Official Protocol Title:	A Study to Assess the Effect of Single Doses of MK -5475 on Pulmonary Vascular Resistance in Patients with Moderate to Severe Pulmonary Arterial Hypertension
NCT number:	NCT03744637
Document Date:	16-JUN-2020

Title Page

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Protocol Title: A Study to Assess the Effect of Single Doses of MK -5475 on Pulmonary Vascular Resistance in Patients with Moderate to Severe Pulmonary Arterial Hypertension

Protocol Number: 002-03

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):

Approval Date: 16 June 2020

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-5475-002-03	16-JUN-2020	A panel of up to 8 subjects added (Panel D) to evaluate PD effects (PVR and PBV) at 120 mcg and safety at 480 mcg. The data will inform the range of potential efficacious doses for later studies.
MK-5475-002-02	29-MAY-2019	Panel C added to Part 2 and doses change for Panel B to evaluate higher doses based on PK results seen at 120, 165 and 240 µg doses in Part 1. Incorporated ERAs into list of exclusionary criteria /prohibited medications.
MK-5475-002-01	31-OCT-2018	Incorporate flexible language for protocol modifications related to timing of safety and PK procedures based on newly learned data
MK-5475-002-00	22-OCT-2018	Original Version

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

A panel of up to 8 subjects added (Panel D) to evaluate PD effects (PVR and PBV) at 120 mcg and safety at 480 mcg. The data will inform the range of potential safe and efficacious doses for later studies.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Sample size, intervention, duration in study for Panel D added	To expand the range of potential safe and efficacious doses
1.2 Scheme	Panel D added	To expand the range of potential safe and efficacious doses
1.3 SOA	Panel D added. Adjusted PK sample timepoints for Panel D, Period 2 (FRI period).	To expand the range of potential safe and efficacious doses
2	Changed to 4 panels	To expand the range of potential safe and efficacious doses
2.2.2 Pre-Clinical and Clinical Studies	Moved summary of PN003 to completed clinical studies section. Removed AE and PK table for PN 001	AE and PK tables for PN 001 are available in edition 3 of the IB.
2.2.3 Ongoing Clinical Studies	Updated safety and PK data of PN002 to date. Added summary for PN004	New data available

Section # and Name	Description of Change	Brief Rationale
3.0 Hypotheses,Objectives and Endpoints	Panel D added	To expand the range of potential safe and efficacious doses
4.1 Overall Design	Description of Panel D added to study design.	To expand the range of potential safe and efficacious doses
4.2 Scientific Rationale for Study Design	Rationale to explore 120 µg and 480 µg doses added	To expand the range of potential safe and efficacious doses
4.3,2 Maximum Dose/Exposure for this Study	Rationale for the highest dose 480 µg and estimated exposure of this dose added	To expand the range of potential safe and efficacious doses
5.1 Inclusion Criteria	Panel D added	To expand the range of potential safe and efficacious doses
5.2 Exclusion Criteria	Updated a- fib exclusion criteria. Removed Hep B exclusion criteria	To enhance recruitment for Panel D
6.1 Study Interventions Administered	Study interventions of 120µg and 480 µg for Panel D added. Device language removed	To expand the range of potential safe and efficacious doses. Device language is not applicable as it applies to marketed drug/device combination products.
6.3.1 Intervention Assignment	Sample allocation schedule for Panel D added	To expand the range of potential safe and efficacious doses
8.4.8 Device Events, Adverse Device Events	Device language removed	Device language is not applicable as it applies to marketed drug/device combination products

Section # and Name	Description of Change	Brief Rationale
8.7.1 Right Heart Catheterization Procedures	Language added if RHC procedure needs to stop earlier	RHC procedure may need to stop earlier at the discretion of the investigator.
8.11.2 Treatment Visit Period	Panel D added	To expand the range of potential safe and efficacious doses
8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedures	Panel D added	To expand the range of potential safe and efficacious doses
9.1 Statistical Analysis Plan Summary	Panel D added	To expand the range of potential safe and efficacious doses
9.4 Analysis Endpoints	Panel D added	To expand the range of potential safe and efficacious doses
9.6 Statistical Methods	Panel D added	To expand the range of potential safe and efficacious doses
10.4 device Events, Adverse Device Events and Medical Device Incidents: Definitions, Collection and Documentation	Removed	This is not applicable due to drug/device combination is considered investigational
10.8 Blood Volume Table	Blood Volume Table Added for Panel D	To expand the range of potential safe and efficacious doses

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Study to Assess the Effect of Single Doses of MK -5475 on Pulmonary Vascular Resistance in Patients with Moderate to Severe Pulmonary Arterial Hypertension

Short Title: Dosing of MK-5475 in Participants with Pulmonary Hypertension

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study is to be conducted in male and female participants with group 1 pulmonary arterial hypertension (PAH).

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of MK-5475 in participants with pulmonary arterial hypertension (PAH). (All parts)	Safety and tolerability will be evaluated during clinical assessments that include vital signs, safety laboratory testing, physical examinations, ECG readings, PFTs and review of adverse events.
- To assess the duration and effect following a single inhaled dose of MK-5475 on pulmonary vascular resistance (PVR) in participants with pulmonary arterial hypertension (PAH). (Part 2, Period 2 (Panel A) and Period 3 (Panels B, C and D))	Peak reduction from baseline in PVR after a single inhaled dose of MK-5475
Secondary Objectives	Secondary Endpoints
- To estimate the effect of MK-5475 given as single inhaled doses on systemic hemodynamic parameters (heart rate (HR), systolic and diastolic blood pressure (BP)) in participants with pulmonary arterial hypertension. (Part 2 Period 2 (Panel A) and Period 3 (Panels B, C and D))	- HR and BP change from baseline at 0.5, 4.5, and 24 (or prior to discharge) hours post-dose.
- To assess the effect following a single inhaled dose of MK-5475 on pulmonary blood volume (PBV) in participants with pulmonary arterial hypertension. (Part 2, Period 3 (Panel A) and Period 2 (Panels B, C and D))	- Increases from baseline PBV at 1, 3, 8 and 24 hours postdose.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Pulmonary Arterial Hypertension (PAH)
Population	Participants with moderate to severe Group 1 PAH
Study Type	Interventional
Intervention Model	Sequential This is a single-site study.
Type of Control	Not applicable
Study Blinding	Double-blind
Masking	Data Analyst
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 22 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1 (Panel A)	MK-5475	120, 165, 240 µg	Single dose	Inhalation	Once/Periods 1-3	Experi-mental
	Pbo	0µg	Single dose	Inhalation	Once/ Periods 1-3	Pbo contro
	Placebo	0µg	Single dose	Inhalation	Once/ Screening 2	Training
Part 2 (Panel A)	MK-5475	240 µg	Single dose	Inhalation	Once/Periods 2-3	Experi-mental
Part 2 (Panel B)	MK-5475	300, 360 µg	Single dose	Inhalation	Once/Periods 1-3[a]	Experi-mental
	Pbo	0 µg	Single dose	Inhalation	Once/Screeni ng 2	Training
Part 2 (Panel C)	Pbo	0 µg	Single dose	Inhalation	Once/Screeni ng 2	Training
	MK-5475	300, 360 µg	Single dose	Inhalation	Once/Periods 1-3[a,b]	Experi-mental
Part 2 (Panel D)	Pbo	0 µg	Single dose	Inhalation	Once/ Screening 2	Training
Part 2 (Panel D)	MK-5475	480, 120 µg	Single dose	Inhalation	Once/Periods 1 - 3	Experi-mental

Abbreviations: µg=micrograms; pbo=placebo

[a] Panel B and C: The dose of Part 2, Periods 2 and 3 (360 µg) will depend on the observance of adequate safety and tolerability in Part 2, Period 1

[b] Panel C dose will not exceed the maximum dose administered in Panel B.

Total Number	4
Duration of Participation	Each participant will participate in the study for approximately 15- 25 weeks for Panel A, 13 – 19 weeks for Panels B – C and 10 to 12 weeks for Panel D from the time the participant signs the Informed Consent Form through the final contact. After a screening phase of 5 weeks, each participant in Part 1 will receive 3 single doses of MK-5475/placebo over approximately 5 to 7 weeks. Participants in Part 2 will receive up to 2-3 single doses over approximately 3 to 8 weeks. Participants in Part 1 may participate in Part 2. After the end of treatment, each participant will be followed for 14 days.

Number of Participants:

Approximately 8 participants in Part 1 and 24 participants in Part 2 will be allocated/randomized such that 8 evaluable participants in Part 1 and 24 evaluable participants in Part 2 complete the study as described in Section 9.5. Participants from Part 1 can participate in Part 2.

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

The study design is depicted in Table 1. Detailed depiction of Part 2, Periods 2 and 3 are in Figure 1 and Figure 2.

Table 1 Overall Study Design

Panel	Part 1 Period 1	Part 1 Period 2	PK Break	Part 1 Period 3	Part 2 Period 1[c]	Part 2 Period 2[c]	Part 2 Period 3
A (N=8)[b]	120µg/ Pbo[a]	165µg/ Pbo[a]		240µg/ Pbo[a]		240 µg w/ Right Heart Catheterization (RHC)[a, d]	240 w/ Functional Respiratory Imaging (FRI)[a, d]
B (N=4)[d]					300 µg[a,d]	360 µg w/ Functional Respiratory Imaging (FRI)[a]	360 µg w/ Right Heart Catheterization (RHC)[a]
C (N= up to 8)[b]					300 µg[a]	360 µg w/ Functional Respiratory Imaging (FRI)[a]	360 µg w/ Right Heart Catheterization (RHC)[a]
D (N= up to 7)[b]					480 µg[e]	120 µg w/ Functional Respiratory Imaging (FRI)[a]	120 µg w/ Right Heart Catheterization (RHC)[a]

a. The suggested doses may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous intervention periods. Refer to Section 6.6 (Dose Modification) for the safety, pharmacokinetic, and pharmacodynamic data that will be reviewed prior to dose escalation.

b. Participants in Part 1 may continue to participate in Part 2 provided they meet RHC criteria at baseline Part 2 Period 2. The minimum sample size for Panel C = 6 but, may increase based on the number of participants from Panel A who do not move forward to Part 2 or fail to meet the baseline RHC criteria in Period 2. The maximum sample size for Panel D = 7 but, will depend upon the total number of participants enrolled in Panel C at the time Panel D begins. Total sample size in Part 2 equals 24.

c. Participants in Panel A that continue into Part 2 will not have a Period 1 but, will go directly to Period 2 where RHC is performed. This period can occur in parallel with Panel B, Period 1. Panel C, Period 1 may begin following review of PK from Panel B Period 1 (Parallel with Periods 2 or 3 of Panel B).

d. A rolling evaluation of PK may occur for participants in Panel B and C, Period 1. Review of Panel B PK for Period 1 will occur before dosing of Panel B, Period 2 and Panel C, Period 1. Panel C, Period 2 may begin following review of PK for the first 4 participants of Panel C.

e. Panel D, may occur in parallel with participants already actively enrolled in Panel C.

Period 2 Day 1 RHC/Dosing/ Safety and Other Procedures	Wash out	Period 3 Day 1 FRI/Dosing/Safety and Other Procedures	Post Study
Pre RHC > Predose RHC > Dosing > Post dose RHC > D/C	≥ 7 days	Pre scan > Predose FRI > Dosing > Post dose FRI > D/C	~ 14 Days

Figure 1 Part 2 Panel A Study Design (Periods 2 and 3)

Period 2 Day 1 FRI/Dosing/ Safety and Other Procedures	Wash out	Period 3 Day 1 RHC/Dosing/Safety and Other Procedures	Post Study
Pre scan > Predose FRI > Dosing > Post dose FRI > D/C	≥ 7 days	Pre RHC > Predose RHC > Dosing > Post dose RHC > D/C	~ 14 Days

Figure 2 Part 2 Panel B, C and D Study Design (Periods 2 and 3)

1.3 Schedule of Activities (SoA)

				Intervention (Panel A: Part 1, Periods 1-3) (Panel B, C and D: Part 2, Period 1)											
Study Period	Screening														Notes
	≤ 35 days pre-randomization	≤ 7 days pre-randomization	Day 1	Hours											
Scheduled Hour, Day	Screening 1	Screening 2	Pre-dose	0	~0.1 (5min)	0.25 (15min)	0.5 (30min)	1	2	3	4	8	24	Post Study ~14 days	All post study procedures to be performed for participants in Panel A. that do not go onto Part 2.
Administrative Procedures															
Informed Consent	X														
Informed Consent for Future Biomedical Research	X														
Inclusion/Exclusion Criteria	X	X	X												Pre-dose assessment applies to Period 1 only
Participant Identification Card	X														
Medical History	X														
Prior/Concomitant Medication Review	X	X	X----------X											X	
Assignment of Screening Number	X														
Assignment of Allocation Number (Randomization)			X												Period 1 only. All participants receive an allocation number.
MK-5475/pbo Administration				X											Placebo applies to Part 1 – Panel A
Standard Meals											X-------X				See section 5.3.1 for timing of meals and snacks

Study Period	Screening			Intervention (Panel A: Part 1, Periods 1-3) (Panel B, C and D: Part 2, Period 1)											Notes
	≤ 35 days pre-randomization	≤ 7 days pre-randomization	Day 1	Hours											
Scheduled Hour, Day	Screening 1	Screening 2	Pre-dose	0	~0.1 (5min)	0.25 (15min)	0.5 (30min)	1	2	3	4	8	24	Post Study ~14 days	All post study procedures to be performed for participants in Panel A. that do not go onto Part 2.
Domiciling			X----------X												See Section 8.1.11 for domiciling details
Training with Spirometer Device (PFTs)		X													Training will be done for each participant at one occasion for site spirometry measures.
Inhaler Training/Placebo Administration		X													Preferably done at Screening 2 but, may be done at Screening 1 if within 7 days of pre-randomization.
Inspiratory Flow Meter Assessment		X	X												Panels B, C and D only. Day 1 procedure can be done within 3 hours at predose.
Safety Procedures															
Full physical examination (PE)	X		X										X	X	Pre-dose measure is prior to each
Height	X														

Study Period	Screening			Intervention (Panel A: Part 1, Periods 1-3) (Panel B, C and D: Part 2, Period 1)											Notes
	≤ 35 days pre-randomization	≤ 7 days pre-randomization	Day 1	Hours											
Scheduled Hour, Day	Screening 1	Screening 2	Pre-dose	0	~0.1 (5min)	0.25 (15min)	0.5 (30min)	1	2	3	4	8	24	Post Study ~14 days	All post study procedures to be performed for participants in Panel A. that do not go onto Part 2.
Weight	X													X	period. See section 8.3.1 for PE, height and weight procedures and 8.11.5 for timing window.
Heart Rate(HR) & Blood Pressure(BP)	X		X				X	X	X		X	X	X	X	Pre-dose measure is prior to each period. See section 8.3.2 for all appropriate vital sign procedures and 8.11.5 for timing window.
Orthostatic Vital Signs (HR & BP)	X		X					X			X		X	X	
Body Temperature(Temp)	X		X								X		X	X	
Respiratory Rate (RR)	X		X				X	X	X		X	X	X	X	
12-lead ECG	X		X				X	X	X		X	X	X	X	Pre-dose measure is prior to each period. See section 8.3.3 for ECG procedure details and 8.11.5 for timing window.

Study Period	Screening			Intervention (Panel A: Part 1, Periods 1-3) (Panel B, C and D: Part 2, Period 1)												Notes
	≤ 35 days pre-randomization	≤ 7 days pre-randomization	Day 1	Hours												
Scheduled Hour, Day	Screening 1	Screening 2	Pre-dose	0	~0.1 (5min)	0.25 (15min)	0.5 (30min)	1	2	3	4	8	24	Post Study ~14 days	All post study procedures to be performed for participants in Panel A. that do not go onto Part 2.
Pulmonary Function Tests (PFTs)	X		X						X				X	X	Pre-dose measure is prior to each period. See section 8.3.5 for specific parameters to be performed at screening and pre / post-dose and 8.11.5 for timing window.
Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X													X	
Urine Pregnancy Test (WOCBP only)			X												Pre-dose measure is prior to each period
Serum Follicle Stimulating Hormone (FSH) - (WONCBP only)	X														
Echocardiogram (if needed, for Panel B or C participants only)	X														Follow site SOP for assessment of PAH in newly diagnosed participants in Panel B, C or D only
HIV, hepatitis B and C screen (per site SOP)	X														

Study Period	Screening			Intervention (Panel A: Part 1, Periods 1-3) (Panel B, C and D: Part 2, Period 1)												Notes
	≤ 35 days pre-randomization	≤ 7 days pre-randomization	Day 1	Hours												
Scheduled Hour, Day	Screening 1	Screening 2	Pre-dose	0	~0.1 (5min)	0.25 (15min)	0.5 (30min)	1	2	3	4	8	24	Post Study ~14 days	All post study procedures to be performed for participants in Panel A. that do not go onto Part 2.
Urine/Blood Drug Screen (UDS/BDS) (per site SOP)	X		X												Screening and Period 1 UDB/BDS is mandatory, any additional UDS/BDS are conducted per site SOP
Hematology/Chemistry	X		X										X	X	See Appendix 2 for laboratory tests
Urinalysis	X		X										X	X	
PT/aPTT	X		X										X	X	
AE/SAE review	X	X	X----------X											X	See all sections under 8.4
Phone Call for AE/SAE review														X	Panel A participants that go into Part 2 will have a phone call only 14 days after last dosing period.
Pharmacokinetics															
Blood for Plasma MK-5475 parent and/or metabolites			X		X	X	X	X	X	X	X	X	X		Pre-dose measure is prior to each period. See operations manual for sample processing details.

Study Period	Screening			Intervention (Panel A: Part 1, Periods 1-3) (Panel B, C and D: Part 2, Period 1)											Notes
	≤ 35 days pre-randomization	≤ 7 days pre-randomization	Day 1	Hours											
Scheduled Hour, Day	Screening 1	Screening 2	Pre-dose	0	~0.1 (5min)	0.25 (15min)	0.5 (30min)	1	2	3	4	8	24	Post Study ~14 days	All post study procedures to be performed for participants in Panel A. that do not go onto Part 2.
Biomarkers															
Blood for Genetic Analysis			X												Pre-dose Period 1 only – See Section 8.8 and 8.9

Part 2											
Study Period		Intervention (FRI Period) Panel A = Period 3 Panel B, C and D = Period 2									Notes
	Day 1		Hour								
Scheduled Time	Predose and Pre Baseline Scan	Baseline Scan	0	1	3	8	Prior to Discharge post 8 hr scan (if needed)	24	Prior to Discharge post 24 hr scan	Post Study	Post Study procedures are performed following the completion of Period 3 (All Panels)
Administrative Procedures											
Prior/Concomitant Medication Review	X	X	X	X	X			X		X	
MK-5475 Administration			X								
Inspiratory Flow Meter Assessment	X									X	Assessment to be done within 3 hours at predose (Panels B, C and D only). Post Study assessment (Panel A only) An optional predose assessment may be done for Panel A.
Standard Meals				X------X							A standard snack may be given between the 1 and 3 hour CT scans. Meal will be given about 1 hour after 3 hour postdose scan. See 5.3.1
Safety Procedures											
Full physical examination (PE)	X									X	Pre-dose PE may occur w/in 24 hrs of baseline scan
Weight	X										
Heart Rate(HR) & Blood Pressure(BP)	X						X		X	X	See section 8.3.2 for all appropriate vital sign procedures.
Body Temperature(Temp)	X						X		X	X	
Respiratory Rate (RR)	X						X		X	X	
12-lead ECG	X						X		X	X	
Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)										X	

Part 2											
Study Period		Intervention (FRI Period) Panel A = Period 3 Panel B, C and D = Period 2									Notes
	Day 1		Hour								
Scheduled Time	Predose and Pre Baseline Scan	Baseline Scan	0	1	3	8	Prior to Discharge post 8 hr scan (if needed)	24	Prior to Discharge post 24 hr scan	Post Study	Post Study procedures are performed following the completion of Period 3 (All Panels)
Urine Pregnancy Test (WOCBP only)	X										See Appendix 10.2 for details regarding laboratory tests. Pre-dose lab tests may occur w/in 24 hrs of baseline scan
Hematology/Chemistry	X									X	
Urinalysis	X									X	
PT/aPTT	X									X	
PFTs										X	
AE/SAE review	X	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								Panels A, B and C: Predose, 1, 3, 8 and 24 hours postdose. Panel D: Predose, 15 min, 30 min, 1, 2, 3, 4, 8 and 24 hours postdose See operations manual for sample processing details
Pharmacodynamics											
CT Scan for Functional Respiratory Imaging (FRI)		X		X	X	X		X			Baseline scan to occur w/in 30 minutes of dosing

Part 2												
Study Period	Intervention (RHC Period) Panel A = Period 2 Panel B, C and D = Period 3											Notes
	Day 1	Day 1	Hour									
Scheduled Hour, Day	Pre RHC	Pre dose	0	0.25	0.5	1	2	3	4	4.5	24h or prior to D/C	See FRI flowchart for Poststudy procedures to be completed following Period 3.
Administrative Procedures												
RHC Inclusion/Exclusion Criteria		X										Pre-dose assessment applies to Period 2 if Panel A and Period 3, if Panel B, C or D
Prior/Concomitant Medication Review	X----------										-----X	
MK-5475 Administration			X									
Inspiratory Flow Meter Assessment		X										Assessment to be done within 3 hours at predose (Panels B, C and D). An optional predose assessment may be done for Panel A.
Standard Meals							X			X		See section 5.3.1 for timing of meals and snacks
Domiciling	X----------										-----X	See Section 8.1.11
Pharmacodynamic Procedures												
Right Heart Catheterization (RHC) Measurements		X			X	X	X	X	X	X		See section 8.7.1 and operations manual for RHC details
Pulmonary Arterial Pressure (PAP)		X	X ----------								X	q 30 minutes
Arterial O_2 Saturation (pulse oximetry)		X			X	X	X	X	X	X		On room air
Mixed Venous O_2 Saturation (MVO_2)		X			X	X	X	X	X	X		On room air
Safety Procedures												
Full physical examination	X										X	Pre RHC PE may occur w/in 24 hours of dosing
Heart Rate (HR) & Blood Pressure (BP)	X	X			X----------						X	HR/BP q 30 minutes
Body Temperature (Temp)	X										X	See section 8.3.2 for all appropriate vital sign procedures.
Respiratory Rate (RR)	X				X	X	X	X	X	X	X	
12-lead ECG	X									X	X	See section 8.3.3 for ECG procedure details

Part 2												
Study Period	Intervention (RHC Period) Panel A = Period 2 Panel B, C and D = Period 3											Notes
	Day 1	Day 1	Hour									
Scheduled Hour, Day	Pre RHC	Pre dose	0	0.25	0.5	1	2	3	4	4.5	24h or prior to D/C	See FRI flowchart for Poststudy procedures to be completed following Period 3.
Urine Pregnancy Test (WOCBP only)	X											
Hematology/Chemistry	X										X	See Appendix 10.2 for details regarding laboratory tests. Pre RHC labs may occur w/in 24 hrs
Urinalysis	X										X	
PT/aPTT	X										X	
AE/SAE review	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		See operations manual for sample processing details

2 INTRODUCTION

This is a two-part, four-panel, single-site, single-dose trial of MK-5475 in participants with moderate to severe group 1 pulmonary arterial hypertension (PAH). MK-5475 has already been successfully administered to healthy participants and is now being introduced to the target patient population. This study will assess safety, tolerability, pharmacokinetics, and pharmacodynamics of single inhaled doses of MK-5475 in patients with PAH.

2.1 Study Rationale

The objective for this study is to evaluate the safety, pharmacokinetic and pharmacodynamic profiles of single inhaled dose of MK-5475 in participants with moderate to severe group 1 PAH.

2.2 Background

Refer to the Investigator's Brochure (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 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 must be 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.

MK-5475 is a small-molecule stimulator of sGC which has been formulated as a dry powder for inhaled delivery with the Merck TWISTHALER® device. [redacted]

CCI [redacted]

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 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.

Completed Clinical Studies

As of May 2020, MK-5475 has been evaluated in 2 completed clinical studies (PN001 and PN003). Data for these studies are summarized below.

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 (t1/2) 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.

Assessment of pulmonary blood volume (PBV) performed via functional respiratory imaging (FRI) at the 165 µg dose level showed an increase in pulmonary blood volume from baseline measures of 7.1 and 6.2% at 1 and 3 hours post dose, respectively, when compared to placebo.

In the multiple ascending dose study (PN003) of 40 healthy male and female participants, MK-5475 ranging from 30 to 165 µg for 10 days and 240 µg for 5 days was generally well-tolerated. AEs ranged from mild to moderate in intensity. No SAEs or events of clinical interest were reported. No participants discontinued early from the study. Overall, the most commonly reported AEs after administration of MK-5475 by 2 or more participants included headache (N=10), palpitations (N=6), cough (N=4), fatigue (N=4), dermatitis contact, (N=3), throat irritation (N=3), abdominal discomfort (N=3), diarrhea (N=3) oral herpes (N=3),

oropharyngeal pain (N=2), nausea (N=2), catheter site pain (N=2), back pain (N=2), musculoskeletal chest pain (N=2), and dizziness postural (N=2).

Multiple-dose PK data in PN003 showed that the geometric mean t1/2 on Day 5 and 10 was approximately 2 hours and is similar to the geometric mean t1/2 achieved on Day 1 in the first in human study PN001 (1.88 hours). The geometric mean AUC0-24 ranged from 0.129 to 1.71 nM·hr on the first day for the 30 to 240 µg dose levels. On the last day the geometric mean AUC0-24 ranged from 0.218 to 2.00 nM·hr. Following administration of the 240µg dose for 5 days, the GM AUC0-24 was 2.00 nM·hr, which is approximately 2.25 times below the AUC0-24 (4.5 nM·hr) corresponding to the NOAEL in the dog.

2.2.3 Ongoing Clinical Studies

PN002: Dosing of MK-5475 in Participants with Pulmonary Hypertension (Current Study)

In this 2-part study evaluating the safety, PK and PD [right heart catheterization (RHC) and functional respiratory imaging (FRI)], single-dose MK-5475 ranging from 120 to 360 µg in participants with moderate to severe group 1 PAH is generally well-tolerated. To date, 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 45 AEs in 15 of 18 participants were reported. Of these, 9 AEs were considered related to study drug by the investigator. AEs deemed related were rhinitis (1), dizziness (1), ALT increased (2.94 x ULN) (1) bilirubin increased (1.18 and 2.13 x ULN)(2) hyperkalemia (1.02 to 1.07 xULN) (3) and platelet count decreased (0.33 below LLN) (1). Refer to the Investigator's Brochure for a full listing of AEs to date.

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 4.28 nM*hr for the 120 to 360 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 4.28 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). 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.

PN004: MK5475 Sildenafil DDI Study

This is a randomized, placebo-controlled, 2-period, 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 and randomized 1:1 to 2 treatment sequences. Sildenafil was administered TID for 3 days in each period. Participants were randomized to the sequence to which they would receive single-dose of MK-5475 240 µg and placebo on Day 3 of sildenafil dosing. 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. 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. Thus, MK-5475 does not add to the BP lowering effects of sildenafil.

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.

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

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study is to be conducted in male and female participants with group 1 pulmonary arterial hypertension (PAH).

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of MK-5475 in participants with pulmonary arterial hypertension (PAH). (All parts)	Safety and tolerability will be evaluated during clinical assessments that include vital signs, safety laboratory testing, physical examinations, ECG readings, PFTs and review of adverse events.
• To assess the duration and effect following a single inhaled dose of MK-5475 on pulmonary vascular resistance (PVR) in participants with pulmonary arterial hypertension (PAH). (Part 2, Period 2 (Panel A) and Period 3 (Panels B, C and D))	Peak reduction from baseline in PVR after a single inhaled dose of MK-5475
Secondary	
• To estimate the effect of MK-5475 given as single inhaled doses on systemic hemodynamic parameters (heart rate (HR), systolic and diastolic blood pressure (BP)) in participants with pulmonary arterial hypertension. (Part 2 Period 2 (Panel A) and Period 3 (Panels B, C and D))	• HR and BP change from baseline at 0.5, 4.5, and 24 (or prior to discharge) hours post-dose.
• To obtain preliminary plasma pharmacokinetic (PK) data of MK-5475 (e.g. area under the curve (AUC) 0-24, AUC 0-∞, Cmax, C24, Tmax, t1/2) in participants with pulmonary arterial hypertension. (Part 1 and 2)	• AUC 0-∞, AUC 0-24, Cmax, C24, Tmax, apparent terminal half-life
• To assess the effect following a single inhaled dose of MK-5475 on pulmonary blood volume (PBV) in participants with pulmonary arterial hypertension. (Part 2, Period 3 (Panel A) and Period 2 (Panels B, C and D))	• Increases from baseline PBV at 1, 3, 8 and 24 hours postdose.

Objectives	Endpoints
Tertiary/Exploratory	
[redacted]	
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study. (Parts 1 and 2)	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

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.

This is a 2-part, 4-panel, single-site, study of MK-5475 in participants with group 1 PAH.

Up to 25 participants will be enrolled. Clinical indication for right heart catheterization (RHC) is needed in order to participate in the study.

Part 1 of this study is a double-blind, randomized, single-ascending dose assessment of safety, tolerability and pharmacokinetics (PK) of inhaled MK-5475 in participants with group 1 PAH. One panel (Panel A) of up to 8 participants will dose in up to 3 dosing periods. In each dosing period, 6 participants will receive MK-5475 and 2 will receive placebo (Pbo). Two (2) different participants will receive placebo in each of the dosing periods. There will be a minimum washout of 7 days between dosing periods. Review of available safety data (e.g. vital signs, ECG, labs, PFTs and AEs) up to 24 hours post dose of at least the first 4 participants must occur prior to escalating to the next dose level. A break to review PK data from Periods 1 and 2 will occur after completion of Period 2. Review of safety will occur after completion of Period 3 in all participants from Panel A, prior to initiation of Part 2. An optional break to review rolling PK data from Panel A Period 3 will be dependent upon exposures observed in Periods 1 and 2. Participants from Part 1 may continue into Part 2.

Part 2 of this study will assess the safety, tolerability, PK and pharmacodynamics of inhaled MK-5475. Three additional panels of participants (Panels B, C and D) will be enrolled into Part 2. Participants in Panel B (N=4), C (N= up to 8) and D (N= up to 7) will participate in up to 3 dosing periods. Period 1 of Panel B will be an open label assessment of, safety/tolerability and PK. where participants will receive MK-5475. A review of available safety data up to 24 hours post dose and a rolling PK assessment will occur following completion of Panel B, Period 1, prior to going to the FRI period. Panel C, Period 1 will be an open label assessment of MK-5475. Panel C may begin once PK and safety data are reviewed from Panel B, Period 1. A rolling PK and safety data review of the first 4 participants of Panel C will occur prior to moving to the FRI period. The remaining participants in Panel C may enter Period 1 while this review is in progress. Following a review of individual safety along with a review of PK from first four participants in Panel C, the remaining participants will proceed to Period 2 (FRI period). The sample size of Panel C may increase based on number of participants from Panel A who do not continue into Part 2. Further enrollment of Panel C may end once screening of Panel D has begun. Panel D, Period 1 will be an open label safety/ tolerability and PK assessment of MK-5475. Following a review of individual safety of Period 1, participants will then proceed to Periods 2 (FRI period) and 3 (RHC period). The maximum sample size of Panel D is 7 but, may be less based on the final number of participants enrolled in Panel C and review of data from previous participants in Panel D. The total number of participants enrolled in Part 2 will be up to 24.

FRI Period

In Part 2, Period 2 for Panels B, C and D and Period 3 for Panel A, participants will undergo FRI. Participants will undergo a series of computed tomography (CT) scans to assess baseline and changes after dosing in pulmonary blood volume (PBV) through functional respiratory imaging (FRI) with an intravenous (IV) iodinated contrast agent.

RHC Period

In Part 2, Period 2 for Panel A and Period 3 for Panels B, C and D, assessment of safety and up to 4 baseline pulmonary hemodynamic measurements taken about 10 minutes apart, including pulmonary vascular resistance (PVR) calculated from data obtained by thermodilution (see Manual of Operations) will occur prior to dosing of MK-5475. Values from two consecutive PVR measurements should be within 15% of each other (highest PVR value will define the 15%) to confirm stable baseline. If the PVR data from the first two measurements deviates by more than 15%, up to 2 additional PVR measurements may be obtained. If a stable baseline PVR cannot be obtained after 4 measurements, the subject will not be eligible to continue dosing and will be discontinued from the study.

1. Pulmonary Arterial Pressure (mPAP) ≥ 25mmHg. Predose mPAP obtained from 3 individual measurements taken about 10 minutes apart. The mean value from the 2 last measurements will serve as the PVR baseline value.

2. Pulmonary Vascular Resistance (PVR) ≥ 300 dynes/sec/cm^5.

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.

Following dosing of MK-5475 in Part 2, Period 2 (Panel A) and 3 (Panels B, C and D), assessment of safety as well as systemic (HR and BP) and pulmonary [cardiac output (CO), cardiac index (CI), pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), systemic vascular resistance (SVR) and PVR] hemodynamic changes will be performed as outlined in the SoA.

Because this is a Phase 1 assessment of MK-5475 in humans, the pharmacokinetic (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 8.12 for examples of modifications permitted within the protocol parameters.

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 a single dose to participants with PAH. Preclinical studies as well as the first-in-human study with this compound support the conduct of this study, given the evidence that the compound appears to be safe, well-tolerated, and has suitable pharmacokinetics to support a pharmacodynamic evaluation.

Because this is the first introduction of this compound into participants with PAH, Part 1 of the study was designed to evaluate safety, tolerability, and pharmacokinetics in this population. As a conservative measure to ensure participant safety, dosing began at 120 µg, a level below the maximum dose of 165 µg that was given to healthy participants in PN001. The dose was gradually escalated first to 165 µg and then to the maximum dose of 240 µg in Part 1. In Part 2 Panels B and C, the dose will begin at 300 µg and escalate to 360 µg (See Section 4.3.2). Given the favorable safety profile observed in the preclinical 3-month toxicology studies and in clinical studies at doses up to 360 µg and to further explore the range of possible safe and effective doses of MK-5475, a dose of 480 µg of MK-5475 will be given in the first period of Panel D. In periods 2 and 3 of Panel D, a dose of 120 µg will be given in order to explore the PK/PD relationship at a lower dose.

Once the safety, tolerability, and pharmacokinetics have been established in Part 1 and Part 2, Period 1, pharmacodynamic assessments will be performed in a larger group of participants. These assessments (right heart catheterization and functional respiratory imaging) are directly related to the ultimately desired clinical efficacy endpoints for this compound and are well-validated in the published literature [Grimminger, F., et al 2009].

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no efficacy endpoints for this study.

4.2.1.2 Safety Endpoints

This will be the second introduction of MK-5475 into humans (See Section 2.2.3). The first introduction was supported by preclinical safety and toxicological testing in rats and dogs (See Investigator's Brochure).

Safety and tolerability will be monitored through clinical assessments of AEs, repeat physical exams, vital sign measurements, standard lab safety tests, ECGs and spirometry tests.

4.2.1.3 Pharmacokinetic Endpoints

MK-5475 is an inhaled drug being developed for the management of PAH. Pharmacokinetic end-points including systemic assessments of $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}\infty}$ C_{max}, $C_{24,}$, T_{max}, apparent terminal half-life will be assessed through the duration of this study.

4.2.1.4 Pharmacodynamic Endpoints

The primary pharmacodynamic endpoint will be PVR, which is calculated from variables obtained by RHC. Secondary pharmacodynamic endpoints include the systemic hemodynamic parameters of HR and BP as well as PBV using FRI.

4.2.1.5 Planned Exploratory Biomarker Research

There are no exploratory biomarkers planned.

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 Part 1 (Panel A), a placebo-controlled study will facilitate an unbiased assessment of safety and tolerability. Because this is the first assessment in PAH participants, and they will not receive clinical benefit from MK-5475, 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 example 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. For dogs, 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.

The starting dose for this study will be 120 µg inhaled in a single dose, allowing approximately a 4-fold safety margin below the NOAEL. In terms of systemic exposure, at this dose, the observed systemic AUC 0-24h was 0.663 nM*hr, which is approximately 1/7th of the systemic NOAEL of 1-month dog toxicology exposure level of 4.5 nM*hr AUC 0-24h. Because the 1-month dog NOAEL was set according to a local finding rather than a systemic finding, and no systemic effects of this compound have been observed except for hemodynamic changes at much higher exposures in preclinical species, this would provide an adequate safety margin. Higher doses have already been administered to humans in the other studies for this compound, with acceptable safety, tolerability, and pharmacokinetic data.

4.3.2 Maximum Dose/Exposure for This Study

As above, because of the inhaled route of delivery, estimated lung burden was used to determine the maximum allowable exposure based on the lung burden at the dog NOAEL dose. As demonstrated, the dog NOAEL dose corresponds to a delivered human dose of 500 µg. However, in general there were few preclinical findings in either rat or dog safety studies. The NOAEL dose in dogs was 0.02 mg/kg/day; at the three-fold higher dose of 0.06 mg/kg/day, only mild focal bronchial artery thickening was observed, that occurred in one animal in the study.

For the studies in healthy volunteers, the maximum human dose was 240 µg, which provided a ~2-fold safety margin below the NOAEL. In accordance with EMA guidance for first-in-human studies (*Guideline on Strategies to Identify and Mitigate Risks for First in Human and Early Clinical Trials with Investigational Medicinal Products*), this conservative safety margin was applied because the study involved healthy participants. At this dose level, the compound was well tolerated and all safety data was within normal parameters. In addition, the observed pharmacokinetic data established that systemic exposures to the compound were well below the systemic NOAEL level established in dogs.

Having established the tolerability of 240 µg in normal healthy participants, the present study will involve participants in the target population for this therapy. The maximum dose will be advanced to a maximum of 480 µg, which is below the NOAEL dose. The preclinical finding that was noted in dogs appears to be due to a vasoactive pharmacological effect within the

lung, presumably vasodilation induced by MK-5475. Since pulmonary hypertension patients suffer from chronic vasoconstriction, it is likely that they would be better able to tolerate acute vasodilation of blood vessels in the lung without harmful sequelae than healthy participants. In addition, we note that although 100% deposition in humans is assumed in these calculations, the true deposition based on the fine particle fraction is lower (~30-60%), affording an additional safety margin. Therefore, the true lung exposure will be lower than projected above. Thus, a less conservative safety margin is appropriate in patients than in healthy participants, as these participants may potentially benefit directly from development of an additional therapy for their disease.

Finally, although systemic exposure is considered less relevant for inhaled compounds, based on the observed PK data from the prior study, it was initially projected that systemic exposure will also be approximately 2-fold below the observed AUC 0-24h of 4.5 nM*hr from the dog NOAEL dose at the 240 µg dose. Based on the initial PK data observed in this study for participants in Panel A, the observed systemic PK at a dose of 240 µg was substantially lower than projected, with AUC 0-24h of 1.42 nM*hr. Given the low gastrointestinal bioavailability of this compound, and the observed direct proportionality between delivered dose and systemically measured PK, this reduced exposure was thought to be related to the decreased ability of diseased patients to generate adequate inhaled exposure compared with healthy subjects (as the lung deposition of inhaled DPI compounds is directly affected by the inspiratory flow generated by the subject). As the dose in this study was increased to 300 and then 360 µg, subsequent participants have exhibited higher exposures. In order to further explore the relationship between systemic exposure and delivered dose at higher doses, the maximum dose will be increased in this study to 480 µg. At this dose, the resulting systemic exposure is projected to be approximately 3.5nM*hr AUC 0-24h. While participants may exceed the NOAEL systemic exposure, this exposure was set on the basis of a local finding in the lung in a 30-day toxicology study. In contrast, the finding which was used to set the NOAEL is expected to be driven by lung burden, which at this dose remains below the NOAEL dose of 500 µg. While higher systemic exposures from a single dose may lead to hemodynamic changes, such changes were only observed in preclinical species at systemic exposures far above the NOAEL exposure in pharmacology studies. No evidence of any impact on systemic hemodynamics including heart rate or blood pressure has been observed thus far in any clinical study of MK-5475, and given the short systemic half-life of this compound, it is expected that any such change after a single dose of compound would be self-limited. Finally, a subsequent 3-month GLP toxicology study showed that the finding used to establish the NOAEL was no longer present in a longer duration study.

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, Panel A participants were dosed with single doses of 120 µg, 165 µg, and 240 µg in successive dosing periods. In Panels B and C doses up to 360 µg were given. In the initial clinical studies in healthy volunteers with this compound, 120 µg, 165 µg and 240 µg doses were delivered with acceptable safety, tolerability, and pharmacokinetic data. These doses were delivered with the following supportive data: MK-5475, a sGC stimulator, is not considered a compound with a high degree of uncertainty related to the potential risk of harm to participants, according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" (European Medicine Agency [EMA]) released July 2017. The degree of uncertainty was determined by careful evaluation of the following: mode of action of MK-5475, presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies, and the study population.

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 the initiation of clinical trials in people with this compound via the inhaled route. No dose-limiting toxicities were observed in 1 month rat and dog toxicity trials, and substantial preclinical safety margins were obtained over initial human doses. As with the previous study, 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 potential for risk of harm, 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. There will be at least a 7-day washout period between doses for any given participant, which is supported by the half-life of MK-5475 observed in humans (approximately 2 hours).

In Part 2 of the study, participants will receive single doses of 240 µg (Panel A) or 300 µg to 360 µg (Panels B and C) in each of two or three successive periods. Single doses will be given in Panel D (480 µg and 120 µg) in three successive periods. For all panels extensive safety monitoring, and with at least a 7-day washout period will occur between doses for any given participant.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, 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. The overall study end will then not be identified until the Sponsor has made the decision to end the study following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [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. 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

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.

5 STUDY POPULATION

Male/Female participants with group 1 PAH between the ages of 18 and 70 years (inclusive).

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Be judged to have no untreated, clinically significant health issues from other co-morbidities (e.g. uncontrolled diabetes) based on medical history, physical examination, vital sign (VS) measurements and electrocardiograms (ECGs) performed at screening visit.

2. Be judged to have no untreated, clinically significant health issues from other co-morbidities (e.g. uncontrolled diabetes) based on laboratory safety tests obtained at the screening visit(s). Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 9 provides an algorithm for the assessment of out of range laboratory values.

3. Have a Body Mass Index (BMI) ≤35 kg/m^2, inclusive at screening. See Section 8.3 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$. Weight should not exceed 160 kg.

Demographics

4. Participant is male or female.

(Panel A)

5. Participant is from 18 years to 70 years of age inclusive, at the time of signing the informed consent.

(Panel B, C and D)

6. Participant is from 18-70 years of age inclusive, at the time of signing the informed consent.

Female Participants

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

  - She is a woman of nonchildbearing potential (WONCBP), as defined in Appendix [5]

    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) 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.

Male Participants

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) 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

Informed Consent

7. The participant provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

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

9. Be or have suspected Group 1 pulmonary hypertension as defined by the Nice 2013 Clinical Classification, including:

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

10. Be deemed clinically stable by the investigator.

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

12. Have a clinical indication for RHC as part of initial work-up or ongoing medical management.

a. **(Panel A) Inclusion Criteria** Have history of right heart catheterization within three years of starting study medication demonstrating mean pulmonary artery pressure of ≥ 27 mmHg and PVR of ≥ 300 dynes/sec/cm5 (RHC may have been performed prior to initiation of participant's prescribed background therapy); if subject is status post-surgical repair of congenital heart defect, these criteria must be met at least one year after surgery.

(Panel B, C and D) Inclusion Criteria

b. Have history of right heart catheterization within three years of starting study medication demonstrating mean pulmonary artery pressure of ≥ 27 mmHg and PVR of ≥ 300 dynes/sec/cm5 (RHC may have been performed prior to initiation of participant's prescribed background therapy); if subject is status post-surgical repair of congenital heart defect, these criteria must be met at least one year after surgery.

OR

Have an echocardiogram performed by the investigator (or appropriate designee) at screening or within 1 year of screening demonstrating pulmonary artery systolic pressure ≥ 50 mmHg in conjunction with one or more of the following: tricuspid regurgitation velocity > 3.0 m/s and or significant right heart enlargement and or reduced right heart function.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

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

Clinical Classification:

1.4.2. HIV infection

1.4.3. Portal hypertension

1.4.5. Schistosomiasis

1.4.6. Chronic hemolytic anemia

1'. Pulmonary veno-occlusive disease (PVOD) and or pulmonary capillary hemangiomatosis (PCH) 1". Persistent pulmonary hypertension of the newborn (PPHN)

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

3. Pulmonary hypertension owing to lung diseases and/or hypoxia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4. Sleep-disordered breathing

3.5. Alveolar hypoventilation disorders

3.6. Chronic exposure to high altitude

3.7. Developmental abnormalities

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

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 (not including stable diabetes mellitus), gastrointestinal, cardiovascular, hematological, hepatic (not including chronic stable Hep B and C), immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator. Participants with controlled hypertension are allowed to be enrolled.

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 that the investigator feels poses a risk to the participant if they participate in the study. 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 ≥10 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. This includes milk or lactose allergy/intolerance.

6. Has known hypersensitivity to iodine or iodine containing products.

7. Is positive for HIV.

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 or controlled atrial fibrillation with no clinically significant arrhythmia may be allowed per the judgment of the investigator).

10. Has significantly impaired gas exchange.

11. Has an active respiratory infection (e.g. common cold, bronchitis, influenza, pneumonia) with lung function values (FEV_1 and/or FVC) outside of the normal range at pre-dose Period 1 (May be rescreened upon resolution of the active respiratory infection).

Prior/Concomitant Therapy

12. Is currently on monotherapy calcium channel blockers as a specific treatment for pulmonary hypertension based on a history of positive vasoreactivity testing.

13. Has taken nitrates within 24 hours of anticipated dosing.

14. Has taken inhaled prostacyclin within 24 hours of anticipated dosing (iloprost or treprostinil).

15. Has taken diltiazem immediate release taken within 24 hours or extended release taken within 48 hours of anticipated dosing.

16. Has taken sildenafil or valdenafil within 24 hours or tadalafil within 7 days of anticipated dosing. Participants in whom sildenafil, valdenafil or tadalafil has been stopped prior to these respective time points are eligible.

17. Has taken sGC activator for PAH within 24 hours of anticipated dosing.

18. Has taken endothelin receptor antagonists (ERAs) (e.g. bosentan, ambrisentan, macitentan) within 24 hours of anticipated dosing.

19. 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).

Prior/Concurrent Clinical Study Experience

20. 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

21. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females) at screening and Predose Period 1

22. Has a systolic BP <100 mmHg, Diastolic BP < 40 mmHg or HR >100/min at baseline. Mean of these values will be used at screening and Predose Period 1. (See exclusion criteria #9 for HR associated with uncontrolled a-fib).

23. Participant has an estimated creatinine clearance of < 60 mL/min based on the Cockcroft-Gault equation; the Cockcroft-Gault equation is 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)

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

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.

Other Exclusions

24. Is unable to correctly use the TWISTHALER® device (after instruction by the study staff) at a visit prior to randomization.

25. Is under the age of legal consent.

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

27. Part 2 only: Suffers from claustrophobia and would be unable to undergo CT scan.

28. Part 2 only: Has participated in a PET research study or other 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 this period with a radiation burden over 10 mSv (such as a CT scan exam or nuclear medical exam).

29. 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.

30. 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.

31. 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 urine drug screen (UDS) prior to randomization or assignment of allocation number.

32. 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.

5.3 Lifestyle Considerations

Women of childbearing potential (WOCBP) can be enrolled.

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Part 1 Periods 1-3, Part 2 Period 1

In each treatment period, participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration and lab safety tests. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Standardized meals will be provided by the investigator at about 4 and 10 hours post-dose. A snack will be offered at about 7 and 13 hours post dose. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same in each treatment period. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Part 2 Periods 2-3 (RHC and FRI Periods)

Participants will fast from all food and drink except water for at least 4 hours prior to lab safety tests, study drug administration or insertion of the RHC or the start of the baseline CT scan. In the RHC Period, participants may be permitted a snack at approximately 2 hours post dose and a standard meal at the completion of the RHC procedure, after which they may be given a meal at the investigator's discretion. After completion of dosing in the FRI Period, snacks may be provided by the investigator between the 1 and 3 hour post dose scans and a standard meal will be provided about 1 hour after the 3 hour post dose scan. At the investigator's discretion, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

In both parts, up to 240 mL of water may be provided after the last inhalation of study drug. Water will be restricted 1 hour prior to initial inhalation and 1 hour after the last inhalation of study drug in each period.

Instructions on whether to take MK-5475 with or without food and/or drink may be modified during the study based on newly available data.

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 including the washout intervals between treatment periods and until the poststudy visit.

Participants also will refrain from the consumption of all fruit juices 24 hours prior to and after study drug administration. On all other days during the study, consumption of 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 and from 12 hours prior to and after study drug administration in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 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 and from 24 hours prior to and after study drug administration in each treatment period. 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 not be permitted to smoke 24 hours prior to and on the day of dosing. At all other times, participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the Clinical Research Unit (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 or assigned an allocation number in the study. A minimal set of screen failure information may be included, as outlined in the electronic case report forms (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 supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Part 1	Placebo Comparator	Placebo	Drug	Dry Powder	0 µg	0 µg	Inhalation	One time in each period	Placebo	IMP	Sponsor
Part 1 Periods 1-3	Experimental	MK-5475	Drug	Dry Powder	15 µg, 60 µg	120 µg, 165 µg, 240 µg	Inhalation	Each dose will be given only 1 time	Experimental	IMP	Sponsor
Part 2 Periods 1-3	Experimental	MK-5475	Drug	Dry Powder	15 µg, 60 µg	240 µg, 300 µg, 360 µg	Inhalation	One time in each period	Experimental	IMP	Sponsor
Part 2 Periods 1-3 Panel D	Experimental	MK-5475	Drug	Dry Powder	60 µg	120 µg, 480 µg	Inhalation	One single dose in a period	Experimental	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.

These supplies are being provided as open label bulk supplies and will be assigned and dispensed by the unblinded pharmacist at the site.

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.

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 inSection 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. A sample allocation schedule is provided in Table 3 below.

Table 3 Sample Allocation Schedule

Panel A [a]					
Participant (N)	Part 1 Period 1	Part 1 Period 2	Part 1 Period 3	Part 2 Period 2	Part 2 Period 3
N=2	120µg	Placebo	240 µg	240µg	240µg
N=2	120µg	165µg	Placebo	240µg	240µg
N=2	120µg	165µg	240µg	240µg	240µg
N=2	Placebo	165µg	240µg	240µg	240µg
[a] The participants in Panel A will be randomly assigned. A total of 20 participants will participate in Part 2 (Panels A+B+C)					

Panel B

Participant (N)	Part 2 [a] Period 1	Part 2 [a,] Period 2	Part 2 [a,] Period 3
N= 4	300 µg	360 µg	360 µg
Panel C			
N = 16[b]	300 µg	360 µg	360 µg
Panel D			
N=7[c]	480 µg	120 µg	120 µg
[a] A total of up to 24 participants will participate in Part 2. (Panels A+B+C+D) [b] The sample size for Panel C may be adjusted depending on the number of participants from Panel A that continue into Part 2 and the start of Panel D. Panel C will not exceed 16 evaluable participants. Participants in Panels B and C will be non-randomly assigned. [c] The sample size for Panel D may be adjusted and will be dependent upon the final number of participants that are enrolled in Panel C. Panel D will not exceed 8 evaluable participants. Participants in Panel D will be non-randomly assigned.			

6.3.2 Stratification

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

6.3.3 Blinding

In Part 1 (Panel A) of this study, a double-blinding technique will be used. MK-5475 and placebo will be packaged identically so that blind is maintained. 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. Part 2 of this study is conducted as open label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

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

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication 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.

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. Certain calcium channel blockers (e.g. amlodipine) not being used for the treatment of PAH based on vasoreactivity testing.
5. Trimetazidine.
6. Mineralcorticoid receptor antagonists (e.g. spironolactone, eplerenone)
7. Oral hypoglycemic agents
8. Diuretics.

9. Digoxin

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

13. 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.

    All permitted prescribed medications may be taken on the morning of the RHC/FRI.

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

1. PDE5 inhibitor for PAH; sildenafil or vardenafil taken up to 24 hours prior to dosing of study drug; tadalafil taken within 7 days of anticipated dosing. PDE5 inhibitor treatment may be initiated after 2 days have elapsed from the time of MK-5475 dosing.

2. sGC activator for PAH taken up to 24 hours prior to dosing of study drug. sGC activator may be initiated after 2 days have elapsed from the time of MK-5475 dosing.

3. Nitrate taken up to 24 hours prior to dosing of study drug. Nitrates may be initiated after 2 days have elapsed from the time of MK-5475 dosing.

4. Inhaled prostacyclin taken up to 24 hours prior to dosing of study drug.

5. Immediate release diltiazem taken up to 24 hours or extended release diltiazem taken up to 48 hours prior to dosing of study drug. Dilitazem may be initiated after 2 days have elapsed from the time of MK-5475 dosing.

6. ERAs (e.g. bosentan, ambrisentan, macitentan) taken up to 24 hours prior to dosing of study drug. ERAs may be initiated after 2 days have elapsed from the time of MK-5475 dosing.

7. Verapamil

- **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

Clinical Research Units (CRUs) will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention. Sites will use their standard operating procedures to manage any acute hemodynamic changes as deemed clinically appropriate (e.g. Trendelenberg position, intravenous fluids).

6.6 Dose Modification (Escalation/Titration/Other)

In Part 1 and Part 2, all dose escalation decisions will be made jointly by the investigator and the Sponsor. Each dose escalation decision may occur after at least 4 evaluable participants in Part 1 (all periods) and 4 evaluable participants in Part 2, Period 1 have completed the previous dose level.

Dose escalation decisions will be based on key safety variables including, vital signs, 12-lead ECG, laboratory safety tests, AEs, and PFTs from the previous dose levels up to at least 24 hours. Pharmacokinetic data may be included in the dose escalation decisions (Section 8.6).

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 a Serious Adverse Event considered related to the study drug by the investigator.

2. Two (2) or more participants within a Panel (at the same dose level) report Severe Non-serious Adverse Events considered related to the study drug by the investigator.

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

Panel wide stopping criteria

a. 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.

1. Individual stopping criteria:

a. Hemodynamic changes that exceed the pre-specified limitations (See Appendix 10)

6.7 Intervention After the End of the Study

If adequate standard of care (SoC) treatment is not obtainable via the local health insurance system, participants who complete the study or discontinue the study for non-personal reasons (e.g. AEs, does not meet RHC criteria) may be provided with a standard of care treatment (e.g. bosentan) that is determined to be appropriate for the participant by the participant's treating physician. After completion of this phase, participants will be reevaluated and transferred to the local standard of care treatment for PAH. For part 1 participants, this SoC may be provided up to 6 months after study completion. For part 2 participants, this SoC may be provided up to 12 months after study completion. For part 1 and Part 2 participants, this SoC may be provided up to 18 months after study completion.

6.8 Clinical Supplies Disclosure

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

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 and 8.11.3.

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.
- Part 1 only: The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- 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.
- The participant does not meet the baseline RHC criteria in Part 2 Period 2 or 3 (See Section 4.1).

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, he/she 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 or trained 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 500 mL (Appendix 8).

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 consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (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 dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

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.

At least 2 days should elapse between dosing of MK-5475 and initiating or restarting sildenafil, valdenafil or tadalafil, sGC activators, prostacyclins, nitrates, ERAs and/or diltiazem.

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 in Panel A and Panel B will be randomly allocated and all eligible participants in Panel C will be allocated, by nonrandom assignment. All participants 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

Administration of study medication will be witnessed by the investigator and/or study staff.

8.1.8.1 Timing of Dose Administration

After it is confirmed that the participant meets eligibility in Period 1 of Part 1 (Panel A) or Part 2 (Panels B, C and D), each dose of MK-5475 or placebo (placebo for Part 1 Panel A participants only) will occur after the completion of predose procedures. The time of the dose will be designated as time "0" and the exact time of administration will be recorded. At least a 7-day washout will occur between intervention periods.

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 8.11.4) 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 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 principal 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 Periods 1-3 and Part 2 Period 1, participants may report to the clinical research unit (CRU) the evening prior to the scheduled day of administration of the study intervention at the discretion of the investigator. Participants will remain in the unit until the 24-hour, postdose procedures have been performed.

In Part 2, participants will report to the clinic at the time instructed by the CRU in preparation for the CT scan and dosing procedures in the FRI period and the RHC and dosing procedures in the RHC Period.

In the FRI Period, participants will be discharged approximately 1 hour following completion of the 8 hour post dose CT scan but, participants may remain domiciled overnight in preparation for the 24 hour CT scan, at the discretion of the investigator. Those participants that are discharged after 8 hour CT scan will be asked to return for the 24 hour CT scan and discharge procedures.

In the RHC Period, participants will remain domiciled overnight or may be discharged on the same day at the discretion of the investigator if the following discharge criteria are met:

- If present, resolution of any hemodynamic-related clinically significant symptoms with potential relationship to study intervention/procedure
- BP and HR are within 25% of baseline measures
- Participants have a SBP $\geq$ 90 mmHg, HR < 110 bpm (Triplicate HR and BP should be measured at least three times separated by a minimum of 15 minutes. The median values of each set of measurements must meet the criteria above in order to be eligible for same day discharge).
- All AEs have been reviewed by the investigator who confirms clinical appropriateness for same day discharge.

At the discretion of the investigator, participants may be requested to remain in the CRU longer.

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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study; surrogate markers of efficacy are outlined in Section 8.7.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue 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 Appendix 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. Body weight and height will be obtained with the participants shoes off, jacket or coat removed. Body weight will be measured following an 8 hour fast.

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

Body Mass Index (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 0.1-0.4 round down and 0.5-0.9 round up.

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 semi-recumbent OR supine position for at least 10 minutes prior to having vital sign (VS) measurements obtained. Semi-recumbent OR supine vital signs (VS) will include heart rate (HR) and blood pressure (BP). 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 across the study.

Predose heart rate (HR) and blood pressure (BP) will be triplicate measurements, obtained at least 1-2 minutes apart within 3 hours of dosing of study drug in Parts 1 and 2 all periods. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Screening, post-dose and post-study HR and BP measurements will also be done in triplicate measurements, obtained at least 1-2 minutes apart.

In Part 1, Periods 1-3 and Part 2, Period 1, participants will continue to rest semi-recumbent from dosing until 4 hours postdose except to stand for the measurement of orthostatic vital signs (VS) (if needed) or other study-related procedure.

Body Temperature

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 Oxygen Saturation

In Part 2, RHC Period, O_2 saturation will be measured using pulse oximetry on each participant at the timepoints noted in the SoA (See Section 1.3)

8.3.2.3 Orthostatic Vital Signs

In Part 1, Periods 1-3 and Part 2, Period 1, orthostatic vital signs (VS) (HR and 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.

8.3.3 Electrocardiograms

Prior to each period, predose electrocardiograms (ECGs) will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing MK-5475 or placebo. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Screening, post-study and post-dose ECG measurements will be single measurements.

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 position for at least 10 minutes prior to each electrocardiogram (ECG) measurement.

The correction formula to be used for QTc is Fredericia.

If repeat electrocardiograms (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.

If the QTc interval is 500 msec, 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.

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 case report form (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 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.

8.3.5 Pulmonary Function Tests (PFTs (Spirometry)

At all visits (except Part 2, Periods 2 and 3), 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.

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 of 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.

The following pulmonary function tests: (FEV_1, FVC and FEV_1/FVC ratio, PEF), DLCO (DLCO, DLCO adjusted for Hb 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.

Spirometry (FEV_1, FVC and FEV_1/FVC ratio, PEF) will be done at all other timepoints noted in the SoA and will be done at the site using calibrated spirometers.

8.3.6 Inhalation Airflow Meter Assessment

At least 3 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.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), 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 consent form is signed 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 treatment, 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 drug-related.

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 4.

Table 4 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:**
Nonserious Adverse Event (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
Serious Adverse Event (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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (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	Note required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Note required	Within 24 hours of learning of 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, events of clinical interest (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 suspected unexpected serious adverse reactions (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 (ECIs)

Selected nonserious and SAEs 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, that is not associated with clinical symptoms or abnormal laboratory results.

- 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

The participant has taken (accidentally or intentionally) any drug administered as part of the protocol that exceeds the dose as 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 study operations manual.

8.7 Pharmacodynamics

Pharmacodynamic assessments that are part of the right heart catheterization (RHC) and the functional respiratory imaging (FRI) procedures will be performed according to the Study Operations and CT scan procedures manuals.

8.7.1 Right Heart Catheterization Procedures

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

Pressure measurements should be taken at end-expiration and should include at least 3 complete respiratory cycles. 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 or mean). Cardiac output (CO), oxygen saturation and MVO_2 will also be collected at timepoints noted in the SoA.

Investigators may use clinical judgment to determine whether the central catheter may be maneuvered during the catheterization procedure for the purpose of measuring RAP, RVSP, and RVEDP. If the investigator determines that the participant's condition prohibits the maneuvering of the catheter during the procedure, the catheter may remain in place for the measurements of PAWP, sPAP/dPAP or mPAP, and CO.

Participants will undergo monitoring of systemic hemodynamics and for adverse events throughout the RHC. The study-related portion of RHC will continue until completion of all measurements at the 4.5 hr postdose timepoint after which it may be removed unless clinically indicated it is needed to stop earlier.

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

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 of the 5 scanning sessions (Pre-dose baseline, 1, 3, 8 and 24 hours post-dose), participants will be prepped and placed in a supine position on the scanner bed.

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.

8.8 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 future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

- 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 signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- 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 35 days (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 Visit

Part 1

After Period 1 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. In Periods 1-3, at the discretion of the investigator, participants will be discharged from the CRU after completion of the 24-hour post-dose procedures.

Prior to Intervention Periods 2 and 3, clinical (VS, ECG, AEs and spirometry) and laboratory safety parameters from the previous intervention period up to 24 hours post dose will be reviewed by the investigator and the sponsor to confirm advancement to the next higher dose level.

Participants from Part 1 may continue into Part 2. If a participant opts to continue into Part 2, an assessment of AEs/SAEs will occur via a phone call about 14 days after the last dose of study drug in Part 1.

Part 2

After Panel B, C and D, Period 1 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 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 24-hour post-dose procedures.

Prior to Periods 2 and 3, clinical (VS, ECG, AEs and spirometry) and laboratory safety parameters from the previous intervention period up to 24 hours post dose will be reviewed by the investigator and the sponsor to confirm advancement to the next higher dose level. Pharmacokinetic parameters for all 4 participants in Panel B and the first 4 participants in Panel C will also be reviewed from Period 1 of each panel before going to Period 2.

In Period 3 (Panel A) and 2 (Panel B, C and D), participants will report to the clinical research unit (CRU) at a time as provided by the CRU for CT scanning. MK-5475 administration and associated procedures as defined in the SoA will be performed. At the discretion of the investigator, participants may be discharged from the CRU after completion of the 8 hour postdose scan and pre-discharge procedures or participants may remain domiciled overnight at the discretion of the investigator in preparation for the 24 hour CT scan. Participants that were discharged will be asked to return for the 24 hour post dose scans and pre-discharge procedures.

In Period 2 (Panel A) and 3 (Panel B, C and D), participants will proceed to RHC procedures to confirm eligibility based on pulmonary hemodynamic measures as outlined in Sections 4.1 and 8.7.1 will be performed.

Once baseline RHC measurements are complete and continuation into RHC period is confirmed, participants 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, including pulmonary and hemodynamic assessments will be performed according to the SoA. Participants may be discharged at 24 hours post dose, or on the day of the RHC procedure at the discretion of the investigator if all discharge criteria are met (See Section 8.1.11).

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 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.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

In Part 1 Periods 1- and Part 2 Period 1 of this 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, Period 2 (Panel A) and Period 3 (Panels B, C and D) of this study, RHC measurements, in particular PVR, is the critical procedure.

At any postdose time point, RHC measurements need 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, Period 3 (Panel A) and Period 2 (Panels B, C and D) of this study, FRI measurements are the critical procedure.

At any postdose time point, FRI measurements need 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.

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 5.

Table 5 Pharmacokinetic Blood Collection Windows

PK Collection	PK Collection Window[1]
0 – < 6 min	2 min
≥ 6 min to < 1hr	5 min
≥ 1 hr in Part 1 and Part 2 Period 1 ≥ 1 hr in Part 2 Period 2/3	15 min 20 min
≥ 24 hr	30 min
[1] Window is +/- from collection time	

- Predose standard safety evaluations: vital signs (including HR, BP, RR,body temperature and weight) spirometry and ECG up to 3 hrs; laboratory safety tests and physical exam up to 24 hrs

- Part 2: Predose inspiratory flow meter assessment up to 3 hours prior to dosing
- Predose Baseline CT scan: up to 30 minutes prior to dosing
- Predose RHC, including PAP, measurements: up to 15 minutes from the scheduled procedure time
- Predose arterial O_2 saturation (pulse oximetry) and MVO_2: up to 15 minutes from the scheduled procedure time
- Postdose standard safety evaluations: vital signs, ECG, laboratory safety tests, spirometry and physical exam
    - 0 to < 1 hr postdose within 10 minutes of the theoretical sampling/procedure time
    - ≥1 to <24 hr postdose within 15 min of the theoretical sampling/procedure time
    - ≥24 hr postdose within 1 hr of the theoretical sampling/procedure time
- Postdose RHC, including PAP and VS measurements: within 15 minutes of the theoretical sampling/procedure time
- Postdose arterial O_2 saturation (pulse oximetry) and MVO_2: within 15 minutes of the theoretical sampling/procedure time
- Postdose CT scan:
    - ≥1 to <24 hr postdose within 20 minutes of the theoretical sampling/procedure time
    - ≥24 hr postdose within 1 hr of the theoretical sampling/procedure time

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 is 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/panel

- Interchange of doses between panels
- Entire period(s) or panel(s) may be omitted
- 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 interval between dosing and the post dose RHC measurements in Part 2
- Changes to the time interval between dosing and the post dose CT scans in Part 2
- Change sequence of RHC and FRI procedure in Periods 2 and 3 of Part 2.
- 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 (Section 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

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

9.1 Statistical Analysis Plan Summary

Statistical Methods

Primary Objective (PVR): For the primary pharmacodynamic parameter PVR, the peak percent reduction compared to baseline in PVR after a single inhaled dose of MK-5475 will be analyzed for Part 2, the RHC period. The difference from baseline will be assessed on the log scale and then back-transformed for reporting (percent change from baseline).

Primary Objective (Safety): Incidence of AEs will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the VS, ECG parameters, and selected laboratory safety parameters for participants, as deemed clinically appropriate. 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, ECGs, and/or VS may also be computed, as deemed clinically appropriate.

Secondary Objective (HR, BP, and PBV): The predose baseline values for HR and BP will be obtained as outlined in Section 8.3.2.1. The mean change from baseline for the HR and BP will be calculated at 0.5, 4.5, and 24 hours post-dose for Part 2, Period 2 or 3 only.

PBV will be measured using CT scans with an IV iodinated contrast agent before and after administration of MK-5475. An increase from baseline in measured PBV would be calculated at 1, 3 and 8 hours for Part 2, the FRI period only.

Secondary Objective (PK): Separately for each PK parameter (Panel A, Part 1, Periods 1, 2 and 3, and Panels B-D, Part 2, Period 1), individual values of $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}\infty}$, C_{max}, C_{24}, at each dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for treatment, and Panel a random effect for participant. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Ninety-five percent confidence intervals for the least squares means for each treatment will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration

with the Quantitative Pharmacology and Pharmacodynamic Department and Translational Pharmacology Department of the Sponsor.

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 Objectives:

- To evaluate the safety and tolerability of MK-5475 in participants with pulmonary arterial hypertension (PAH).

- To assess the duration and effect following a single inhaled dose of MK-5475 on pulmonary vascular resistance (PVR) in participants with pulmonary arterial hypertension (PAH).

Secondary Objectives:

- To estimate the effect of MK-5475 given as single inhaled doses on systemic hemodynamic parameters (heart rate (HR), systolic and diastolic blood pressure (BP)) in participants with pulmonary arterial hypertension.

- To obtain preliminary plasma pharmacokinetic (PK) data of MK-5475 (e.g. area under the curve (AUC) 0-24, AUC 0-∞, Cmax, C24, Tmax, t1/2) in participants with pulmonary arterial hypertension.

- To assess the effect following a single inhaled dose of MK-5475 on pulmonary blood volume (PBV) in participants with pulmonary arterial hypertension.

Exploratory Objectives:

- To explore the relationship of MK-5475 concentration and summarize changes in pulmonary vascular resistance, pulmonary arterial pressure, cardiac output/cardiac index (CO/CI), systemic vascular resistance, mixed venous oxygen saturation and arterial oxygenation in participants with pulmonary arterial hypertension.

- To explore the effect of single doses of MK-5475 on the ratio of change from baseline in pulmonary vascular resistance / change from baseline in systemic vascular resistance.

- •To explore the relationship between mean change differences in pulmonary vascular resistance (PVR) and baseline changes in pulmonary blood volume (PBV) following a single dose of MK-5475.

9.4 Analysis Endpoints

Primary Pharmacodynamic

The primary pharmacodynamic variable in this study is PVR in Part 2, Period 2 (Panel A) and Period 3 (Panels B, C and D).

Primary Safety

The primary safety endpoints in this study include all types of AEs, in addition to laboratory safety assessments, ECGs, PFTs and VS.

Secondary Endpoints for PD

The secondary endpoints in this study include HR and BP.

- Increases from baseline PBV at 1, 3, 8 and 24 hours postdose in Part 2, Period 3 (Panel A and Period 2 (Panels B, C and D).

Secondary Endpoints for PK

The secondary endpoints in this study include AUC0-24hr, AUC0-inf, Cmax, C24hr, Tmax and apparent terminal t1/2 after administration of single doses in Panel A Periods 1-3 and Panels B, C and D, Period 1.

Exploratory Endpoints

- Mean pulmonary artery pressure (mPAP), systemic vascular resistance (SVR), cardiac output (CO)/cardiac index (CI) and mixed venous and arterial oxygenation in Part 2, Period 2 (Panel A) and Period 3 (Panels B, C and D).

- PVR/SVR change from baseline at 0.5 through 4.5 hours post-dose Part 2, Period 2 (Panel A) and Period 3 (Panels B, C and D).

- Change from baseline PVR and PBV at 1 and 3 hours postdose in Part 2, Periods 2 and 3.

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 (APasT) – 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 primary PD, secondary PK and exploratory PK and PD analyses.

9.6 Statistical Methods

Primary (PVR): Fold change from baseline individual PVR in Part 2, RHC Period only will be calculated for each postdose time point. The largest reduction from baseline will be identified for each participant. These reductions will be natural log-transformed and mean and 95% confidence interval calculated based on a t-distribution at each dose-level. These will be exponentiated and expressed as percents to obtain the geometric mean and 95% CI for percent reduction in PVR.

Primary (Safety): Incidence of AEs will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the VS, ECG parameters, and selected laboratory safety parameters for participants, as deemed clinically appropriate. 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, ECGs, and/or VS may also be computed, as deemed clinically appropriate.

Secondary (HR and BP): Each of these parameters will be analyzed separately for Part 2, RHC period only. Individual PD parameters (HR, SBP, and DBP) will be natural log transformed and analyzed in a linear mixed effects model with fixed effects for dose, time (0.5, 4.5, and 24 hours), dose by time interaction and a random effect for participant. The dependent variable is: PD_postdose – PD_predose (PD=HR, SBP, DBP). An unstructured covariance matrix for each time point will be used to allow for unequal variances via the REPEATED statement in SAS PROC MIXED (a similar model would be acceptable using R) Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). If the model fails to converge, a simpler covariance structure such as compound symmetry may be used. The difference in least squares means with 95% CI will be calculated for post dose of MK-5475 versus predose of MK-5475 at each dose level by time.

Secondary (PK): Separately for each PK parameter (in Panel A, Part 1, Periods 1~3, and Panel B-D, Part 2, Period 1), individual values of $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}\infty}$, C_{max}, C_{24} (as appropriate, if <50% C_{24} values are BLOQ) at each dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for treatment and panel, and a random effect for participant. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Ninety-five percent confidence intervals for the least squares means for each treatment will be

constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

Secondary (PBV): Individual PBV will be natural log transformed and analyzed in a linear mixed effects model with fixed effects for dose, time, dose by time interaction and a random effect for subject. The dependent variable is: log(PBV at X hour) – log(PBV at 0 hour). An unstructured covariance matrix for each treatment will be used to allow for unequal variances and different correlations across time and treatment via the REPEATED statement in SAS PROC MIXED (a similar model would be acceptable using R) Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). If the model fails to converge, a simpler covariance structure such as compound symmetry may be used. The difference in least squares means on the log scale will be calculated for MK-5475 postdose vs. predose at each time point (1, 3, 8 and 24 hours) at each dose level. These mean differences will be exponentiated to obtain the ratio of geometric means for PBV (MK_postdose / MK_predose) at each dose level.

Exploratory

The relationship between dose or plasma concentration and pharmacodynamic variables

PVR, pulmonary arterial pressure, cardiac output/cardiac index (CO/CI), systemic vascular resistance, mixed venous oxygen saturation and arterial oxygenation in participants with pulmonary arterial hypertension will be explored graphically. Upon visual inspection, additional model-based analysis might be employed to further explore the pharmacokinetic-pharmacodynamic relationship.

9.7 Interim Analyses

There is no interim analysis involved in this study.

9.8 Multiplicity

Since there are no hypotheses, no adjustments for multiplicity are needed.

9.9 Sample Size and Power Calculations

There are no variability estimates for PK or PD are available for this participant population from which to estimate power or precision. Nevertheless, a sample size of twenty, along with PD evaluations at 2 dose levels, is considered adequate to meet the needs of the study.

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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, 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 (ie, 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 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 general principles of 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-noncompliance 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 primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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 representative), 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 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 (eg, 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

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 Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (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 Conference on Harmonization 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 Studies.

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 signed ICF, 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 8.1.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	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/aPTT • Mixed venous oxygen saturation (MVO_2) • Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum/Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • 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)] [if applicable] Pregnancy testing requirements for study inclusion are described in Section 5.1			
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, 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.
- 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 electronic data collection (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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, 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] ● Intrauterine hormone-releasing system (IUS) [c,d] ● Intrauterine device (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 treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
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 Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c.) Male condoms must be used in addition to the 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 lactational amenorrhea method (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

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 drugs/vaccines may interact with
- 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.

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**

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' 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 gender, 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

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

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 principal 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

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**

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**

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**

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**

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 Conference on Harmonization [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

Not applicable

10.8 Appendix 8: Blood Volume Table

Panel A (Part 1 and 2)	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test [a]
Laboratory Safety Tests	1	9	1		5.0	55
HIV/Hepatitis Screen (at the discretion of the investigator)	1*			1	5*	5
Serum βHcg (if applicable)	1*		1	1	5	5
FSH (if applicable)	1*			See footnote		
PT aPTT	1	9	1	11	5	55
Mixed Venous Oxygen		8		8	5	40
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-5475		43		43	6 mL	258
* Pre-study HIV/Hepatitis Screen, FSH and Serum HcG will be assayed from a single 5 mL blood sample Total Blood Volume is for participants from Part 1 and continue into Part 2						Female:~ 426.5mL Male: 421.5 mL
[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.						

Panel A (Part 1 only)	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	6	1	8	5.0	40
HIV/Hepatitis Screen (at the discretion of the investigator)	1*			1	5*	5
Serum βHcg (if applicable)	1*		1	1	5	5
FSH (if applicable)	1*			See footnote	-	-
PT aPTT	1	6	1	8	5	40
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-5475		30		30	6 mL	180
* Pre-study HIV/Hepatitis Screen, FSH and Serum HcG will be assayed from a single 5 mL blood sample						Female:~278.5 mL [a] Male:273.5 mL [a]
[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.						

Panel B and C	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	5	1	7	5	35
HIV/Hepatitis Screen (at the discretion of the investigator)	1*			1	5	5
Serum βHcg (if applicable)	1*		1	1	5	5
FSH (if applicable)	1*			See footnote	-	-
PT aPTT	1	5	1	7	5	35
Mixed Venous Oxygen		8		8	5	40
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-5475		23		23	6 mL	138
* Pre-study HIV/Hepatitis Screen, FSH and Serum HcG will be assayed from a single 5 mL blood sample						Female: ~266.5 mL[a,] Male: ~ 261.5 mL[a,]
[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.						

Panel D	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	5	1	7	5	35
HIV/Hepatitis Screen (at the discretion of the investigator)	1*			1	5	5
Serum βHcg (if applicable)	1*		1	1	5	5
FSH (if applicable)	1*			See footnote	-	-
PT aPTT	1	5	1	7	5	35
Mixed Venous Oxygen		8		8	5	40
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-5475		27		27	6 mL	162
* Pre-study HIV/Hepatitis Screen, FSH and Serum HcG will be assayed from a single 5 mL blood sample						Female: ~290.5 mL[a,] Male: ~ 285.5 mL[a,]
[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.						

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 not clinically significant (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 any of the treatment periods, if a particular participant demonstrates a ***sustained change*** (defined below) in any *one* of the following parameters, that participant will not participate in additional dose escalation. For assessing change from baseline, post-dose values will be compared to the Day 1 predose baseline established by 3 semi-recumbent 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 any of the treatment periods if a particular participant demonstrates change in any *one* of the following parameters lasting ≥ 90 minutes, dose escalation 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

Definitions for HR and BP

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

Baseline HR and BP: Predose baseline values will be determined for each specific period. 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 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 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 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.

Notes

If an assessment of the present and previous periods raises safety and tolerability concerns though individual participant/participants do *not* meet the criteria described above, and after discussion with the investigator and the Merck monitor, dose escalation for the entire panel may end.

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

In the event that 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
AE	adverse event
BDS	blood drug screen
BP	Blood pressure
CI	Cardiac index
CO	Cardiac output
CRF	Case Report Form
CRU	clinical research unit
CT	computed tomography
DILI	drug-induced liver injury
DLCO	Diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FRC	functional respiratory capacity
FSH	Follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
Hgb	hemoglobin
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
MVO_2	mixed venous oxygen saturation
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PBO	placebo
PBV	pulmonary blood volume
PDE5i	Phosphodiesterase type 5 inhibitor
PEF	peak expiratory flow
PFT	pulmonary function tests
PK	pharmacokinetic
PT	prothrombin time
aPTT	activated partial thromboplastin time
PVR	Pulmonary vascular resistance
QP2	department of quantitative pharmacology and pharmacometrics
RAP	Right atrium pressure
RHC	Right heart catheterization
RNA	ribonucleic acid

Abbreviation	Expanded Term
RR	respiratory rate
RV	residual volume
RVSP	right ventricular systolic pressure
RVEDP	right ventricular end diastolic pressure
SAC	Scientific Advisory Committee
SAE	serious adverse event
sGC	Soluble guanylate cyclase
SoA	schedule of activities
SVR	Systemic vascular resistance
SUSAR	suspected unexpected serious adverse reaction
TEMP	temperature
TLC	Total lung capacity
UDS	urine drug screen
VC	Vital capacity
WOCBP	woman/women of childbearing potential
WONCBP	Woman/women of non-childbearing potential

11 REFERENCES

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