound in the deep lung. If this is the case, a second 7-day dosing period will be triggered using a higher dose of MK-5475, up to 380 µg inhaled twice daily. The expectation is that this higher dose will not approach or exceed the NOAEL AUC 0-24h exposure of 4.5 nM*hr. The timing of this divided dose will be determined based on the PK data from Part 1. See below Table 1 for GM exposures previously observed in PN 002 and PN003 as well as predicted exposures in the PH-COPD population.

Table 1 Geometric Mean AUC0-24 Actual and Predicted

	Actual: Following Multiple 240 µg Inhaled Administration in Healthy Subjects in PN003	Actual: Following Single 360 µg Inhaled Administration in PAH Participants in PN002	Predicted Following Multiple 360 µg Inhaled Administration in PH-COPD Patients	Predicted Following Multiple 380 µg Inhaled Administration in PH-COPD Patients
Geometric Mean AUC0-24hr (nM*hr)	2.00	2.58	~2.58	~2.0

The estimated total radiation burden per participant after the completion of all CT scans will not exceed the maximum limit of 10 mSv [Directorate-General, Environment Nuclear Safety

and Civil Protec 1998]. If there is a need for fluoroscopy during RHC, the total radiation exposure during RHC will be equivalent to the amount of radiation the participant would receive if fluoroscopy was performed during RHC for initial diagnosis or follow-up. This study does take into account the desired yearly limit for study participants as per ICRP publication 62.

4.3.3 Rationale for Dose Interval and Study Design

In this study, participants will be dosed with 360 µg of MK-5475 in Part 1 and 380 µg in Parts 2 and 3 daily. As noted above, this dose has been previously administered to PAH patients in PN002, and a lower dose that resulted in higher systemic exposures has been previously administered to healthy participants in PN003. These studies were delivered with the following supportive data: MK-5475 acts via a well-established mechanism (sGC stimulator), for which a marketed agent acts similarly [riociguat]. Safety assessment toxicity trials and ancillary pharmacology trials with MK-5475 provide no contraindications to clinical trials in people with this compound via the inhaled route. No dose-limiting toxicities were observed in 1- or 3-month rat and dog toxicity trials, and substantial preclinical safety margins were obtained over initial human doses. As with the previous studies, safety will be ensured by the inclusion of extensive safety monitoring in the clinic, and the fact that MK-5475 is not considered a compound with a high degree of uncertainty, which is supported by both preclinical and clinical evidence. There will be frequent, careful assessments of adverse events throughout the postdose period. This recommendation is in keeping with the projected safety profile and the ability of the clinical site to monitor each participant closely.

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 from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

A primary objective of this early Phase 1 study is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve PK, pharmacodynamic, and/or biologic

targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/Female participants with PH-COPD between the ages of 40 and 80 years (inclusive) (Parts 1and 2) or between the ages of 40 and 85 years (inclusive) (Part 3).

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets the following criteria:

Type of Participant and Disease Characteristics

1. Be judged to have no untreated, clinically significant health issue from other co-morbidities based on medical history, physical examination, vital signs and electrocardiograms performed at the screening visit(s). Health issues associated with severe obesity (BMI 35 to 40 kg/m^2) and considered not clinically significant may be permissible at the discretion of the investigator and in consultation with the Sponsor.

2. Be judged to have no untreated, clinically significant health issue from other co-morbidities based on laboratory safety tests performed at the screening visit(s). Appendix 10.10 provides an algorithm for the assessment of out of range laboratory values. Health issues associated with severe obesity (BMI 35 to 40 kg/m^2) and considered not clinically significant may be permissible at the discretion of the investigator and in consultation with the Sponsor.

3. Have a body mass index (BMI) ≤ 40 kg/m^2, inclusive at screening. Investigator site should verify CT scan equipment can accommodate participant size. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI= weight(kg)/height (m) ^{2}. Body weight should not exceed 160 kg.

Demographics

4. Is male or female, from 40 years to 80 years of age inclusive (Parts 1 and 2) and from 40 to 85 years of age inclusive (Part 3), at the time of signing the informed consent. For Part 1, a minimum of 3 participants that will be randomized need to fall in the range of 70 to 80 years of age.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

5. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 14 days, corresponding to time needed to eliminate study intervention(s) (eg, 5 terminal half-lives) plus an additional 90 days (a spermatogenesis cycle) after the last dose of study intervention.

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual 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, corresponding to the time needed to eliminate any study intervention(s) (eg, 5 terminal half-lives) after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

    - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

    - Additional requirements for pregnancy testing during and after study intervention are located in Appendix [2].

    - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

8. Is willing to comply with the study restrictions (See Section 5.3 for a complete summary of study restrictions).

9. Have been diagnosed with mild to severe COPD according to GOLD diagnostic criteria (postbronchodilator FEV1/FVC ratio < 0.7)

10. Has MMRC Dyspnea Score in the range of 1 thru 3 at screening.

11. Be deemed clinically stable by the investigator.

12. Have a hemoglobin (Hgb) > 75% of the lower limit of the normal range (at screening).

13. Be or have suspected Pulmonary Hypertension Group 3 in particular:

    3.1 Chronic Obstructive Pulmonary Disease (COPD)

14. Have a history of RHC within 3 years of starting study medication demonstrating mPAP ≥ 25mmHg and PVR ≥ 3.75 Woods units or 300 dynes/sec/cm^5.

OR

Have an echocardiogram performed by the investigator (or appropriate designee) at screening or within 1 year of screening demonstrating pulmonary artery systolic pressure ≥ 38 mmHg (Part 1 only) or ≥ 50 mmHg (Part 2 only) in conjunction with one or more of the following: tricuspid regurgitation velocity >3 m/s or significant right heart enlargement and or reduced right heart function. In the event that echocardiography is technically challenged, the PI may elect to accept other echocardiographic evidence (i.e. morphologic or functional measurements of the heart chambers, valves or great vessel) of good quality of pulmonary hypertension in consultation with the sponsor (Parts 1 and 2 only).

NOTE: For Part 3, prior history of RHC is required for inclusion.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has pulmonary hypertension subtypes including the following according to Nice 2013

   Group 1 Pulmonary arterial hypertension (PAH)

   - 1.1. Idiopathic PAH
   - 1.2. Heritable
     a) BMPR2
     b) ALK1, endoglin, SMAD9, CAV1, KCNK3
     c) 1.2.3. Unknown
   - 1.3. Drug and toxin-induced
   - 1.4. Associated with
     d) 1.4.1. Connective tissue disease
     e) 1.4.2 HIV infection

f) 1.4.3 Portal hypertension

g) 1.4.4. Congenital heart disease (unrepaired and not requiring repair or repaired simple cardiac defects at least 1year status post corrective surgery, with no clinically significant residual shunt)

h) 1.4.5 Schistosomiasis

i) 1.4.6 Chronic hemolytic anemia

1.5 Persistent pulmonary hypertension of the newborn (PPHN)

1' Pulmonary veno-occlusive disease (PVOD) and or pulmonary capillary hemangiomatosis (PCH)

Group 2 Pulmonary hypertension owing to left heart diseases

- 2.1. Left ventricular Systolic dysfunction
- 2.2. Left ventricular Diastolic dysfunction
- 2.3. Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Group 3 pulmonary hypertension owing to lung diseases or hypoxia not associated with COPD

3.2. Interstitial lung disease

3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4. Sleep-disordered breathing. Participants with mild OSA may be permitted in consultation with the Sponsor provided OSA is not the cause of pulmonary hypertension.

3.5. Alveolar hypoventilation disorders

3.6. Chronic exposure to high altitude

3.7. Developmental abnormalities

Group 4 Pulmonary hypertension defined as Chronic thromboembolic pulmonary hypertension [CTEPH])

Group 5 Pulmonary Hypertension with unclear multifactorial mechanisms

5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleimyomatosis, neurofibromatosis, vasculitis

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

2. Has a history of clinically significant endocrine , gastrointestinal, cardiovascular (e.g. HFpEF and HFrEF), hematological, hepatic (not including chronic stable Hep B and C), immunological, renal, respiratory (not including PH-COPD), genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases.

3. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

4. 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 and **with agreement of the SPONSOR** (eg, malignancies which have been successfully treated ≥2 years prior to the prestudy [screening] visit).

5. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

6. Is positive for hepatitis B surface antigen (acute infection) or HIV. Participants with positive hepatitis B surface antigen that demonstrate low viral load (chronic stable infection) are permitted.

7. Has known sensitivity to iodine or iodine containing products (Parts 2 and 3 only).

8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

9. Has persistent or permanent atrial fibrillation with an uncontrolled ventricular rate (i.e. ventricular rate > 90 bpm) (participants with paroxysmal atrial fibrillation or controlled atrial fibrillation with no clinically significant arrhythmia may be allowed per the judgement of the investigator).

10. Has history of combined pulmonary fibrosis and emphysema (CPFE) or severe bullous emphysema. If no history, a confirmed negative high-resolution CT scan (HRCT) for these conditions needs to have been performed within last 2 years. In Parts 2 and 3, the baseline FRI scan may be used to aid in assessment of this criteria.

11. Has an active respiratory infection (common cold, influenza, pneumonia, acute bronchitis) with lung function values (FEV1 and/or FEV1/FVC ratio) that do not meet eligibility range (See INCL no. 9, EXCL no. 19) (May be rescreened upon resolution of the active infection).

12. Has a physical limitation that will inhibit the participant to effectively perform low-intensity exercise testing (e.g. severe arthritis of the hip or knee).

Prior/Concomitant Therapy

13. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

14. Is currently on monotherapy calcium channel blockers as a specific treatment for pulmonary hypertension.

15. Is currently taking nitrates, inhaled prostacyclin, immediate or extended release diltiazem, PDE5 inhibitors or sGC activators for the treatment of pulmonary hypertension. Participants previously using medications to treat PAH may be enrolled provided they have been off therapy for at least 2 weeks prior to the start of the screening period.

    NOTE: A medication should not be stopped for the purposes of meeting study criteria. However, the decision to stop/interrupt medication is based on the judgement of the investigator.

Prior/Concurrent Clinical Study Experience

16. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

17. Has a QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females) at screening and Predose Day 1 (Part 1 Period 1) or Baseline Day -1 (Part 2 and 3).

18. Has a systolic BP < 100 mmHg, diastolic BP < 40 mmHg or HR > 100 bpm at screening and Predose Day 1 (Part 1 Period 1) or Baseline Day -1 (Part 2 and 3). The mean of these values will be used to determine eligibility.

19. Has FEV1 < 30% predicted based on PFTs at screening. This is indicative of very severe COPD.

20. Does not meet the RHC criteria defined in Section 4.1 at baseline (Part 2 only).

21. Participant has an estimated creatinine clearance of ≤ 30 mL/min based on the Cockcroft Gault equation at screening:

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{72)(\text{serum creat [mg/dL]})}$$

*When creatinine is measured in micromole/litre, use the following formula: (*for females multiply result by 0.85)

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L] x } 0.0113)}$$

An actual creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the Cockcroft-Gault equation.

NOTE: Investigator is to use clinical judgement to determine appropriate degree of renal impairment and use of contrast agent for CT scans.

Other Exclusions

22. Suffers from claustrophobia and is unable to undergo a CT scan.

23. Has participated in a PET research study or other research study involving administration of a radioactive substance or ionizing radiation within 12 months prior to the screening visit or has undergone or plans to have extensive radiological examination within the period with a radiation burden over 10 mSv (such as CT scan or nuclear medicine exam) (HRCT to rule out CPFE or severe bullous emphysema in the last 2 years or any radiological examination as part of the study does not fall under plans for extensive radiological examination).

24. Is under the age of legal consent.

25. Does not agree to follow the smoking restrictions as defined by the CRU.

26. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

27. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

28. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 12 months. Participants must have a negative UDS prior to randomization.

29. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

30. Has been committed to an institution by way of official or judicial order.

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

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

On **full PK sampling days (ie, Days 1 and 7 in Part 1)** participants will fast from all food and drinks, except water, for at least 8 hours prior to the first dose of study drug administration on these days. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the Schedule of Activities. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals per individual CRU will be the same on each full PK sampling day. Upon discharge from the CRU for at home dosing (if applicable), meals and snacks will be unrestricted in caloric content, composition and timing.

On **intermediate days (Days 2-6)** in Part 1 participants will fast from all food and drink, except water, for 8 hours prior to first dosing on each of these days. There are no fasting requirements post dose. Meals and snacks will be unrestricted in caloric content, composition and timing.

In **Parts 2 and 3 Days 1, 15 and 28,** participants will fast from all food and drinks, except water, for at least 8 hours prior to first dose of study drug administration on these days. There are no fasting/meal requirements post dose and at other intermediate dosing days.

Fasting/ meal requirements prior to initiation of exercise testing, FRI and RHC (Part 2 only) will be determined by the investigator as per local SOP.

Up to 240 mL of water may be provided following the last inhalation of study drug administration. Additional water will be restricted 1 hour prior to and 1 hour after study drug administration on full PK sampling days. There are no water restrictions on intermediate days.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study and until the poststudy visit.

On **full PK sampling days (ie, Days 1 and 7 in Part 1; Days 1 and 28 in Parts 2 and 3),** participants will refrain from the consumption of all fruit juices 24 hours prior to study drug administration.

On all other days during the study, the consumption of all fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the prestudy and poststudy visits. On **full PK sampling days (ie, Days 1 and 7 in Part 1; Days 1 and 28 in Parts 2 and 3),** participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to study drug administration. In Part 1, caffeine restrictions will continue for 12 hours post study drug administration and in Parts 2 and 3 caffeine restrictions post dose will continue until the completion of the 3 hour post dose procedures on Day 1 and the 6 to 8 hour post dose procedures on Day 28.

At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the prestudy and poststudy visits. On **full PK sampling days (ie, Days 1 and 7 in Part 1; Days 1 and 28 in Parts 2 and 3)** participants will refrain from consumption of alcohol 24 hours prior to and after study drug administration.

At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) from the prestudy (screening) visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

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 may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention OR withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

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 and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study 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 Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Part 1	Placebo Com-parator	Pbo	Drug	Dry Powder	0 µg	0 µg	Oral	Oral inhalation once daily for 7 days	Placebo	IMP	Sponsor
Part 1	Experi-mental	MK-5475	Drug	Dry Powder	60 µg	360 µg	Oral	Oral inhalation once daily for 7 days	Experi-mental	IMP	Sponsor
Parts 2 and 3	Placebo Com-parator	Pbo	Drug	Dry Powder	0 µg	0 µg	Oral	Oral inhalation once daily for 28 days	Placebo	IMP	Sponsor
Part 2	Experi-mental	MK-5475	Drug	Dry Powder	60 µg	360 µg	Oral	Oral inhalation once daily for 28 days	Experi-mental	IMP	Sponsor
Parts 2 and 3	Experi-mental	MK-5475	Drug	Dry Powder	380 µg	380 µg	Oral	Oral inhalation once daily for 28 days	Experi-mental	IMP	Sponsor
Parts 2 and 3	Experi-mental	MK-5475	Drug	Dry Powder	100 µg	100 µg	Oral	Oral inhalation once daily for 28 days	Experi-mental	IMP	Sponsor
Parts 2 and 3	Experi-mental	MK-5475	Drug	Dry Powder	195 µg	195 µg	Oral	Oral inhalation once daily for 28 days	Experi-mental	IMP	Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Parts 2 and 3	Experi-mental	MK-5475	Drug	Dry Powder	32 µg	32 µg	Oral	Oral inhalation once daily for 28 days	Experi-mental	IMP	Sponsor

The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Abbreviations: µg = micrograms; Pbo=placebo

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon 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

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

MK-5475 and placebo for inhalation will be dosed per the instructions outlined in the Study Operations Manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule.

See Table 3 and Table 4 for sample allocation schedule.

Table 3 Sample Allocation schedule (Parts 1 and 2)

Sample Size (N)	Part 1 Period 1	Part 1 Period 2 *	Part 2
16	MK-5475 dose 1	MK-5475 dose 2	MK-5475
8	Placebo	Placebo	Placebo

*if applicable

9 subjects will participate in Part 1. 24 subjects will participate in Part 2. Participants from Part 1 may participate in Part 2 upon agreement with Sponsor and if deemed eligible.

The first 9 allocation numbers on the schedule will be used for Part 1. Replacement numbers in the 100s will be used to replace subjects that don't complete Part 1 as well as any subject that completes Part 1 but either doesn't participate in Part 2 or discontinues during Part 2. This is to ensure that the treatment that the Part 1 subject would have received in Part 2 is given to the Part 2 "replacement" subject in order to maintain the desired 2:1 randomization.

Replacement numbers in the 200s will be used to replace those subjects that discontinue who were assigned a replacement number in the 100s.

Replacement numbers in the 300s will be used as rescue numbers, as needed

Table 4 Sample Allocation schedule (Part 3)

Sample Size (N)	Part 3
10	MK-5475
5	Placebo

6.3.2 Stratification

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

6.3.3 Blinding

A double-blinding technique will be used. MK-5475 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant to ensure that proper technique was performed during inhalation of the study intervention.

When participants self-administer study intervention(s) at home, adherence with study intervention will be assessed. Adherence will be assessed via telephone or virtual technology contact [direct questioning, verbal or visual verification of dosing, proper inhalation technique] and documented in the source documents and CRF. In case virtual technology is used in Parts 2 and 3, a smartphone application will be used to video record dosing with the aid of facial recognition and artificial intelligence technology to ensure study medication is correct and properly dosed. The application's interactive software sends information to a secure server and the CRU will be able to access the information via a secure web portal to monitor participant adherence.

Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the DPI device dispensed and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

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

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

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

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

Listed below are specific examples of permitted (but are not limited to) concomitant therapy or vaccination:

1. Paracetamol/acetaminophen for minor ailments without sponsor consultation.
2. Angiotensin converting enzyme inhibitors (e.g., enalapril)
3. Angiotensin receptor blockers (e.g., losartan)
4. Medications for the treatment of COPD (e.g. LABA, SABA, LAMA, mucolytics and ICS).

   NOTE: There should be a minimum of 3 minutes elapsed between dosing of any inhaled COPD medication and dosing of MK-5475/pbo.
5. Certain calcium channel blockers (e.g. amlodipine) not being used for the treatment of PAH based on vasoreactivity testing.
6. Trimetazidine
7. Mineral corticoid receptor antagonists (e.g. spironolactone, eplerenone)
8. Hypoglycemic agents
9. Diuretics
10. Beta-blockers.
11. Aspirin, warfarin, low-molecular weight heparin. Anticoagulation management and risks with regard to performance of the RHC will be managed according to the investigator's clinical judgment.
12. HRT

13. Local anesthetic (e.g. lidocaine) when performing RHC insertion procedure per site SOPs.

14. If needed for the RHC period, intravenous sedatives (e.g., midazolam) or analgesics (e.g., fentanyl) may be given preferably before the procedure and may be used judiciously during the procedure per standard of care.

Listed below are specific examples of prohibited concomitant therapy or vaccination:

1. PDE5 inhibitors

2. sGC activators

3. Nitrates

4. Inhaled prostacyclin

5. Dual endothelin receptor antagonists

6. Immediate release or extended release diltiazem

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

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 (Escalation/Titration/Other)

Following the completion of 7 days of dosing in Part 1 in at least 4 participants, the decision to proceed to BID or increased dosing for an additional 7 days will be based on key preliminary data of safety variables (including, vital signs, 12-lead ECG, laboratory safety tests, AEs and assessment for V/Q mismatch (Oxygen saturation via pulse oximetry and arterial blood gases) from the previous dose levels up to at least 24 hours from the last dose of study drug and preliminary pharmacokinetic data (based on PK data up to at least 24 hours after Day 1 dosing). Pharmacodynamic data may be included in the dose escalation decisions (Section 8. 6). Part 2 may begin following review of safety and PK of at least 7 participants in Part 1, if needed. The timing of the start of Part 3 will be based on review of preliminary PD data from Part 2 and will be triggered at the discretion of the Sponsor. Upon the triggering of Part 3, Part 2 may continue to run in parallel at the Sponsor's discretion.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, participants may:

- Receive the same dose level to further explore safety and tolerability at that level,

- Receive a lower dose of the study intervention,
- Receive the same or lower dose as a divided dose,
- Receive a lower dose with or without food, or
- Dosing may be stopped.

Participant discontinuation criteria are outlined in Section 7.

6.6.1 Stopping Rules

The following stopping rules will be employed during the conduct of this study.

If any of the below stopping rules are met, the study will be paused and no further dosing will occur until the Sponsor has reviewed the totality of data available. In order to continue the study (upon joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study drug by the investigator.

2. Three (3) or more participants report severe non-serious AEs (ex. hypoxia AEs) considered related to study drug by the investigator.

If any of the below stopping rules are met, subsequent doses may be lowered based upon joint agreement of the Sponsor and investigator in order for the study to continue.

1. Should the emerging PK (mean) data indicate that the maximum clinical exposure (Cmax or AUC), as defined in Section 4.3 will be exceeded, subsequent higher doses will be adjusted based upon joint agreement of the Sponsor and investigator.

2. Individual stopping criteria: Hemodynamic changes that exceed the pre-specified parameters (See Appendix 10.11)

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity for this study]. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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 prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9.

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 interrupts study intervention administration for more than 2 consecutive days or has 3 cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen (confirmed by recheck) at any time during the course of the study.
- Part 1 participant does not meet the echocardiogram or baseline RHC or exercise criteria for Part 2 (See Sections 4.1 and 5.2).

For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 8.1.9, or if available, a protocol clarification letter.

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 future biomedical research, 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.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 500mL (See operations/laboratory manual).

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 5 weeks before screening.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

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 identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

On clinic visit days in Parts 1, 2 and 3, administration of study intervention(s) will be monitored by the investigator and/or study staff.

During at home dosing, telephone contact or virtual technology use will occur to ensure study intervention adherence (Section 6. 4).

8.1.8.1 Timing of Dose Administration

After it is confirmed that the participant meets eligibility, the first dose of study intervention will occur after the completion of predose study procedures. The time of the dose will be designated as time “0” and the exact time of administration will be recorded. Dosing will continue once daily in the morning. In Part 1 dosing will occur at or near the same time

everyday within the allowable window noted in Section 8.11.5. In Parts 2 and 3, a window of +/- 2 hours from the time of Day 1 dosing will be permitted on remaining dosing days. Following review of PK in Part 1, Period 1, if it is determined that subsequent dosing (Part 1, Period 2 and Part 2) is split into 2 administrations each day, the first dose will be designated as time "0" and all postdose procedures will be anchored off this dose. For any participants from Part 1 that may go into Part 2, a minimum 14-day washout will occur prior to dosing.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.11 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that 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.

8.1.11 Domiciling

In Part 1, participants may report to the CRU the evening prior to the scheduled day of administration of the study intervention at the discretion of the investigator on Days 1 and 7. Participants will remain in the unit until the Day 2, 1-hour postdose and Day 7, 24-hour postdose procedures have been performed. At the discretion of the investigator, participants may be requested to remain in the CRU longer. The decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

In Parts 2 and 3, participants will report to the CRU for Day -1(up to Day -5) for baseline PD procedures RHC (done in Part 2 only), FRI and CPET and will remain in the CRU post procedure as determined by the investigator. Participants may report to the CRU the evening prior (or sooner at a date specified for some of the baseline activities) to the scheduled day of administration of the study intervention, at the discretion of the investigator on Day 1. Participants will remain in the unit until the 3-hour, postdose procedures have been performed. At the discretion of the investigator, participants may be requested to remain in the CRU longer. Participants will report to the CRU for study intervention and study procedures on Day 15. On Day 28 (+4/-1 days) participants may report to the CRU the evening prior to the scheduled day of administration of the study intervention and will remain in the CRU post PD procedures as determined by the investigator. If the CRU is unable to domicile the participant overnight the evening prior to Day 28 (+4/-1 days), (in Part 2 or Part 3), the participant will be domiciled at a facility (e.g. hotel) in close proximity to the CRU in order to ensure timely reporting for dosing and study procedures.

8.1.12 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.

8.2 Efficacy Assessments

The 6MWT, as an assessment of functional capacity will be performed in accordance with "Guidelines of the Six-minute Walk Test" [American Thoracic Society 2002] by the American Thoracic Society (ATS)." This assessment requires the participant to walk as far as possible on a flat surface (e.g. hallway) over a period of 6 minutes. Participants will be asked to rate their level of dyspnea and fatigue at baseline and following completion of the 6MWT with the use of the Borg Dyspnea Clinical Rating Scale. Details of the 6MWT can be found in the study operations manual.

The SOBQ asks participants to rate their level of breathlessness on a 6-point scale when they perform or if they were to perform certain tasks associated with daily living. Questions about limitations due to breathlessness are also asked.

Refer to SOA for planned timepoints of these assessments.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded. The screening physical examination should include an assessment of arterial blood flow to the hands by Allen Test to determine suitability of radial artery for ABG collection.

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

In Parts 2 and 3, targeted physical examination will consist of assessment of cardiovascular and respiratory systems.

BMI

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body Mass Index will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

8.3.2 Vital Signs

- Oral, Tympanic or Temporal temperature, pulse rate, respiratory rate, and blood pressure will be assessed. The same method should be used for all measurements.
- Blood pressure and pulse measurements will be assessed in a supine or semi-recumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semi-recumbent OR supine position for at least 10 minutes prior to having VS measurements obtained. Semi-recumbent OR Supine VS will include HR, systolic and diastolic BP, respiratory rate and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements. Position used for participants should be consistent during the study.

The screening and Day 1 predose (baseline) HR and BP will be triplicate measurements, obtained approximately 1-2 minutes apart. Day 1 Predose measurements will occur within 3 hours of dosing MK-5475/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose and poststudy VS measurements will be single measurements.

On Day 1 and Day 7 or 28, as applicable, participants will continue to rest semi-recumbent/sitting from dosing until 3 hours postdose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedure.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained. Participants should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic VS.

8.3.2.3 Oxygen Saturation

Indirect measurements of O_2 saturation will be obtained using pulse oximetry on each participant at the times noted in the SOA (See Section 1.3)

Direct measurements of O_2 saturation will be obtained via ABGs on each participant at the times noted in the SOA (See Section 1.3)

Indirect and direct measurements of O2 saturation will be performed on room air, so long as it is tolerated by the participant.

8.3.3 Electrocardiograms

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

In all parts, triplicate ECGs are required at predose on Day 1. The 3 individual ECG tracings should be obtained approximately 1 to 2 minutes apart. The full set of triplicates should be completed in less than 6 minutes. The mean of the measurements will be used as the baseline to calculate change from baseline for safety evaluations and rechecks, if needed. Screening, post-dose and poststudy ECG measurements will be single assessments.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in the semirecumbent OR supine for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin marker pen to ensure reproducible electrode placement.

During each treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose

time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is ≥500 msec on any postdose ECG, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a cardiac or intensive care unit) is available.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 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.

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 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

AEs, SAEs, and other reportable safety events that occur after the provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation/randomization through 14 days following cessation of 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 any time outside of the time period specified in the previous paragraph also 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 he/she 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 5.

Table 5 Reporting Time 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 - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours 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 towards 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 SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

- An overdose of Sponsor's product, as defined in Section 8.5.
- 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 must trigger 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).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug

concentrations). 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.

Additional PK samples may be drawn, if RHC (Part 2 only) , FRI and exercise testing are not performed on the same day (Day 28).

8.7 Pharmacodynamics

Pharmacodynamic assessments that are part of the RHC (Part 2 only) and FRI procedures will be performed according to the study operations and procedures manuals.

8.7.1 Right Heart Catheterization Procedure (Part 2)

Before beginning the RHC procedure, monitoring equipment should be calibrated and zeroed.

Because all of these subjects have substantial lung disease, it is recommended that pressure measurements are taken averaged over the respiratory cycle (i.e. computer-generated mean) rather than at end-expiration [Nathan, S. D., et al 2019]. At least 3 complete respiratory cycles should be included in the screen shot from which the mean value is derived. Pressures measured at each study time point will include right atrium pressure (RAP), right ventricular systolic and end diastolic pressure (RVSP, RVEDP), pulmonary artery wedge pressure (PAWP), and pulmonary artery pressure (PAP) (systolic, diastolic and mean). Cardiac output (CO), oxygen saturation and MVO_2 will also be collected.

The baseline portion of RHC will occur on Day -1 but no earlier than 5 days before (Day -5) the first dose of study intervention. In the case where the baseline RHC was performed and the participant was not randomized within 35 days from Day 1, if the participant is rescreened, the initial baseline RHC will be considered the Baseline (Day -1) measurement provided the RHC was performed within 10 weeks of randomization Day 1.

The study-related portion of the RHC will occur on Day 28 (+4/-1 days) at the 6 to 8 hour postdose timepoint. All PAP (systolic, diastolic and mean) PAWP, right atrium pressure (RAP), right ventricular systolic and end diastolic pressure (RVSP, RVEDP), will be single measurements. All measurements will be performed twice no less than 5 minutes apart after which the RHC may be removed unless clinically indicated to do earlier. The number of CO measurements at each timepoint are described in the study operations manual. Participants will undergo monitoring of systemic hemodynamics and adverse events throughout the RHC. Up to 4 measurements may be performed at baseline, if needed, as per Section 4.1.

Waveform analysis will be performed through the use of a blinded central reader.

Standard operating procedures for RHC will be developed with the site. All specifications and details will be provided in the Study Operational Manual.

8.7.2 CT Scan for Functional Respiratory Imaging (Parts 2 and 3)

The CT scans will be performed at the local imaging center according to clinical site standard operating procedures in conjunction with instructions provided in the study operations manual.

For each scanning session (Day -1 Baseline and Day 28 at 6 to 8 hours post-dose), participants will be prepped and placed in a supine position on the scanner bed. The Day -1 scan may be performed no earlier than 5 days before (up to Day -5) the first dose of study intervention. In the case where the baseline FRI was performed and the participant was not randomized within 35 days from Day 1, if the participant is rescreened, the initial baseline FRI will be considered the Baseline (Day -1) measurement provided the FRI was performed within 10 weeks of randomization Day 1.

The Day 28 scan will have a window of +4/-1 days.

An iodinated contrast agent will then be administered by IV bolus prior to each CT scan to allow for acquisition of images.

Time in the scanner for each scheduled acquisition will last under 15 minutes (window +15 minutes).

Additional details regarding imaging procedure and contrast agent are outlined in the vendor imaging manual and/or study operations manual.

8.7.3 Cardiopulmonary Exercise Testing (CPET)

In Parts 2 and 3 of the study, a novel technique for cardiopulmonary exercise testing will be performed at baseline Day -1 (Up to Day -5) and on Day 28 (+4/-1day) at 5.5 hours post dose. Participants will be asked to perform a low-intensity exercise test for a minimum of 2 minutes to a maximum of 3 minutes. Cardiopulmonary parameters including but not limited to VO2 max, exercise capacity, ventilatory efficiency, cardiopulmonary vs. pulmonary limit to exercise and ventilation/perfusion matching will be obtained.

In the case where the baseline CPET was performed and the participant was not randomized within 35 days from Day 1 (e.g. rescreening, RHC/FRI delayed), the initial baseline CPET will be considered the Baseline (Day -1) measurement provided the CPET was performed within 10 weeks of randomization Day 1.

Under special circumstances, the CPET procedure may be omitted for the reasons outlined in Section 4.1.

Additional details regarding CPET are outlined in the study operations manual.

8.7.4 Pulmonary Function Tests (PFTs- Spirometry)

PFTs should be performed as per the SoA.

Spirometry should be performed in accordance with guidelines established by the American Thoracic Society/European Respiratory Society (ATS/ERS) Standardization of Lung Function Testing: Standardization of Spirometry; 2005 [American Thoracic Society 2005]. Additional details regarding spirometry procedures will follow manufacturer's instructions and site SOPs. Every attempt must be made to use one spirometer consistently on each participant. The spirometry should be performed with the participant sitting in a chair with arms and no wheels; however, if it is necessary to test the participant standing or in another position, this should be noted on the spirometry report. The participant position should be consistent throughout the study.

In Part 1, at least three measurements (to obtain 2 reproducible) for FEV_1 and FVC will be performed at each scheduled time point. The largest FEV_1 and the largest FVC should be recorded after the data are examined from all the acceptable measurements, even if they do not come from the same measurement.

The site normal ranges are to be used to determine percent predicted.

The spirometer is to be calibrated following the principles of the ATS/ERS Guidelines and the device manual on the days when spirometry is performed. The calibration records should be kept in a reviewable log.

It is preferred that the calibration equipment that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

In all parts: The following pulmonary function tests: (FEV_1, FVC, FEV_1/FVC ratio and PEF), DLCO (DLCO, DLCO adjusted for Hgb and DLCO/VA) and lung volume (TLC, VC, IC, FRC and RV) will be captured by the pulmonary function lab as per their standard procedures at the screening visit.

PFTS performed as part of standard of care may be used for the screening visit PFTs provided these assessments were performed within 35 days of Day 1(randomization).

Part 1, Day 1 and 7 PFTs will be performed via spirometer at the CRU.

In Parts 2 and 3, the following pulmonary function parameters will be captured during the CPET procedure: FVC actual and percent predicted; FEV1 actual and percent predicted and FEV1/FVC ratio; IC actual.

In special cases where the CPET is not performed, assessment for FVC actual and percent predicted; FEV1 actual and percent predicted and FEV1/FVC ratio will be performed by spirometry.

8.7.5 Inspiratory Flow Meter Assessment

Measurements (at least 3-5 minutes apart) for inspiratory flow rate will be performed at timepoints as per the study flowchart.

The meter is to be reset following each measurement as per the instructions in the device manual. All measurements obtained will be recorded

Additional details regarding Inspiratory Flow Meter Assessment are outlined in the study operations manual.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and 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 drawn 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.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided 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

8.10 Health Economics Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

Approximately up to 5 weeks prior to intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.11.2 Treatment Period

Part 1

After pre-dose procedures have been completed and it is confirmed that the participant meets eligibility, the participant will be assigned a unique randomization number. The participant will be administered MK-5475 or placebo as an inhalation. The time of the dose will be designated as time "0" and the exact time of administration will be recorded. Post-dose study procedures will be performed according to the SoA. At the discretion of the investigator, participants will be discharged from the CRU after completion of the final post dose procedure on Day 2. Participants will return daily on Days 3 thru 6 for witness dosing and any scheduled study procedures as defined in the study flowchart. Participants will be readmitted in preparation for Day 7 study procedures (can be admitted on site the evening before) and will remain in the CRU until 24-hour postdose procedures are complete.

If a second dosing period is needed, participants will do the same as described above. If a second daily dose is required and it is determined the dose will occur at home, the CRU will contact the participant via phone to ensure dosing adherence and proper dosing technique.

Participants from Part 1 may continue into Part 2, if agreed upon by the SPONSOR. If it is determined that a participant can continue into Part 2, an assessment of AEs/SAEs will occur via a phone call about 14 days after the last dose of study intervention in Part 1.

Part 2

Participants will report to the CRU on Day -1 for baseline PD measurements (RHC, FRI and exercise testing). Performance of these procedures may occur on the same day or can span across several days but, not to exceed 5 days prior to first dosing on Day 1. On Day 1, after all pre-dose procedures are complete and it is confirmed that the participant meets eligibility, the participant will be assigned a unique randomization number (participants coming over from Part 1 and eligible for Part 2 will keep the same randomization number as in part 1). The participant will be administered MK-5475 as an inhalation. The time of the dose will be designated as time "0" and the exact time of administration will be recorded. Post-dose study procedures will be performed according to the SoA. Participants will be dispensed study intervention and a dosing diary for at home dosing and will be discharged from the CRU after completion of the final scheduled study procedure on Day 1. Participants are to bring

their study intervention and dosing diary back with them on clinic visit days (Days 15 and 28).

On at home dosing days (Days 2-14, 16-27) participants will be contacted by site personnel via telephone or virtual technology will be used to ensure dosing adherence and proper dosing technique.

Participants will return to the CRU for witness dosing and scheduled study procedures as per the SOA on Day 15 (+/-1 day).

On Day 28 (+4/-1 days), participants will have witnessed dosing, PD measurements and other study procedures as per the SOA. The Day 28 Part 2 PD assessments will occur 5.5 to 8 hours post dose. To allow flexibility in scheduling of the PD procedures, dosing may extend to a maximum of 32 days and can be performed on the same day or across a 6-day window. Additional witnessed dosing may occur if PD measurements span across several days. Additional PK measurements may be obtained and will be dependent on the timing of the PVR, PBV and the CPET assessments.

Following completion of CPET, PVR and PBV assessments, participants may be discharged from the CRU at the discretion of the investigator per local SOPs.

Part 3

Participants will report to the CRU on Day -1 for baseline PD measurements (FRI and exercise testing). Performance of these procedures may occur on the same day or can span several days but, not to exceed 5 days prior to first dosing on Day 1. On Day 1, after all pre-dose procedures are complete and it is confirmed that the participant meets eligibility, the participant will be assigned a unique randomization number. The participant will be administered MK-5475 as an inhalation. The time of the dose will be designated as time "0" and the exact time of administration will be recorded. Post-dose study procedures will be performed according to the SoA. Participants will be dispensed study intervention and a dosing diary for at home dosing and will be discharged from the CRU after completion of the final scheduled study procedure on Day 1. Participants are to bring their study intervention and dosing diary back with them on clinic visit days (Days 15 and 28).

On at home dosing days (Days 2-14, 16-27) participants will be contacted by site personnel via telephone or virtual technology will be used to ensure dosing adherence and proper dosing technique.

Participants will return to the CRU for witness dosing and scheduled study procedures as per the SOA on Day 15 (+/-1 day).

On Day 28 (+4/-1 days), participants will have witnessed dosing, PD measurements and other study procedures as per the SOA. The Day 28 Part 3 PD assessments will occur 5.5 to 8 hours post dose. To allow flexibility in scheduling of the PD procedures, dosing may extend to a maximum of 32 days and can be performed on the same day or across a 6-day window. Additional witnessed dosing may occur if PD measurements span across several days.

Additional PK measurements may be obtained and will be dependent on the timing of the PBV and the CPET assessments.

Following completion of CPET and PBV assessments, participants may be discharged from the CRU at the discretion of the investigator per local SOPs.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all OR a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.11.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If Part 1 Period 2 is not needed, the poststudy visit after Period 1 will occur within approximately 14 days after the decision being communicated. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

Part 1 participants should complete their 14-day post -study visit. Upon SPONSOR agreement, if they enroll in Part 2 within 30 days of completing the Part 1 post-study visit, Screening 1 assessments will not be required, and the participant can move forward to baseline Day -1.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

In Part 1 of the study, the blood sample for MK-5475 is the critical procedure.

At any postdose time point, the blood sample for MK-5475 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

In Part 2 of the study, RHC measurements and, in particular, PVR, are the critical procedure. RHC measurements should be collected as close to the scheduled timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

In Part 3, FRI measurement is the critical procedure. FRI measurements should be collected as close to the scheduled timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 6.

Table 6 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window [a]
0 - < 6 min	2 min
≥ 6 min	5 min
≥ 1 hr in Part 1 ≥ 1 hr in Part 2 and 3	15 min 20 min
≥ 24 hr	30 min
[a] Window is +/- from collection time on each dosing day versus the first dose given	

- Predose Day 1 safety evaluations: vital signs, indirect oxygen saturation (pulse oximetry) and ECG up to 3 hrs; laboratory safety tests, direct oxygen saturation (ABGs) and physical exam up to 24 hrs
- Baseline RHC (Part 2 only) related procedures, FRI and CPET: Day -1(up to 5 days prior to Day 1)
- Predose Day 1 6MWT w/ Borg Dyspnea Score and SOBQ: up to 3 hrs
- Day 1, 15 and 28 Postdose evaluations: vital signs, ECG, laboratory safety tests, direct and indirect oxygen saturation, PFTs (Part 1); 6MWT w/ Borg Dyspnea Score and SOBQ and physical exam
  - 0 to <1 hr postdose may be obtained within 10 min of the theoretical sampling time
  - ≥ 1 hr to < 24 hr postdose may be obtained within 15 min of the theoretical sampling time
  - ≥ 24 hr postdose within 1 hr of the theoretical sampling time
- In Part 1, study intervention within 30 minutes of Day 1 dosing time on Days 2-7
- In Parts 2 and 3, study intervention administration (each subsequent dosing day): within -2 hrs of Day 1 actual dosing time

- Day 28 (+4/-1 Days) CPET within 30 minutes of theoretical scheduled time of 5.5 hours post dose
- Day 28 (+4/-1 Days) FRI and RHC (Part 2 only) related procedures within 30 minutes of theoretical scheduled time of 6 to 8 hours post dose
- In Part 2, It is preferred that FRI procedure occurs prior to RHC and is as close to 6 hours post dose as possible to allow RHC to be complete by 8 hours post dose.
- In Part 2, It is preferred that FRI and RHC occur on the same day, however, If FRI is scheduled on a different day from RHC, dosing of study drug may occur at home and the participant will report to the CRU at the time of scheduled CT Scan for FRI.
- In Part 3, it is preferred that FRI and CPET occur on the same day, however if CPET is scheduled on a different day from FRI, dosing of study drug may occur at home and the participant will report to the CRU at the time of scheduled CPET procedure.

8.11.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MK-5475 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the study intervention administered in any given period/part.
- Entire parts may be omitted
- Decrease in the duration of study intervention administration (eg, number of days)
- Adjustment of the dosing interval (eg, divided doses [bid to qd, qd to bid, tid, or vice versa])
- Lengthening of the wash-out period between doses
- Remove a planned PK pause if agreed by Sponsor and investigator if no further increases in total daily dose
- Addition of PK pause

- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data
- Changes to the time intervals between dosing and FRI scans, RHC and CPET.

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2-9.9).

Pharmacodynamics/Efficacy: Individual Day 28 PVR percent change from baseline values from Part 2 will be analyzed in an ANCOVA model with a categorical effect for treatment group and a continuous covariate for baseline MPAP. To test the primary hypothesis, the posterior probability that the true mean treatment difference (MK-5475 – Placebo) in PVR percent change from baseline is less than -15% will be calculated using a non-informative prior. If this posterior probability exceeds 60%, then the primary research hypothesis will be supported.Percent changes from baseline on Day 28 for secondary (PBV from FRI) and exploratory (Exercise Test, 6 MWT, NTproBNP) endpoints from Part 2 and Part 3 will be analyzed in a similar model as described above, with summary statistics provided for the treatment comparisons. A subset of exploratory endpoints (Mean pulmonary artery pressure

(mPAP), systemic vascular resistance (SVR), cardiac output (CO)/cardiac index (CI) and mixed venous and arterial oxygenation) will be analyzed in a similar fashion only for Part 2.

Descriptive statistics will be provided by study part for all other pharmacodynamic/efficacy endpoints.

Safety: Summary statistics and plots will be generated for the change from baseline values, as deemed clinically appropriate by study part and treatment. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, vital signs, ECG, labs and AEs may also be computed, as deemed clinically appropriate.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Pharmacology Statistics Department of Merck Research Laboratories in collaboration with the Pharmacokinetics and Pharmacodynamic Drug Metabolism (PPDM) and Clinical Pharmacology Departments.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

Primary: MK-5475 reduces mean pulmonary vascular resistance following 28 days of dosing in participants with pulmonary hypertension associated with chronic obstructive pulmonary disease when compared to placebo. A true mean difference (MK-5475-placebo) of 15% is considered clinically meaningful (Part 2).

9.4 Analysis Endpoints

Primary

Pharmacodynamics: The primary pharmacodynamic endpoint will be the % change from baseline for PVR on Day 28 in Part 2, which will be calculated from variables obtained by RHC. Baseline is the Day -1 measurement.

Safety: Safety and tolerability will be evaluated during clinical assessments that include vital signs, safety laboratory testing, physical examinations, ECG readings, and review of adverse events (All Study Parts).

Secondary

Pharmacodynamics: The secondary pharmacodynamic endpoint will be the % change from baseline for PBV on Day 28 in Part 2 and Part 3, obtained via FRI. Baseline is the Day -1 measurement.

Pharmacokinetics: AUC0-24, AUC0-inf, Cmax, C24, Tmax, apparent terminal half-life, and the accumulation ratio of MK-5475 from all study parts.

Exploratory

Pharmacodynamics: The exploratory pharmacodynamic endpoint will be the % change from baseline for results from the Exercise Test (VO2max, exercise capacity, ventilatory efficiency, cardiopulmonary vs. pulmonary limit to exercise and ventilation/perfusion matching) , and NTproBNP on Day 28 in Part 2 and Part 3. Baseline is the Day -1 measurement. Mean pulmonary artery pressure (mPAP), systemic vascular resistance (SVR), cardiac output (CO)/cardiac index (CI) and mixed venous and arterial oxygenation will also be measured and analyzed for Part 2.

Efficacy: The Borg Dyspnea Score, UCSD SOBQ and 6-minute walk Test (6MWT) are potential endpoints for later clinical studies and will be included as additional exploratory endpoints from all study parts.

9.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Participants as Treated (ASaT) –This population includes all participants who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) –The population includes the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the primary analysis dataset. This population will be used for the PD, PK and efficacy analyses.

9.6 Statistical Methods

Primary

Pharmacodynamics

Individual Day 28 PVR percent change from baseline values from Part 2 will be analyzed in an ANCOVA model with a categorical effect for treatment group, and a continuous covariate for baseline MPAP. To test the primary hypothesis, the posterior probability that the true

mean treatment difference (MK-5475 – Placebo) in PVR percent change from baseline is less than -15% will be calculated using a non-informative prior. If this posterior probability exceeds 60%, then the primary research hypothesis will be supported.

Plots of % change from baseline for PVR will be plotted by site to assess site variability.

Safety

Summary statistics and plots will be generated for the change from baseline values, as deemed clinically appropriate by study part and treatment. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, vital signs, ECG, labs and AEs may also be computed, as deemed clinically appropriate.

Secondary

Pharmacodynamics

Percent change from baseline for PBV from Part 2 and Part 3 will be analyzed in a similar model as described above for PVR, with summary statistics provided for the treatment comparisons.

Pharmacokinetics

Individual values will be listed for each PK parameter by study part treatment, and the following (non - model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

Exploratory

Pharmacodynamics

Percent change from baseline for Exercise Test results, and NTproBNP from Part 2 and Part 3 will be analyzed in a similar model as described above for PVR, with summary statistics provided for the treatment comparisons.

Efficacy

Descriptive statistics will be provided for results from the Borg Dyspnea Score, UCSD SOBQ and 6-minute walk Test (6 MWT) by study part and treatment.

9.7 Interim Analyses

Following the completion of Part 1 Period 1, pharmacokinetic data will be reviewed to determine if Part 1 Period 2 is necessary before starting Part 2. The data from Part 2 will be analyzed, specifically the incoming FRI and CPET data, to decide if a larger sample size is necessary for these measurements. This will govern the timing of the start of Part 3.

9.8 Multiplicity

Since there is only one testable hypothesis, no multiplicity adjustment is required.

9.9 Sample Size and Power Calculations

The operating characteristics calculations for percent change from baseline for PVR are based on an assumed true between subject standard deviation of 19.2%. The variance estimate is based on currently available data from MK-5475 P002, using PVR values calculated based on Fick-derived cardiac output.

With 24 subjects completing the study (16 on MK-5475 and 8 on placebo) and a posterior probability threshold of 60%, there is 83% probability of supporting the primary hypothesis if the true difference in PVR reduction between MK-5475 and placebo is -25%.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, 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 local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also 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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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.

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 fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees 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. 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. 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.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. 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.

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 chart 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, commonly 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 prior to 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 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 International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, 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 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 trial directive 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 directive, 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.

10.1.6 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, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 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.

10.1.7 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.

10.1.8 Source Documents

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

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 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 7 will be performed by the local laboratory for Part 1 and central laboratory for Parts 2 and 3.

- Local laboratory results are only required in the event that 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 CRF.

- Protocol-specific requirements for inclusion or exclusion 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.

- 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 monthly intervals during intervention.

    - Pregnancy testing (urine or serum as required by local regulations) should be conducted 14 days after the last dose of study intervention.

    - 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 subject's participation in the study.

Table 7 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit			WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• PT/INR and aPTT • Mixed Venous oxygen saturation (MV02) (Part 2 only) • Arterial blood gas (ABG) • NTproBNP • Follicle-stimulating hormone (FSH) (as needed in women of nonchildbearing potential only) • Serum or urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable • Serum/ urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • [Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) In Parts 2 and 3, all study-required laboratory assessments will be performed at least by a central laboratory, with the exception of the following tests (some tests may also be done in extra using the local lab at the discretion of the investigator at baseline and day 28): • MVO2 (Part 2 only), ABG, FSH, βhCG, Serum/urine drug screen, HIV, HBsAg, HeP C virus antibody			
NOTES: Urea is acceptable of BUN if not available as per institutional standard; WBC differential = absolute				

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

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

10.3.1 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 (also referred to as Sponsor's product) 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 pre-existing 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.

  Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 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 pre-existing condition that has not worsened is not an SAE.) A pre-existing 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.

10.3.3 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

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product 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 Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product 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 Sponsor's product? 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 Sponsor's product 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 Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product 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, or (2) the study is a single-dose drug study; or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT 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 Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her 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 Sponsor's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

    - No, there is not a reasonable possibility of Sponsor's product relationship:

        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- 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 his/her 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.

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

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 two 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 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c,d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to hormonal contraception. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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 are 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 which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3,4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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 future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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 main 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 utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

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@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

N/A

10.8 Appendix 8: Blood Volume Table

Part 1	Pre-study	Treatment Period	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	2 to 4	1	4 to 6	13	52 to 78
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	5	5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Serum βHcg (if applicable)	1		1	2	5	10
FSH (if applicable)	1				3.5	3.5
PT/aPTT	1	2 to 4	1	4 to 6	5	20 to 30
ABGs		2 to 4		2 to 4	1	2 to 4
Blood for MK-5475		24 to 48		24 to 48	6	144 to 288
Total Blood Volume per Participant						245 mL or 427[b]

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: not to exceed 50 mL
b. Additional blood samples will only apply if a second dosing period is performed

Part 2	Pre-study (Screening)	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	3	1	5	5.5	27.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	5	5
Hepatitis B DNA (if applicable)	1			1	5	5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Serum βHcg (if applicable)	1		1	2	5	10
FSH (if applicable)	1				3.5	3.5
PT/aPTT	1	3	1	5	5	25
NTproBNP		2		2	2.5	5
Local lab safety test (at discretion of investigator)		2 (baseline and day 28)			13	26
ABGs		2		2	1	2
MV02		5		5	15	75
Blood for MK-5475		12[b]		12	6	72[b]
Total Blood Volume per Participant[a]						Up to 264.5[b] or 254.5[b] mL

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: not to exceed 50 mL.
[b] Up to 1 additional PK samples may be drawn if RHC, FRI are performed on separate days Day 28 (+4/-1 days) (up to 6mL).

Part 3	Pre-study (Screening)	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	3	1	5	5.5	27.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	5	5
Hepatitis B DNA (if applicable)	1			1	5	5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Serum βHcg (if applicable)	1		1	2	5	10
FSH (if applicable)	1			1	3.5	3.5
PT/aPTT	1	3	1	5	5	25
NTproBNP		2		2	2.5	5
Local lab safety test (at discretion of investigator)		2 (baseline and day 28)		2	13	26
ABGs		2		2	1	2
Blood for MK-5475		12[b]		12	6	72[b]
Total Blood Volume per Participant [a]						Up to 184.5 or 178.5 mL

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: not to exceed 50 mL.
[b] Up to 1 additional PK samples may be drawn if CPET and FRI are performed on separate days Day 28 (+4/-1 days) (up to 6mL).

10.9 Appendix 9: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    1. The participant may be excluded from the study;

    2. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

        a. If the repeat test value is within the normal range, the participant may enter the study.

        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.10 Appendix 10: Hemodynamic Stopping Criteria

Hemodynamic stopping criteria

Individual stopping criteria

During the treatment period, if a particular participant demonstrates a ***sustained change*** (defined below) in any *one* of the following parameters, that participant will not participate in additional dosing. For assessing change from baseline, post-dose values will be compared to the Day 1 predose baseline of each Part/Period established by 3 semi-recumbent/supine measurements of heart rate and blood pressure obtained ~1-2 minutes apart within 3 hours prior to dosing.

Participants meeting individual hemodynamic stopping criteria may be re-challenged in this study only after consultation or discussion between the primary investigator and the sponsor.

During the treatment period if a particular participant demonstrates change in any *one* of the following parameters lasting ≥ 90 minutes, dosing in that participant will be halted and the participant may be withdrawn from the study or re-challenged at the same dose or at a lower dose. Participants that meet criteria listed below will be followed up until parameters no longer meet stopping rule criteria. Each participant will individually define his limit for continuation. Stopping rules will apply for a particular participant when he demonstrates a *sustained change* (at least 4 triplicate measurements or at least 1 triplicate measurement every 30 min of which the median result of each triplicate measurement will account for checking the stopping criteria) of *≥90 minutes* in any *one* of the following criteria during the postdose period:

Heart rate:

1) Resting HR increase over the predose baseline of ≥ 25 bpm.

2) Resting HR > 120 bpm

Blood pressure:

1) Resting SBP reduction > 25 mmHg over the predose baseline.

2) Resting SBP < 90 mmHg or participant placed in the Trendelenburg position.

3) Resting SBP ≥ 180 mmHg

4) Resting DBP < 50 mmHg or DBP ≥ 110 mmHg

Blood pressure and heart rate:

1) For any participants: > 20 mmHg drop in resting SBP and > 20 bpm rise in resting HR

2) For any participants: > 30 mmHg drop in orthostatic SBP and > 30 bpm rise in orthostatic HR

On intermediate dosing days (Part 1, Days 2-6, Parts 2 and 3, Day 15) and Day 28, if the predose HR or BP measurements meet one of the criteria listed above the site will perform an immediate recheck in triplicate of the vital sign parameter out of range.

- If the median of the triplicate recheck value is normal, the dose of study drug can be given.
- If the median recheck value remains abnormal, the vital sign parameter is to be rechecked in triplicate every 30 minutes until it returns to near baseline.
- If the median recheck vital sign parameter returns to normal in less than 90 minutes, this is not considered sustained (stopping criteria not met) and the participant can be dosed.

Definitions for HR and BP

Participants must be resting and semirecumbent/supine for *at least* 10 minutes prior to obtaining *any* measurements (except for changes noted while obtaining orthostatic signs).

Baseline HR and BP: Predose baseline values will be determined for each specific participant. For the investigator, the baseline will be calculated using the median from the triplicate measurements obtained approximately 1-2 minutes apart within approximately 3 hours prior to dosing on Day 1 to determine that change from baseline. For all formal statistical testing, the mean baseline will be used to calculate the change from baseline.

Sustained changes are defined as lasting greater than or equal to 90 minutes. If any of the resting, semi-recumbent or orthostatic parameters defined above are exceeded, that participant must remain resting and semi-recumbent/supine for at least the next 90 minutes. During that time, BP (systolic and diastolic) and HR will be obtained every 30 minutes (i.e., at 30, 60, and 90 minutes following). If a participant's BP (systolic *or* diastolic), *or* heart rate exceeds the parameters for the median of *all three* of the following three 30-minute periods, this is defined as a sustained finding, and dosing will end for that particular participant. Following 90 minutes, if, in the opinion of the investigator, the participant requires further observation, the participant will remain resting and semi-recumbent/supine until HR and/or BP return to baseline. For HR and BP that are out of range, if the recheck is within normal range this is not considered a sustained change.

10.11 Appendix 11: Guidelines for the Treatment of Hypo/Hypertension

The following is guidance for the investigator with the understanding that the investigator must always use his/her own clinical judgment in carrying out this guidance and/or deviating from them, with a principle focus on ensuring the safety of study participants.

Severe Hypotension

In the event that a participant develops severe hypotension (systolic blood pressure <80 with or without symptoms or <90 accompanied by symptoms) the following is suggested:

- Participant may be placed in the Trendelenburg position (supine with head downward/feet elevated above the heart).
- Intravenous access should already be in place.
- Bolus intravenous normal saline as appropriate until SBP is >100 mmHg or until symptoms resolve.
- The participant should be frequently monitored for HR and BP.
- The participant should be rapidly evaluated. Evaluations will include a physical examination. 12-lead ECG and laboratory safety panel may be performed at the discretion of the investigator.
- If/when appropriate, efforts should be made to ensure the participant has two functioning and open intravenous access sites.
- If participant remains hypotensive and/or there has been no resolution of any associated symptoms despite the above, the participant should be rapidly transferred to a location where definitive care (i.e., an Emergency or Intensive Care Unit) is available.

Severe Hypertension

If a participant develops severe hypertension (systolic blood pressure >170 mmHg and/or diastolic blood pressure >105 mmHg) the following is suggested:

- Participant should be placed in a semi-recumbent position.
- Intravenous access should already be in place in the participant.
- The participant should be frequently monitored for HR and BP until BP returns to baseline.
- The participant should be rapidly evaluated. Evaluations will include a physical examination. 12-lead ECG and laboratory safety panel may be performed at the discretion of the investigator.

- Treatment should be considered per local standards, based upon the degree of hypertension and/or presence/absence of symptoms (e.g., headache, evidence of heart failure or coronary insufficiency).

- Blood pressure should be reduced within a few hours.

Participants who are symptomatic or with evidence of end-organ damage should be rapidly transferred to a location where definitive care (i.e., Emergency Room or Intensive Care Unit) is available.

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
6MWD	6-minute Walk Distance
6MWT	6-minute Walk Test
ABG	arterial blood gas
AE	adverse event
APaT	All-Participants-as-Treated
AR	adverse reaction
AUC	area under the curve
BDS	blood drug screen
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
CI	cardiac index
CG	Cockcroft-Gault
CO	Cardiac output
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CL	clearance
CMAX	maximum concentration
CPET	cardiopulmonary exercise test
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CV	cardiovascular
DC	discharge
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DPI	dry powder inhaler
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FAS	Full Analysis Set
FMF	final market formulation
FRC	functional respiratory capacity
FRI	functional respiratory imaging
FVC	forced vital capacity
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hgb	hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HR	heart rate
hr	hour
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC	Inspiratory capacity
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
MMRC	Modified Medical Research Council
MTD	maximum tolerated dose
MVO2	mixed venous oxygen saturation
NCS	not clinically significant
NDA	New Drug Application
NOAEL	no observed adverse effect level
NTpro BNP	N-terminal pro-hormone b-type natriuretic peptide
OSA	Obstructive sleep apnea
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PBO	placebo
PBV	pulmonary blood volume
PD	pharmacodynamic
PE	physical exam
PEF	peak expiratory flow
PET	positron emission tomography
PFT	pulmonary function tests
PH	pulmonary hypertension
PK	pharmacokinetic
PT	prothrombin time
aPTT	activated partial thromboplastin time
PVR	Pulmonary vascular resistance
PP	per-protocol
QP2	department of quantitative pharmacology and pharmacometrics
RAP	right atrium pressure
RHC	right heart catheterization
RNA	ribonucleic acid
RR	respiratory rate
RV	residual volume
RVSP	right ventricular systolic pressure
RVEDP	right ventricular end diastolic pressure
SABA	Short-acting beta agonist

Abbreviation	Expanded Term
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
sGC	Soluble guanylate cyclase
SoA	schedule of activities
SOBQ	Shortness of Breath Questionnaire
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVR	systemic vascular resistance
TLC	total lung capacity
Tmax	Time to maximum concentration
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
V	volume of distribution
VO2max	maximal oxygen uptake
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

11 REFERENCES

[Directorate-General, Environment Nuclear Safety and Civil Protec 1998]	Directorate-General ENSaCP. European Commission - radiation protection 99: Guidance on medical exposures in medical and biomedical research.	[03R6BL]
[American Thoracic Society 2002]	American Thoracic Society. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.	[00QTB2]
[Nathan, S. D., et al 2019]	Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53:1801914.	[05FW3V]
[American Thoracic Society 2005]	American Thoracic Society. ATS Documents: Statements, Guidelines & Reports: ATS/ERS standardisation of lung functioning testing: Standardisation of spirometry. http://www.thoracic.org/statements/	[00V3HY]