Official Protocol Title:	A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-4482 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus
NCT number:	NCT05559905
Document Date:	15-Mar-2023

Title Page

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Protocol Title: A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-4482 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus

Protocol Number: 017-01

Compound Number: MK-4482

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

	Not Applicable

Approval Date: 15 March 2023

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	15-MAR-2023	The key reason for this amendment is to revise inclusion criterion #6 to align with contraception requirements for the overall MK-4482 program. Clarifications from the prior 4 PCLs were also incorporated into the amendment.
Original Protocol	15-JUL-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The key reason for this amendment is to revise inclusion criterion #6 to align with contraception requirements for the overall MK-4482 program. Clarifications from the prior 4 PCLs were also incorporated into the amendment.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 10.2 Appendix 2: Clinical Laboratory Tests 10.8 Appendix 8: Blood Volume Table	aPTT as opposed to PTT will be measured at Screening.	The clinical safety laboratory is measuring aPTT as opposed to PTT. There is no impact to participant safety as aPTT measures the same function but with a more narrow reference range (as documented in PCL #3 dated 20-DEC-2022).
5.1: Inclusion Criteria	Added acceptable user dependent contraception methods for WOCBP to inclusion criterion #6.	Corrected to align with contraception requirements for the overall MK-4482 program.
8.1.3 Participant Identification Card	Section updated to reflect that participants will be provided with a participant identification (ID) card upon discharge from quarantine on Day 12 as opposed to providing immediately following informed consent signature.	As participants will remain in quarantine until Day 12, the ID card will be provided upon discharge to ensure participants do not misplace.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	The table note in Table 8 indicates "laboratory safety tests (hematology and chemistry) will be performed after approximately 8-hour fast". Modified text to indicate that the Day -3/-2 laboratory safety tests do not require an 8-hour fast. However, all other fasting requirements within the protocol remain as stated.	Fasting laboratory tests prior to admission are logistically challenging, and fasting before these tests does not provide additional safety information compared to laboratory tests conducted in the fed state. Therefore, the fasting requirement has been removed (as documented in PCL #1 dated 11-OCT-2022).
10.5.2 Contraception Requirements	Table has been revised to include highly effective contraceptive methods that are user dependent.	Corrected to align with contraception requirements for the overall MK-4482 program.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-4482 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus

Short Title: Phase 2a RSV Human Challenge Study of MK-4482 in Healthy Participants

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

This study is to be conducted in healthy adult male and female participants.

Objectives	Endpoints
Primary	
To determine if MK-4482 (800 mg Q12 x 5 days) results in a reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to placebo. Hypothesis (Prophylaxis): MK-4482 (800 mg Q12 x 5 days), when administered to begin prior to intranasal inoculation with respiratory syncytial virus (RSV-A Memphis 37b), reduces the Peak Viral Load (PVL) after viral inoculation compared to placebo. Hypothesis (Treatment): MK-4482 (800 mg Q12 x 5 days), when administered following infection with respiratory syncytial virus (RSV-A Memphis 37b), reduces the Area Under the Viral-Load-time (VL-AUC) after MK-4482 administration compared to placebo.	Prophylaxis: • Peak Viral Load (PVL) as defined by the maximum viral load determined by viral quantitative culture (plaque assay) starting from Day 2 up to planned discharge from quarantine (Day 12 am) Treatment: • Area Under the Viral Load-time Curve (VL-AUC) determined by viral quantitative culture (plaque assay) starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day12 am)

Objectives	Endpoints
Secondary	
To estimate the effect of MK-4482 (800 mg Q12H x 5 days) on the reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	Prophylaxis: • Area Under the Viral Load-time Curve (VL-AUC) determined by viral quantitative culture (plaque assay) starting from Day 2 up to planned discharge from quarantine (Day 12 am) • Area Under the Viral Load-time Curve (VL-AUC) determined by qRT-PCR starting from Day 2 up to planned discharge from quarantine (Day 12 am) • Peak Viral Load (PVL) defined by the maximum viral load determined by qRT-PCR starting from Day 2 up to planned discharge from quarantine (Day 12am) Treatment: • Peak Viral Load (PVL) as defined by the maximum viral load determined by viral quantitative culture (plaque assay) starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am) • Time (days) to confirmed negative test by viral quantitative culture (plaque assay) measurements starting at initial administration of MK-4482/placebo to first confirmed undetectable (<LLOQ) assessment after peak measure. • Area Under the Viral Load-time Curve (VL-AUC) determined by qRT-PCR starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am)

Objectives	Endpoints
	• Peak Viral Load (PVL) defined by the maximum viral load determined by qRT-PCR starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Time (days) to confirmed negative test by qRT-PCR starting at initial administration of MK-4482/placebo to first confirmed undetectable (<LLOQ) assessment after peak measure.
To estimate the effect of MK-4482 (800 mg Q12 x 5 days) on course of clinical symptoms after intranasal inoculation (with RSV A Memphis 37b) compared to placebo	Prophylaxis: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring starting from Day 2 up to planned discharge from quarantine (Day 12 am). • Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system starting from Day 2 up to planned discharge from quarantine (Day 12 am). • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system starting from Day 2 up to planned discharge from quarantine (Day 12 am). • Peak daily symptom score: individual maximum daily sum of symptom score starting from Day 2 up to planned discharge from quarantine (Day 12 am).

Objectives	Endpoints
	Treatment: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring system starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Peak daily symptom score: individual maximum daily sum of symptom score from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at initial administration of MK-4482/placebo to time of returning to baseline score.

Objectives	Endpoints
To estimate the effect of MK-4482 (800 mg Q12 x 5 days) on the incidence of RSV infection and symptomatic RSV infection after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	Prophylaxis: • RT-PCR-confirmed RSV infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 2 up to Day 12. • Occurrence of at least 1 positive quantitative (≥LLOQ) cell culture measurement in nasal samples, from Day 2 up to Day 12. • RT-PCR-confirmed symptomatic RSV infection, defined as: o RT-PCR-confirmed RSV infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND o Symptoms score ≥2 at a single time point. • RT-PCR-confirmed moderately severe symptomatic RSV infection, defined as: o RT-PCR-confirmed RSV infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND o Any symptoms of Grade ≥2 at a single time point.

Objectives	Endpoints
	• Culture lab-confirmed symptomatic RSV infection, defined as: o Lab-confirmed culturable RSV infection (1 quantifiable [≥LLOQ] cell culture measurement), from Day 2 up to Day 12, AND o Symptoms score ≥2 at a single time point.
To evaluate the safety and tolerability of MK-4482 (800 mg Q12 x 5 days) compared to placebo	• Safety data including, but not limited to, occurrence of adverse events (AEs) from initial administration of MK-4482/placebo up to the Day 28 follow-up. • Occurrence of serious AEs (SAEs) from initial administration of MK-4482/placebo up to the Day 28 follow-up.
To monitor the safety of the challenge virus	• Occurrence of AEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Use of concomitant medications from viral challenge (Day 0) up to the Day 28 follow-up.
To evaluate plasma NHC concentrations after administration of MK-4482 (800 mg Q12 x 5 days)	Plasma NHC concentrations at specified timepoints

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment and Prevention
Indication	Respiratory Syncytial Virus
Population	Serosuitable healthy male and female participants 18 to 55 years (inclusive) of age
Study Type	Interventional
Intervention Model	Parallel This is a single-site study.
Type of Control	Placebo-controlled
Study Blinding	Double-blind
Blinding Roles	Investigator Participants or Subjects Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 105 participants will be allocated/randomized.

Intervention Groups and Duration:

Inter-vention Groups

Panel	Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Use
A	Prophylactic Dosing	MK-4482	800 mg	Q12H x 5 days (from Day -1pm to Day 4am inclusive)	Oral	Experimental
	Matched Placebo	Placebo	0 mg	Q12H x 6 days (from Day 4pm to Day 10am inclusive)	Oral	Experimental
B	Triggered Dosing	MK-4482	800 mg	Q12H x 5 days after triggering for a total of 10doses	Oral	Experimental
	Matched Placebo	Placebo	0 mg	Q12H x 6 days (when not receiving MK-4482)	Oral	Experimental
C	Matched Placebo	Placebo	0 mg	Q12H x 11 days (from Day -1pm to Day 10am inclusive)	Oral	Experimental

Q12H=every12 hours

Total Number of Inter-vention Groups/ Arms	3
Duration of Participa-tion	Each participant will participate in the study for approximately 9 weeks from the time the participant provides documented informed consent through the final contact. Participants will be screened for suitability for the study under a separate study site generic screening process. Following signing the study specific Informed Consent Form (ICF) eligibility will be confirmed and then each participant will be randomized to receive the assigned intervention on Day -1. Up to 3 days prior to RSV A Memphis 37b inoculation the participants will be admitted to quarantine where they will stay until 12 days post inoculation. After the end of the quarantine period, each participant will be followed through Day 28.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Table 1 and Figure 1.

Table 1 Study Schema

Panel	Treatment Arm	Number of Participants	Treatment Day	Inoculation Day	Poststudy Visit (+/- 3 days)
A	MK-4482 (Prophylactic Administration)	35	Day -1 pm through Day 4 am inclusive)[a]	Day 0	Day 28
B	MK-4482 (Triggered Dose Treatment)	35	Day 2/5 through Day 6/10 am[b]	Day 0	Day 28
C	Matched Placebo	35	Day -1 through Day 10 am	Day 0	Day 28

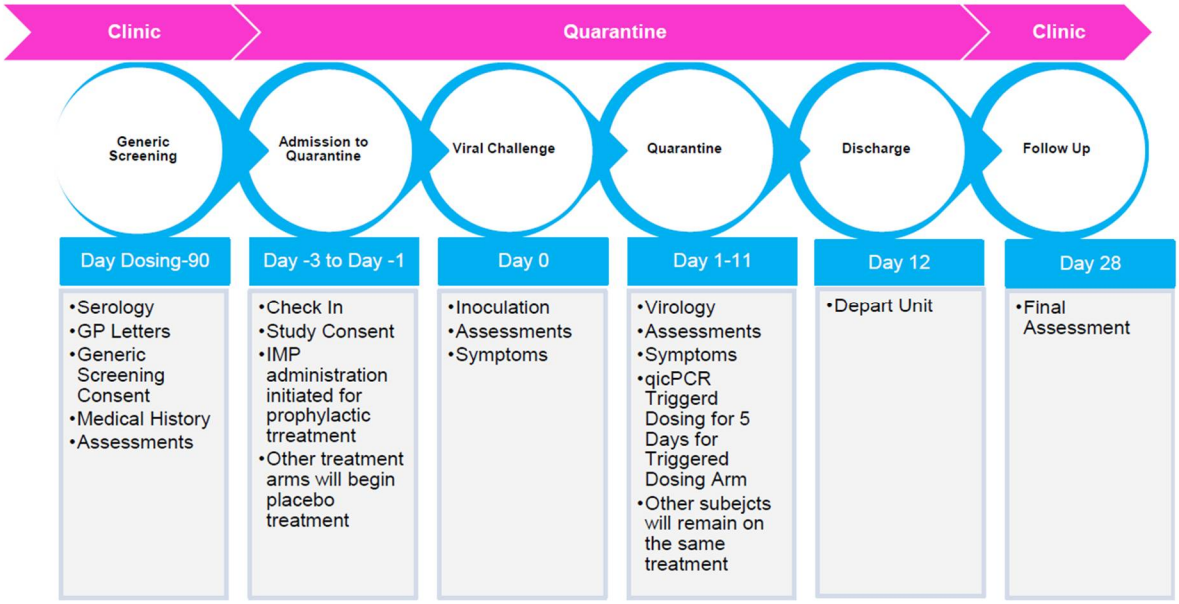
qicPCR=qualitative integrative cycler PCR

All participants will be treated with either active or placebo from Day -1 of the study through Day 10 am of the study.

[a]Participants will receive MK-4482 on Day -1 pm through Day 4 am and placebo from Day 4 pm through Day 10 am.

[b]Participants will receive placebo until they test positive by qicPCR at which point MK-4482 dosing will be triggered.

Figure 1 Study Design Diagram



1.3 Schedule of Activities

Study Phase:	**Screen-ing[a]**	**Inpatient Quarantine[b]**																	**Follow-up**	**Early Withdrawal**	
Scheduled Day[c]	**D-90 to D-2**	**D-3/ D-2**	**D-1**	**D0**			**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D28 (+/- 3d)**	**Post-Challenge**	**Notes**
				Predose	Viral Challenge	Postdose															
Administrative /Study Procedures																					
Informed Consent[a]	X	X																			Sec. 5.1, 8.1.1.1
Informed Consent for FBR		X																			Sec. 5.1, 8.1.1
Participant ID Card		X																			Sec. 8.1.3
Inclusion/Exclusion Criteria	X	X	X																		Review of IC/EC criteria will occur at Screening & specific criteria from Day -3 to predose & after predose procedures (if applicable) on Day 1 only. Sec. 5.1, 5.2, 8.1.2
Medical History	X	X																			Sec. 8.1.4
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec 5.2, 6.5, 8.1.5
Domiciling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Sec. 8.1.11
RSV A Memphis 37b Inoculation					X																Sec. 8.12.3
MK-4482/Placebo Administration			X	X		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X					Intervention will be administered Q12H. Sec. 8.1.8, Sec. 5.3.1

Study Phase:	**Screen-ing[a]**	**Inpatient Quarantine[b]**																	**Follow-up**	**Early With-drawal**	
Scheduled Day[c]	**D-90 to D-2**	**D-3/ D-2**	**D-1**	**D0**			**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D28 (+/- 3d)**	**Post-Chal-lenge**	**Notes**
				Predose	Viral Challenge	Postdose															
Participant Visits to Clinical Research Unit	X	X																	X		Sec. 8.1.11, 8.12.5
Assignment of Screening Number	X																				Sec. 8.1.6
Assignment of Treatment/ Randomization Number			X																		Assigned prior to study drug administration. Sec. 5.5, 8.1.7
Safety Procedures																					
Full Physical Examination	X	X																X	X	X	Physical exam may be conducted up to 24 hrs prior to randomization. Sec. 8.4.1
Directed Physical Examination (including nasal)		(X)	(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)				Sec. 8.4.1
Vital signs (HR, RR, SBP, DBP, SpO_2)	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.4.2 AM Predose only
Temperature	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.4.2
RSV Symptom Diary Card		X	3X	3X			3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	X			Sec. 8.3.1

Study Phase:	Screen-ing[a]	Inpatient Quarantine[b]																Follow-up	Early Withdrawal	
Scheduled Day[c]	D-90 to D-2	D-3/ D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3d)	Post-Challenge	Notes
				Predose	Viral Challenge	Postdose															
24-Hour Tissue Count & Nasal Discharge Weight			X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	Distribution of paper tissues and bags will start on Day -1, with first collection on Day 0. Thereafter, collection of paper tissues will occur at the same time each day (±1 hour) with tissues distributed 24 hours ahead. Sec. 8.3.4, 8.4
Spirometry	X																				Sec. 5.1
12-Lead ECG	X	X	X										X				X		X	X	Predose ECG should be obtained on Day -1 within 3 hours of dosing. All subsequent ECGs will be single measurements and performed in the AM within 3 hours of dosing. Sec. 8.4.3.
Height, Weight, BMI	X	X																X	X	X	Height is only required at Screening. Sec. 8.4.1
Alcohol Breath Test	X	X																	X		App. 2

Study Phase:	Screen-ing[a]	Inpatient Quarantine[b]																	Follow-up	Early Withdrawal	
Scheduled Day[c]	D-90 to D-2	D-3/ D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3d)	Post-Chal-lenge	Notes
				Predose	Viral Challenge	Postdose															
Urine Drugs of Abuse and Nicotine Screen	X	X																	X		UDS will be conducted per hVIVO standard operating procedures. Sec. 8.4.4, App. 2
Urine Pregnancy Test	X																	X	X	X	Sec. 8.4.5, App. 2
Laboratory Procedures/ Assessments																					
Hematology	X	X											X				X		X	X	Sec. 8.4.4, App. 2 & 8 (Hematology)
Urinalysis	X	X											X				X		X	X	
Chemistry	X	X											X				X		X	X	
Coagulation (PT/aPTT)	X																				Sec. 4.2.1.2, App. 2 & 8
Cardiac Enzymes (CK and Troponin)	X	X											X				X				Sec. 4.2.1.2, App. 2 & 8
Thyroid Function Test	X																				Sec. 4.2.1.2, App. 2 & 8
Serum FSH	X																				Postmenopausal females only. Sec. 5.1, App. 2 & 5
Serum β-HCG Pregnancy Test		X																			WOCBP only. Sec. 8.4.5, App. 2 & 8
HIV/Hepatitis B & C Serology	X																				Sec. 8.4.4, App. 2 & 8
AE/SAE Review		X----------X																		X	Sec. 8.5, App. 3

Study Phase:	Screen-ing[a]	Inpatient Quarantine[b]																Follow-up	Early With-drawal	
Scheduled Day[c]	D-90 to D-2	D-3/ D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3d)	Post-Chal-lenge	Notes
				Predose	Viral Challenge	Postdose															
Biomarkers																					
Blood - Serum Markers Humoral Immunity	X	X															X		X	X	
Blood for Genetic Analysis				X																	May be collected any time up to 24 hrs postdose for enrolled participants only. Sec. 8.9.1 & App. 8
Pharmacokinetics and Pharmacodynamic Assessments																					
Blood for Plasma NHC and/or Metabolites Assay			X					X		X	X	X	X								Sampling Times[d] D-1: predose, 12 hr D2, D5, D6: 12 hr D4, D7: predose, 0.5, 1.5, 4, 8, 12 hr. Sec. 8.7.1 & App. 8
Blood for PBMC NHC-TP and/or Metabolites Assay			X							X		X	X								Sampling Times[d] D-1: predose, 12 hr D4, D6, D7: 12 hr. Sec. 8.7.2 & App. 8

Study Phase:	Screen-ing[a]	Inpatient Quarantine[b]																Follow-up	Early Withdrawal	
Scheduled Day[c]	D-90 to D-2	D-3/ D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3d)	Post-Challenge	Notes
				Predose	Viral Challenge	Postdose															
Collection of Respiratory Samples																					
Nasal Swab – BioFire Respiratory Pathogen Screen including SARS-COV-2		X																			Sec. 8.3.3, 8.12.3
Nasopharyngeal Swab – RSV Discharge Test																	(X)	(X)			Sec. 8.3.3
Nasal Wash – Virology and Viral Genomics[e]								2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X			
qicPCR/PCR/viral assay								2X	2X	2X	X										

Study Phase:	Screen-ing[a]	Inpatient Quarantine[b]																Follow-up	Early With-drawal	
Scheduled Day[c]	D-90 to D-2	D-3/ D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3d)	Post-Chal-lenge	Notes
				Predose	Viral Challenge	Postdose															

[a] All screening procedures will be performed under the hVIVO generic screening process. Historical prescreening data collected through the hVIVO generic screening process within 90 days (90 days for viral serology and 56 days for other assessments including safety laboratory test) of randomization may be used to determine eligibility without the need to repeat the assessments following study specific consent. Study-specific consent may occur on day of admission, provided all required eligibility information has been collected through the Health Research Authority approved hVIVO generic screening process.

[b] Day 0 predose procedures may be performed within 3 hours of, but prior to, IMP dosing. All inpatient visits should occur in line with inoculation day.

[c] Participants may report to the CRU for quarantine on either Day -3 or Day -2. All eligibility/baselines assessment may occur on either Day -3 or Day -2 depending upon admission day.

[d] All samples should be collected with respect to the AM dose only, with the exception of D-1 samples, which should be collected with respect to the first dose received. All predose and 12 hr samples should be collected prior to the next scheduled dose. Windows for PK sampling are provided in Section 8.12.6.

[e] Nasal Wash for RSV Virology samples will be taken for RSV quantification (qRT-PCR and plaque assay). Samples may be used for related viral genomics and RSV virus sequencing. Samples collected between the morning of Day 2 and the morning of Day 5 will also be used for assessment of participant RSV infectivity status qic-PCR prior to discharge (Day 12) until a positive result is received to support triggered dosing.

Note:

Parenthesis indicate the assessment may be optional, or at the PI's discretion.

The investigator may perform additional safety assessments as required.

Where any nasal sampling timepoints occur together, the order of sampling will typically be: (1) nasopharyngeal swab followed by; (2) nasal wash.

AM=ante meridiem (before midday); AE=adverse event; β-HCG=beta human chorionic gonadotropin; BDS=blood drug screen; BMI=body mass index; CK=creatine kinase; CRU=clinical research unit; D=day; DBP=diastolic blood pressure; DNA=deoxyribonucleic acid; EC=exclusion criteria; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HR=heart rate; IC=inclusion criteria; ID=identification; NHC=N-hydroxycytidine; NHC-TP=N-hydroxycytidine triphosphate; PI=primary investigator; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; qicPCR=qualitative integrative cycler PCR; qRT-PCR=real-time quantitative reverse transcription PCR; RR=respiratory rate; RSV=respiratory syncytial virus; SAE=serious adverse event; SARS-COV-2=severe acute respiratory syndrome coronavirus 2; SBP=systolic blood pressure; SpO_2=oxygen saturation; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs; WOCBP=women of childbearing potential.

2 INTRODUCTION

2.1 RSV Clinical Manifestations and Epidemiology

RSV causes upper and lower respiratory tract illness worldwide. Globally, RSV is estimated to infect 64 million adults and children and cause 160,000 deaths each year [National Institutes of Health 2008]. Before the COVID-19 pandemic, endemic RSV disease occurred yearly during late fall, winter, and early spring (lasting about 5 months) in temperate climates, and throughout the year with a less predominant cyclical pattern in the tropics [Haynes, A. K., et al 2013] [Stensballe, L. G., et al 2003] [Bloom-Feshbach, K., et al 2013]. Patterns of viral respiratory disease were disrupted with the COVID-19 pandemic, when social distancing reduced transmission, although seasonal RSV infection is re-emerging.

RSV is transmitted primarily via droplets from the sneeze, cough, or breathing of an infected person, or via contamination of environmental surfaces with infectious secretions [Hall, C. B. 1981]. There is a single RSV serotype with 2 major antigenic subgroups, A and B strains [Borchers, A. T., et al 2013]. Both strains often cocirculate during epidemics, though one may predominate [Mufson, M. A., et al 1988] [Akerlind, B. 1986] [Gilca, R., et al 2006] [Borchers, A. T., et al 2013]. By the end of the first year of life, approximately 70% of children will have been infected with RSV; 30% to 75% will have been infected twice by the second year of life [Glezen, W. P., et al 1986] [Hall, C. B., et al 2009] [Ohuma, E. O., et al 2012]. Reinfection with RSV occurs throughout life and is generally associated with mild upper respiratory tract infection in healthy older children and immunocompetent adults [Hall, C. B. 2001] [Borchers, A. T., et al 2013]. The clinical manifestations of RSV reinfection in older adults are variable, with symptoms ranging from a mild cold to severe respiratory distress [Falsey, A. R. 2000] [Walsh, E. E. 2012].

The clinical manifestations of RSV reinfection in older adults are variable, with symptoms ranging from a mild cold to severe respiratory distress [Falsey, A. R. 2000] [Walsh, E. E. 2012].

Elderly individuals (age >65 years), especially those with cardiopulmonary comorbidities (eg, asthma, COPD, CHF), as well as immunocompromised adults (HSCT recipients, hematologic malignancies, lung transplant recipients) are at risk of more severe RSV infection with development of pneumonia and increased rates of hospitalization and death. The global number of hospital admissions for RSV related acute respiratory infection in older adults was estimated at 336,000 with about 14,000 in-hospital deaths in 2015 [Shi, T., et al 2020]. Annual reinfection is common, and individuals may be contagious for days to weeks following infection. As the population ages and with the increase in long-term care institutions over time, the potential for an increasing burden of more severe RSV disease will continue to grow.

2.1.1 RSV Pathogenesis and Immune Mechanisms

The incubation period after RSV exposure ranges from 2 to 8 days after the virus enters the body through the upper respiratory tract. In susceptible individuals (eg, infants, older adults), the virus may spread to the lower respiratory tract where it can cause symptoms of bronchitis,

bronchiolitis, pneumonia and respiratory distress (collectively called LRI). Primary infection and subsequent reinfections result in immune responses to RSV. These immune responses include: (1) the generation of SNA, through antibodies predominantly targeted to the RSV fusion protein; (2) RSV specific mucosal IgA and IgG; and (3) CD4 T-helper and CD8 cytotoxic T cell responses to RSV peptide antigens. Despite these immune responses, reinfection occurs throughout life. Each of these mechanisms may contribute to restrict RSV to the upper respiratory tract in healthy children and younger adults, resulting in milder disease in these individuals.

2.1.2 Summary of RSV Inoculation Model

The RSV human challenge model was developed to not only aid understanding of RSV disease, but to also assess the efficacy of RSV antivirals, immunomodulators and vaccines. The RSV A Memphis 37b challenge strain has been used for over 15 years by both hVIVO and others and has helped assess the efficacy of numerous RSV therapies [Lambkin-Williams, R., et al 2018] [DeVincenzo, J., et al 2020] [Stevens, M., et al 2018] and vaccines [Sadoff, J., et al 2021] [Schmoele-Thoma, B., et al 2022]. Specifically, hVIVO have safely and successfully used the RSV challenge strain in over 1400 healthy participants (18 to 60 years of age) including the inoculation of 24 participants between 60 and 75 years of age. Additionally, another clone of the same strain of live RSV (Memphis 37c) has been used as an inoculation agent and was shown to be safe in over 77 healthy young adults across 3 studies. Healthy RSV challenge study participants have approximately 65% to 85% chance of becoming infected with RSV following the administration of the virus [DeVincenzo, J. P., et al 2010]. Typical RSV illness is characterised by an abrupt onset of rhinitis, nasal stuffiness, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 7 to 10 days. Respiratory syncytial virus, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). Adults and children present with RSV-related myocarditis rarely, with symptomless occurrences likely going undiagnosed in the community.

2.2 Study Rationale

MK-4482 (MOV) is an orally administered prodrug of the ribonucleoside analogue NHC that inhibits the replication of a range of RNA viruses by viral mutagenesis. Clinical development is ongoing for the treatment and prevention of COVID-19 and is planned for the treatment and prophylaxis of other viral respiratory infections. The purpose of this study is to assess the antiviral activity of a dose of MK-4482 (MOV) 800 mg Q12H x 5 days in the treatment of acute RSV infection or in prophylaxis against RSV infection in a human challenge disease model of RSV experimental intranasal inoculation. Data from this study inform as to whether MK-4482 has sufficient antiviral activity to support investigating its efficacy in future field studies.

Extensive preclinical and clinical safety experience have supported the development of MOV as well as the use of a dose of 800 mg Q12H x 5 days for the treatment of mild to moderate COVID-19 as discussed below. The current study will provide further assessments of the safety and tolerability of MK-4482 as well as of the PK of NHC and viral dynamics

following inoculation with RSV. Using a human challenge model, in which a fixed inoculum of RSV A Memphis 37b is administered to healthy adults in a controlled setting, allows a preliminary evaluation of MK-4482 before subsequent, larger studies of safety and efficacy.

2.3 Background

Refer to the IB/approved labeling for detailed background information on MK-4482.

2.3.1 Pharmaceutical and Therapeutic Background

MK-4482 (MOV) is the 5′-isobutyrate prodrug of the broadly active, direct-acting antiviral ribonucleoside analog NHC. MOV is hydrolyzed by esterases either during or after absorption to deliver NHC into systemic circulation. NHC inhibits replication of multiple RNA virus families including pathogenic Coronaviruses (eg, MERS, SARS-CoV and SARS-CoV-2), influenza viruses (seasonal, pandemic and avian subtypes), and RSV. Inside cells, the active nucleoside triphosphate anabolite of MOV (NHC-TP) acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA polymerase that upon incorporation into nascent chain RNA, induces increased mutational frequency in the viral genome resulting in induction of viral error catastrophe and production of nonviable virus [Flavell, R. A., et al 1974] [Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. 2021] [Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. 2021].

Currently, the lack of safe, broadly effective, and generally utilized vaccines or direct acting antiviral agents to prevent or treat RSV infection represents an unmet need. The standard of care for RSV-infected adults consists solely of palliative measures, including administration of fluids and oxygen. Antiviral agents with rapid onset and a high barrier to resistance may provide an effective approach for the treatment and prophylaxis of RSV infection in adults.

2.3.2 Preclinical and Clinical Studies

Primary pharmacology studies demonstrating the antiviral activity of MOV when administered as NHC against SARS-CoV-2 and other RNA viruses were conducted in vitro and in mouse, guinea pig, hamster, and ferret models of viral infection. In vitro, NHC shows broad-spectrum activity against multiple viruses including coronaviruses SARS-CoV-2, SARS-CoV, and MERS-CoV, as well as RSV and influenza virus.

Published studies by Yoon et al. have demonstrated the antiviral activity of NHC with in vitro and in vivo preclinical models [Yoon, J. J., et al 2018]. NHC exhibits dose-dependent inhibition of viral replication against 2 clinical isolates of human RSV in both Hep-2 cell and primary human bronchial tracheal epithelial cell culture systems with EC50 values in the micromolar to submicromolar range. Furthermore, oral administration of NHC at 100 mg/kg twice daily was effective in significantly reducing viral load as well as markers of respiratory distress in a mouse model of RSV infection. A 100-mg/kg dose in mice corresponds to a human-equivalent dose of approximately 8 mg/kg, in line with the 800-mg Q12H dose for this study (~ 13 mg/kg for a 60-kg adult). Comparison of effective dose amounts in in vitro assay an in vivo preclinical models suggest that similar levels of NHC may be effective against both RSV and SARS-CoV2 infection. In vitro assessments of NHC activity against

RSV show EC50 values within a 2-fold range those demonstrated against SARS-CoV2, indicating a similar range of potency, allowing for differences in cell and assay types.

MOV was evaluated in nonclinical safety studies, including a standard battery of in vitro and in vivo safety pharmacology studies, genotoxicity assays (including Ames assays, in vitro and in vivo micronucleus assays, an in vivo Pig-a assay in rats, and an in vivo mutation assay in Big Blue® transgenic rats), tolerability/dose-range-finding studies in mice, rats, and dogs, repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs, fertility studies in male and female rats, embryo-fetal developmental toxicity studies in rats and rabbits, a pre- and postnatal developmental toxicity study in rats, and toxicity studies in juvenile rats. Additional nonpivotal short-term tolerability and/or TK studies were conducted in mice, rats, rabbits, and monkeys.

MOV was devoid of effects on CNS, respiratory, or cardiovascular functions in well-characterized safety pharmacology models. Based on the totality of genotoxicity data, MOV is not mutagenic or genotoxic in in vivo mammalian systems.

Target organs of toxicity identified in the repeat-dose toxicity studies were limited to bone marrow in dogs only, and growth plate in rats only. Hematologic changes observed after 7 days of dosing in the dog 28-day toxicity study were mild and reversible on discontinuation, and hematopoietic effects have not been in clinical studies to date with a dose of 800 mg Q12H x 5 days. The growth plate findings are not relevant to adult humans, because growth plates are no longer present in the mature skeleton of adult humans.

In fertility studies in rats there were no MOV-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.1-/6.1-fold [female/male] the clinical NHC exposure at 800 mg Q12H). In pregnant rats administered MOV during the organogenesis period, developmental toxicity including embryolethality (post-implantation losses) and malformations/teratogenicity was observed at 1000 mg/kg/day (7.5-fold the clinical NHC exposure at 800 mg Q12H), and reduced fetal growth was noted at ≥500 mg/kg/day (≥2.9-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at doses up to 250 mg/kg/day (0.8-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight losses, resulting in the early sacrifice at 1000 mg/kg/day, and decreased body weight gain at ≥500 mg/kg/day. In pregnant rabbits, developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (18-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity in rabbits up to 400 mg/kg/day (6.5-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight gain, and abnormal fecal output at ≥400 mg/kg/day. In the pre- and postnatal developmental study in rats, there was no F0 maternal or F1 generation toxicity up to the highest dose evaluated of 500 mg/kg/day (1.6-fold the clinical NHC exposure at 800 mg Q12H).

Further details of preclinical studies are provided in the IB. Collectively, the safety pharmacology and toxicology results support continued clinical development of MOV.

2.3.3 Completed and Ongoing Clinical Studies

2.3.3.1 Completed Clinical Studies

MOV has been evaluated 9 completed or clinically completed (i.e. the last subject visit was completed but final data are pending) clinical trials as summarized below. (Refer to the IB Section 5 for additional details of the study designs on each study).

Phase 1 Studies:

MK-4482-004 was a randomized, double-blind, placebo-controlled, first in human study designed to evaluate the safety, tolerability, and PK of MOV following oral administration to healthy participants. Oral doses (50 to 1600 mg as a single dose, including 200 mg with a high-fat meal, and 50 to 800 mg as multiple doses [Q12H for 5.5 days]) of MOV or placebo administered to 130 healthy participants were generally well tolerated. Out of these 130 participants, 100 received at least one dose of MOV. No deaths or SAEs were reported.

MK-4482-008 was a single and multiple dose, randomized, placebo-controlled, double-blind study of MOV in healthy Japanese adult male participants. Single doses of MOV up to 1600 mg, including 800 mg with a high-fat meal, and multiple doses of MOV 400 mg and 800 mg Q12H for 5.5 days were generally well tolerated in healthy Japanese male adult participants. Out of 65 randomized participants, 51 received at least 1 dose of MOV. No SAEs, deaths or ECIs were reported.

MK-4482-010 was a randomized, 4-treatment, 4-period crossover, single site, open-label, relative bioavailability study of MOV oral granules and MOV reference capsule formulations in healthy adult participants. A total of 16 participants were randomized into 4 treatment sequences consisting of a single 800-mg dose of MOV administered as oral granules in water, apple sauce or pudding or as the reference capsule formulation with water. Relative bioavailability was assessed through repeat evaluations of plasma NHC PK. No SAEs, deaths or ECIs were reported.

MK-4482-012 was a randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, and PK of MOV. Doses of 400, 600, and 800 mg MOV Q12H for 10.5 days were generally well tolerated in healthy adult study participants. Out of 32 randomized participants, 24 received at least 1 dose of MOV. No SAEs, deaths or ECIs were reported and no study intervention-related clinically meaningful changes in vital sign values, ECGs, or safety laboratory values (including hematology) were observed as a function of dose or treatment.

Phase 1/2, 2a Studies:

MK-4482-005 is a Phase 1/2 randomized, multicenter, seamless, adaptive study to determine the optimal dose, safety, and efficacy of MOV for the treatment of COVID-19. The primary efficacy objective is to determine the ability of MOV to reduce serious complications of COVID-19 including hospitalization, reduction in SaO_2 <92%, or death. As of 14-MAR-2022, 18 participants enrolled in Phase 1 (12 received MOV; 300 mg n=4; 600 mg n=4; 800 mg n=4), and 178 participants enrolled in Phase 2. This study is clinically

completed and final unblinded results are pending. Based on preliminary review of blinded safety data, 5 SAEs were reported, 1 of which (vomiting) was considered related to study intervention by the investigator. No deaths were reported.

MK-4482-006 was a Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of MOV (Q12H for 5 days) in nonhospitalized adults with COVID-19. The time to undetectable SARS-CoV-2 of viral RNA in nasopharyngeal swabs was shorter in participants receiving 800-mg MOV (median: 14 days) compared with those administered placebo (median: 15 days). MOV 200 mg (n=23), 400 mg (n=62) or 800 mg (n=55) or placebo (n=62) was generally well tolerated with a comparable incidence of AEs across the intervention groups. Four SAEs were reported (3 participants in the MOV groups combined, 1 in the placebo group); none were considered related to study intervention by the investigator. No participants died while enrolled in the study.

MK-4482-007 is a Phase 2a randomized, placebo-controlled, double-blind clinical study of MOV in adults who have tested positive for SARS-CoV-2 infection via PCR and are hospitalized with a diagnosis of COVID-19 with symptoms of ≤8 days. The primary efficacy objective is to measure the proportion of nasopharyngeal swabs and saliva from recipients becoming undetectable for SARS-CoV-2 RNA at Day 5 of MOV administration compared with placebo. As of 14-MAR-2022, 71 participants were enrolled in the study and enrollment is closed as of 15-FEB-2022. This study is clinically completed and final unblinded results are pending. Based on preliminary review of blinded safety data, SAEs were reported for 4 participants, none were considered related to study intervention by the investigator. Of the 4 participants who had SAE, one had SAE of hypovolemic shock on Day 12 and died of respiratory failure on Day 28, and one had SAE of worsening bradycardia and hypotension that required discontinuation of study intervention. No other deaths or other AEs requiring discontinuation of study intervention have been reported.

Phase 2/3 or 3 Studies:

MK-4482-001 is a Phase 2/3 randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy, safety, and PK of MOV in hospitalized adults with COVID-19. In the Phase 2 portion of the study (Part 1) a total of 218 hospitalized participants with COVID-19 received at least 1 dose of MOV (72 participants received MOV 800 mg) and 75 participants received placebo. MOV was generally well tolerated with a comparable incidence of AEs across the intervention groups. SAEs were reported for 15.4% participants (15.1% MOV groups, 16.0% placebo), with 1 SAE deemed related to study intervention by the investigator (Grade 3 urticaria) for 1 participant in the MOV 200-mg treatment group. A total of 16 participants had AEs leading to death (6.4% MOV groups combined, 2.7% placebo), none of which were considered study intervention-related by investigator assessment. The study was stopped due to lack of clinical benefit in this population (participants already hospitalized prior to randomization) and did not proceed to the Phase 3 portion of the study (Part 2).

MK-4482-002 is a Phase 2/3, randomized, placebo-controlled, double-blind, multisite study to evaluate the efficacy, safety, and PK of MOV administered to nonhospitalized adults with laboratory-confirmed COVID-19 and symptom onset within 7 days (Part 1, Phase 2) or within 5 days (Part 2, Phase 3) prior to randomization, and all participants must have at least

one risk factor for progressing to severe illness from COVID-19. A final total of 1433 participants were enrolled in the study and the study is completed. Unblinded data are available for Part 1 and Part 2 through Day 29 as well as for the Month 7 visit in both Part 1 and Part 2 which includes collection of survival status, current supplemental oxygen use, and any hospitalizations that occurred since last contact. MOV 200 mg (n=74), 400 mg (n=77), 800 mg (n=74) or placebo (n=74) Q12H for 5 days in Part 1 and MOV 800 mg (n=710) or placebo (n=701) Q12H for 5 days in Part 2 were generally well tolerated. In both Parts, the proportion of participants with AEs, drug-related AEs (per investigator assessment), SAEs, AEs leading to study intervention discontinuation and laboratory values that met predefined limits of change (worsening Grade 3 or 4), were comparable for the intervention groups. No clinically meaningful trends in changes in liver enzymes or hematology parameters as a function of either dose or treatment were observed. In Part 1, one participant had an AE leading to death in the placebo group. In Part 2, AEs leading to death occurred in a higher proportion of participants who received placebo compared with MOV.

2.3.3.2 Ongoing Clinical Studies

MOV is being evaluated in 2 ongoing Phase 1 studies (P003, P016) and 1 ongoing Phase 3 study (P013) (Refer to the IB Section 5 for the additional details on study designs on each study).

Phase 1 studies:

MK-4482-003 is a Phase 1 non-randomized, open-label, single dose, clinical study to evaluate the tolerability and PK of a single 800-mg dose of MOV in participants with severe renal impairment compared to participants with normal renal function (target enrollment of approximately N = 16-18). This study is ongoing.

MK-4482-016 is a Phase 1 non-randomized, open-label, single dose, clinical study to evaluate the tolerability and PK of a single 800-mg dose of MOV in participants with moderate hepatic impairment compared to participants with normal hepatic function (target enrollment of approximately N = 14-17). This study is ongoing.

Phase 2/3 or 3 Studies:

MK-4482-013 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MOV for the prevention of COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) in adults residing with a person with COVID-19. As of 14-MAR-2022, 798 household participants were randomized out of a planned total of 1500 participants.

2.4 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

The totality of the safety data from Phase 1 through Phase 3 clinical studies and post-authorization surveillance for the use of MOV in the treatment of COVID-19 demonstrate an acceptable safety and tolerability profile of MOV.

There were no effects on cardiovascular, neurological, and respiratory function in several well-characterized safety pharmacology experimental models. The integrated assessment of the mutagenic and genotoxic potential of MOV indicates that MOV is not mutagenic or genotoxic in in vivo mammalian systems.

As described in Section 2.2.2, in a 28-day repeat dose toxicity study with MOV in dogs, reversible hematologic toxicities were noted after Day 7 at exposures 0.4-fold those of the anticipated clinical exposures at the 800-mg Q12H dose. However, to date no clinically meaningful hematological changes have been observed in healthy participants up to 800-mg MOV Q12H for up to 10.5 days or in participants with COVID-19 at multiple doses up to 800-mg Q12H for 5 days.

Histopathology results from the 3-month rat toxicity study demonstrated an increase in the thickness of the growth plate/physis, a finding not observed in 1-month studies in rats, dogs, or mice. These findings are not considered to represent a significant new risk to human adults.

In fertility studies in rats there were no MOV-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.1-/6.1-fold [female/male] the clinical NHC exposure at 800 mg Q12H). While embryolethality (post-implantation losses) and teratogenicity were limited to rats exposed to 7.5-fold the clinical NHC exposure at 800 mg Q12H during the organogenesis period, and these developmental findings were not observed in rats up to 2.9-fold the clinical NHC exposure at 800 mg Q12H and rabbits up to 18-fold the clinical NHC exposure at 800 mg Q12H, WOCBP will be required to use effective contraception for the duration of treatment and for at least 4 days postdose.

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 healthy adult male and female participants.

Objectives	Endpoints
Primary	
To determine if MK-4482 (800 mg Q12 x 5 days) results in a reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to placebo. Hypothesis (Prophylaxis): MK-4482 (800 mg Q12 x 5 days), when administered to begin prior to intranasal inoculation with respiratory syncytial virus (RSV-A Memphis 37b), reduces the Peak Viral Load (PVL) after viral inoculation compared to placebo. Hypothesis (Treatment): MK-4482 (800 mg Q12 x 5 days), when administered following infection with respiratory syncytial virus (RSV-A Memphis 37b), reduces the Area Under the Viral-Load-time (VL-AUC) after MK-4482 administration compared to placebo.	Prophylaxis: • Peak Viral Load (PVL) as defined by the maximum viral load determined by viral quantitative culture (plaque assay) starting from Day 2 up to planned discharge from quarantine (Day 12 am) Treatment: • Area Under the Viral Load-time Curve (VL-AUC) determined by viral quantitative culture (plaque assay) starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day12 am)
Secondary	
To estimate the effect of MK-4482 (800 mg Q12H x 5 days) on the reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	Prophylaxis: • Area Under the Viral Load-time Curve (VL-AUC) determined by viral quantitative culture (plaque assay) starting from Day 2 up to planned discharge from quarantine (Day 12 am) • Area Under the Viral Load-time Curve (VL-AUC) determined by qRT-PCR starting from Day 2 up to planned discharge from quarantine (Day 12 am) • Peak Viral Load (PVL) defined by the maximum viral load determined by qRT-PCR starting from Day 2 up to planned discharge from quarantine (Day 12am)

Objectives	Endpoints
	Treatment: • Peak Viral Load (PVL) as defined by the maximum viral load determined by viral quantitative culture (plaque assay) starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am) • Time (days) to confirmed negative test by viral quantitative culture (plaque assay) measurements starting at initial administration of MK-4482/placebo to first confirmed undetectable (<LLOQ) assessment after peak measure. • Area Under the Viral Load-time Curve (VL-AUC) determined by qRT-PCR starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am) • Peak Viral Load (PVL) defined by the maximum viral load determined by qRT-PCR starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Time (days) to confirmed negative test by qRT-PCR starting at initial administration of MK-4482/placebo to first confirmed undetectable (<LLOQ) assessment after peak measure.
To estimate the effect of MK-4482 (800 mg Q12 x 5 days) on course of clinical symptoms after intranasal inoculation (with RSV A Memphis 37b) compared to placebo	Prophylaxis: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring starting from Day 2 up to planned discharge from quarantine (Day 12 am).

Objectives	Endpoints
	• Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system starting from Day 2 up to planned discharge from quarantine (Day 12 am). • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system starting from Day 2 up to planned discharge from quarantine (Day 12 am). • Peak daily symptom score: individual maximum daily sum of symptom score starting from Day 2 up to planned discharge from quarantine (Day 12 am). Treatment: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring system starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am).

Objectives	Endpoints
	• Peak daily symptom score: individual maximum daily sum of symptom score from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at initial administration of MK-4482/placebo to time of returning to baseline score.

To estimate the effect of MK-4482 (800 mg Q12 x 5 days) on the incidence of RSV infection and symptomatic RSV infection after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	Prophylaxis:
	• RT-PCR-confirmed RSV infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 2 up to Day 12.
	• Occurrence of at least 1 positive quantitative (≥LLOQ) cell culture measurement in nasal samples, from Day 2 up to Day 12.
	• RT-PCR-confirmed symptomatic RSV infection, defined as:
	  ○ RT-PCR-confirmed RSV infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND
	  ○ Symptoms score ≥2 at a single time point.

Objectives	Endpoints
	• RT-PCR-confirmed moderately severe symptomatic RSV infection, defined as: o RT-PCR-confirmed RSV infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND o Any symptoms of Grade ≥2 at a single time point. • Culture lab-confirmed symptomatic RSV infection, defined as: o Lab-confirmed culturable RSV infection (1 quantifiable [≥LLOQ] cell culture measurement), from Day 2 up to Day 12, AND o Symptoms score ≥2 at a single time point.
To evaluate the safety and tolerability of MK-4482 (800 mg Q12 x 5 days) compared to placebo	• Safety data including, but not limited to, occurrence of adverse events (AEs) from initial administration of MK-4482/placebo up to the Day 28 follow-up. • Occurrence of serious AEs (SAEs) from initial administration of MK-4482/placebo up to the Day 28 follow-up.

Objectives	Endpoints
To monitor the safety of the challenge virus	• Occurrence of AEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Use of concomitant medications from viral challenge (Day 0) up to the Day 28 follow-up.
To evaluate plasma NHC concentrations after administration of MK-4482 (800 mg Q12 x 5 days)	Plasma NHC concentrations at specified timepoints
Tertiary/Exploratory	
To further explore the effect of MK-4482 (800 mg Q12H x 5 days) on the reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	Prophylaxis: • Duration of quantifiable RSV qRT-PCR measurements starting from Day 2 up to Day 12 am. Duration is defined as the time (days) from first quantifiable detection until first confirmed undetectable (<LLOQ) assessment after peak measure (after which no further virus is detected) • Duration of quantifiable RSV viral quantitative culture (plaque assay) measurements starting from Day 2 up to Day 12 am. Duration is defined as the time (days) from first quantifiable detection until first confirmed undetectable (<LLOQ) assessment after peak measure (after which no further virus is detected)

Objectives	Endpoints
To further explore the effect of MK-4482 (800 mg Q12H x 5 days) on course of clinical symptoms after intranasal inoculation (with RSV A Memphis 37b) compared to placebo	• Clinical symptom-related endpoints may be further explored, as measured with either the full 13 or a subset of the 13 symptoms within the graded symptom scoring system. Prophylaxis: • Duration (days) of Grade 2 symptoms measured from 10 symptoms within the graded daily symptom scoring system starting from Day 2 to planned discharge from quarantine (Day 12 am), as measured by time from first occurrence of Grade 2 or higher symptoms to first 24 hours period without Grade 2 or more symptoms after the peak total symptom score. • Time (days) to peak as measured from 10 symptoms within the graded daily symptom scoring system starting from Day 2 to the time of peak daily symptom score. Treatment: • Time (days) to peak as measured from 10 symptoms within the graded daily symptom scoring system starting from initial administration of MK-4482/placebo to the time of peak daily symptom score.

Objectives	Endpoints
To further explore the effect of MK-4482 (800 mg Q12H x 5 days) on the incidence of RSV infection and symptomatic RSV infection after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	• RT-PCR-confirmed RSV infection, defined as 2 detectable (≥ lower limit of detection [LLOD]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 2 up to Day 12. • RT-PCR-confirmed symptomatic RSV infection, defined as: o RT-PCR-confirmed RSV infection (2 detectable [≥LLOD] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND o Symptoms score ≥2 at a single time point
To estimate the effect of administration of MK-4482 (800 mg Q12H x 5 days) on mucus production after intranasal inoculation (with RSV A Memphis 37b) compared to placebo	Prophylaxis: • Total weight of mucus produced starting from Day 2 up to planned discharge from quarantine (Day 12 am). • Total number of tissues used by participants starting from Day 2 up to planned discharge from quarantine (Day 12 am). Treatment: • Total weight of mucus produced starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am). • Total number of tissues used by participants starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am).

Objectives	Endpoints
To explore baseline immunology and response to infection with RSV and response to MK-4482.	Blood and nasal samples may be used for exploratory assays related to respiratory viral infection and immunology.
To explore NHC-TP concentrations after administration of MK-4482 (800 mg Q12H x 5 days).	NHC-TP concentrations in PBMCs at specified timepoints.
To explore the relationship between drug exposure and virological endpoints.	Exposure/response relationship
To explore the effect of MK-4482 (800 mg Q12H x 5 days) on the rate of low frequency nucleotide substitutions (LNS) after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.	Quantitation by viral sequencing of nasal samples.
To explore genetics and response to infection with RSV and response to MK-4482.	Blood samples may be used for exploratory assays related to respiratory viral infection, response to MK-4482, and genetics.

*Note that tertiary objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, single site, double-blind study of MK-4482 in healthy male and female participants 18 to 55 years (inclusive) of age, screened to be in the bottom quartile of participants for immunogenicity to the RSV A Memphis 37b (inoculation strain) as determined by a serum microneutralization assay. This study will be conducted in conformance with GCP.

Participants will be prescreened under a generic screening process for SNA (PRNT assay) activity against the inoculation strain. Participants in the lower quartile will be screened for eligibility for this study. Historical generic screening data collected through the generic screening process may be transferred to this study after the study-specific ICF has been signed by the participant.

As outlined in Section 1.2 (Table 1, Figure 1), the study will include 3 arms consisting of prophylactic administration, triggered dosed treatment (hereafter also referred to as treatment), and matched placebo. Approximately 105 participants who meet eligibility criteria will be randomized to receive 800 mg Q12H x 5 days of MK-4482 dosed prior to

viral challenge (prophylaxis); 800 mg Q12h x 5 days of MK-4482 dosed following viral challenge on Day 0 (treatment) or placebo in a 1:1:1 ratio according to the Sponsor's computer-generated allocation schedule. Participants who drop out may be replaced as per Section 5.5 to achieve up to 105 participants inoculated. To maintain the blind across treatment and prophylaxis groups for the duration of the study, all participants will receive MK-4482 or placebo beginning on Day -1 through Day 10. Participants in the prophylaxis cohort will receive active study drug beginning on Day -1 and switch to placebo following completion of 5 days of MK-4482 800 mg Q12H. Participants in the treatment cohort will receive placebo until treatment is triggered based on positive PCR testing for RSV infection or by Day 5 if no infection is detected; if 5 days of MK-4482 800 mg Q12H is completed prior to Day 10, participants will resume placebo through Day 10. Switching of the administered treatment from placebo to MK-4482 (and back to placebo) will be managed by unblinded study staff in a manner that maintains the blind for the participants and other clinical study personnel.

Before viral inoculation, quarantined participants will undergo additional screening to exclude those with respiratory pathogens, and participants who are excluded at this time will not undergo dosing of study intervention. On Day 0 of the study, up to 105 participants will be inoculated with RSV A Memphis 37b in order to have the required number of evaluable participants for the analysis (see Section 9.9). Participants will remain domiciled for 12 days post inoculation. Participants will be queried daily while domiciled for symptoms of RSV infection using a standardized questionnaire starting on Day -1. Nasal wash samples will be collected and tested for RSV viral load by qRT-PCR twice daily from Day 2 through Day 11. A single nasal wash sample for RSV viral load by qRT-PCR will be collected on Day 12. Blood samples to measure concentrations of NHC in the plasma and NHC-TP in PBMCs will be collected throughout the study as outlined in the SoA. All participants inoculated with RSV A Memphis 37b will be followed for safety monitoring for approximately 28 days after RSV A Memphis 37b inoculation. Nasal wash samples may be tested for the presence of virus prior to discharge. Participants will be discharged from the quarantine unit on Day 12 (or may remain longer at the discretion of the PI/investigator).

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

4.2 Scientific Rationale for Study Design

MK-4482 is a prodrug ribonucleoside analogue with a high barrier to resistance and activity against a range of RNA viruses, including RSV. The purpose of this RSV challenge study is to provide an assessment of the antiviral activity of MK-4482 against RSV A in humans. Viral challenge with RSV A Memphis 37b was selected based on its ability to generate safe and reproducible mild to moderate infection from a wild-type virus in multiple human challenge studies (discussed in Section 2.1.2). The protocol follows a double blind, placebo-controlled design. Participants will be inoculated with RSV A Memphis 37b (Day 0) following administration of MK-4482 or placebo (Day -1). A regimen of MK-4482 800 mg Q12H x 5 days will begin on Day -1 (Panel A, prophylaxis) or upon evidence of RSV infection (based on positive PCR testing of nasal wash samples), and no later than Day 5

(Panel B, treatment). A reduction in nasal viral load has been chosen as the primary efficacy-related measure as a sensitive and predictable indicator of viral replication. The primary efficacy-related endpoints are reductions in Peak VL or VL-AUC, in the prophylaxis or triggered dosing Panels, respectively. Additional virologic assessments are included as secondary endpoints to support the primary endpoints. The incidence of symptomatic RSV infection, as well as indicators of symptom timing, intensity and duration are additional secondary measures that provide preliminary assessment of whether MK-4482 800 mg Q12H could be effective in treating or preventing RSV disease. Participants will be domiciled for at least 12 days and followed for 28 days after inoculation with RSV A Memphis 37b, which is a sufficient amount of time for participants to clear the RSV A Memphis 37b virus and detect any potential complications of the inoculation, respectively. To understand the relationship between MK-4482 and changes in the viral dynamics of RSV A Memphis 37b, serum will be collected throughout to evaluate exposure-response with plasma NHC, the primary pharmacokinetic measure for MK-4482. PBMCs will also be collected to understand in exploratory analyses how NHC-TP exposures affect RSV A Memphis 37b viral dynamics. As an objective measure of clinical symptoms, total mucus weights are included as an exploratory endpoint, and viral sequencing will provide an additional exploratory endpoint to assess for any relationship between exposure and viral mutation frequency, based on the mechanism of action of MOV. Taken together, the design will provide a robust evaluation of the antiviral activity of MK-4482 in healthy adults inoculated with RSV in a highly controlled setting.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The study will evaluate the antiviral activity of MK-4482 as both a prophylactic and a triggered treatment in healthy adult participants inoculated with RSV A Memphis 37b. This will be assessed by comparing the level of nasal viral load and the rate of symptomatic RSV infection in the MK-4482 dose groups with placebo. Within this human challenge study model, demonstration of antiviral activity is an approximate surrogate for efficacy and will be assessed based on the primary endpoints as outlined below. Additional measures of changes in viral load will also be considered as supportive, as noted in the secondary endpoints. Assessment of symptomatic RSV infection is also considered as supportive, and secondary endpoints regarding incidence of infection and course of clinical symptoms will form the basis of this evaluation.

The rationale for choice of primary endpoints is based on the relevant viral dynamic assessment for the intervention as well as the mechanism of action of MK-4482 in halting productive viral replication. Reduction in peak VL compared to placebo will establish the antiviral activity of a prophylaxis regimen. For demonstration of prophylactic antiviral activity, a reduction of 65% in PVL will allow benchmarking against performance of other antiviral and vaccine therapies for RSV prophylaxis. Similarly, reduction in VL-AUC compared to placebo will establish the antiviral activity of a triggered dosing regimen for treatment of RSV infection. Demonstration of a 70% reduction in VL-AUC with triggered dosing is viewed as comparable, to the performance of other antivirals that have progressed to Phase 2 field efficacy studies.

Evaluation of endpoints relevant to clinical symptoms will be assessed through the secondary and exploratory endpoints. Both symptom scores and mucus weights are key endpoints in later stage clinical trials and their evaluation within the human challenge model may afford an opportunity to improve translation to later field studies. Secondary endpoints relating to symptom scoring will utilize a symptom diary card administered at Day -3 and Day -2 to establish a baseline and 3 times a day following viral inoculation. In conjunction with symptom scoring, the exploratory endpoint of mucus weights provides an objective measure relevant to symptom scores. Analysis of these secondary and exploratory endpoints are more fully described in a SAP.

4.2.1.2 Safety Endpoints

Based on available clinical safety data to date, evaluation of safety will be adequately assessed from the following standard safety assessments: VS, 12-lead ECG, laboratory safety tests (blood chemistry, hematology, urinalysis) and AEs. Additional laboratory safety assessments in the setting of the RSV challenge model are also included (coagulation studies, CK, thyroid function testing). Safety evaluations will be conducted throughout the study at intervals dictated by the viral challenge model and NHC PK properties.

4.2.1.3 Pharmacokinetic Endpoints

Plasma PK for NHC

Blood samples for the assessment of PK of NHC in plasma will be collected (as described in Sec. 1.3) and used to evaluate standard PK parameters (eg, Cmax, Tmax, AUC0-12, Ctrough) following multiple dose administration of MK-4482. Prior analyses from clinical studies have shown that NHC concentrations in the plasma correlate well with NHC-TP concentrations in PBMCs. NHC concentrations will be measured using a validated bioanalytical assay. Exploratory analyses may be conducted to evaluate the relationship between efficacy-related endpoints with exposures of NHC in the plasma, as appropriate. These findings support modeling efforts and will inform dose selection and study design of later trials.

NHC-TP PK in PBMCs

Blood samples for the assessment of intracellular NHC-TP (the pharmacologically active moiety of MK-4482) in PBMCs will also be collected from participants (see Sec. 1.3) to characterize Ctrough of NHC-TP. NHC-TP concentrations will also be measured using a validated bioanalytical assay. Exploratory analyses may be conducted to evaluate the relationship between efficacy-related endpoints with exposures of NHC-TP in PBMCs, as appropriate. These findings support modeling efforts and will inform dose selection and study design of later trials.

4.2.1.4 Pharmacodynamic Endpoints

This study will evaluate the antiviral activity of MK-4482 800 mg Q12H x 5 days against RSV A infection, either in prophylaxis or in triggered dosing. Assessments of antiviral activity as outlined in the primary and secondary objectives will assist in characterizing the

pharmacodynamic effects of MK-4482 in RSV infection. Exploratory analysis of the rate of LNS in nasal samples will also allow further evaluation of the pharmacodynamic effects of MOV against RSV.

Exploratory analyses may be performed to define the antiviral activity of MOV and NHC relative to viral dynamics of RSV. Viral sequencing to assess rates of LNS will also be used to explore the exposure-response relationship for MK-4482 in RSV based on the known mechanism of action. To better characterize the pharmacodynamic effects of MK-4482 on the response to RSV Memphis 37b inoculation, other exploratory assays may be performed with excess serum or nasal samples from PK or excess PBMCs, and with whole blood mRNA, as applicable, at the discretion of the Sponsor.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

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

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

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR 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 and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

This study is being conducted to assess the antiviral activity of MK-4482 administered to study population in an RSV experimental challenge model. To this end, a placebo comparator is required to document the influence of MK-4482 on RSV viral load, symptomatic infection rate and symptoms scores after inoculation with the challenge strain.

4.3 Justification for Dose

An 800-mg dose of MK-4482 will be administered Q12H for 5 days in this study, which is the same as the proposed therapeutic dose for adults and was the dose assessed in the pivotal Phase 3 portion of the Phase 2/3 study for the treatment of adults with COVID-19 (P002 Part 2). This dose is similarly being evaluated in an ongoing clinical study for postexposure prophylaxis of COVID-19 in adults (P013). Preclinical data place the potency of MK-4482 against RSV within the range of the potency against SARS-CoV-2 (see Sec. 2.2.2). Therefore, the same 800-mg dose administered Q12H for 5 days has been selected for evaluation against RSV.

Preclinical data place the potency of MK-4482 against RSV within the range of the potency against SARS-CoV-2. Comparison of effective dose amounts based on in vitro assays and in vivo preclinical models suggest that similar concentrations of NHC may be effective against both RSV and SARS-CoV2 infection. In vitro assessments of NHC activity against RSV show EC50 values within a 2-fold range those demonstrated against SARS-CoV-2, indicating a similar range of potency, allowing for differences in cell and assay types. Pharmacokinetic analyses indicate no difference in NHC exposure between healthy participants and participants infected with SARS-CoV-2. Therefore, the same 800-mg dose administered Q12H for 5 days for patients with SARS-CoV-2 has been selected for evaluation against RSV in this study, as it is expected to produce exposures that are believed to be efficacious based on the totality of preclinical data.

Of note, multiple doses up to 800-mg MOV Q12H for up to 10.5 days and single doses up to 1600-mg, were generally well tolerated in healthy participants.

As this is a Phase 2a assessment of MK-4482 for RSV infection in humans, 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.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final

decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. The participant is in good health based on medical history, physical examination, VS measurements, spirometry, and ECGs performed before randomization.

   Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

2. The participant is in good health based on laboratory safety tests obtained at the screening visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.

   The laboratory safety test parameter value(s) for hemoglobin and platelet levels must be ≥LLN, total white cell count must be ≥3000/μL, and absolute neutrophil count must be ≥1500/μL before the participant can be considered eligible for inclusion. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.

Demographics

3. The participant has a total body weight ≥50 kg and Body Mass Index (BMI) ≥18 kg/m^2 and ≤35 kg/m^2.

4. The participant is male or female, from 18 years to 55 years of age inclusive, at the time of providing informed consent.

Male Participants

Contraception used by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical trials.

5. Male participants must agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:

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

  OR

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

  - Uses 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.

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

Female Participants

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

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses a contraceptive method that is highly effective (a low user dependency method OR a user dependent hormonal method in combination with barrier method), 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 28 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Has a negative highly sensitive pregnancy test (serum) as required by local regulations) within 24 hours before the first dose of study intervention. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

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

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study, including for FBR.

Additional Categories

8. The participant is serosuitable* to the challenge virus within 90 days of study intervention.

    * A participant must be sero-suitable to take part in the study, i.e., he/she must have no or low pre-existing serum levels of antibodies specific to the challenge agent. This antibody titre cut-off for serosuitability will be described in the applicable hVIVO policy and/or generic screening AP.

    * Serum levels of pre-existing RSV A Memphis 37b-specific antibodies will be determined using RSV challenge virus neutralization assay, as described in the AP.

5.2 Exclusion Criteria

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

Medical Conditions

1. The participant has a history of, or currently active, symptoms or signs suggestive of upper or lower respiratory tract infection within 4 weeks prior to the first study visit.

2. The participant has a history of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, 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.

3. The participant has a history of resolved depression and/or anxiety 1 or more years ago may be included at the discretion of the PI. Participants with a history of stress related

illness, which is not ongoing or requiring current therapy, with good evidence of preceding stressors may also be included at the PI's discretion. As required, participants will be assessed prior to enrolment with a Patient Health Questionnaire (PHQ-9) and/or Generalized Anxiety Disorder Questionnaire (GAD-7) which must score less than or equal to 4 on admission.

4. The participant has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies that 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 that have been successfully treated ≥10 years prior to the prestudy (screening) visit).

5. The participant has a history of rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI's discretion.

6. The participant has a history of atopic dermatitis/eczema which is clinically severe and/or requiring moderate to large amounts of daily dermal corticosteroids will be excluded. Participants with mild to moderate atopic dermatitis/eczema, taking small amounts of regular dermal corticosteroids may be included at the PI's discretion.

7. The participant whose reporting physician has diagnosed migraine can be included provided there are no associated neurological symptoms such as hemiplegia or visual loss. Cluster headache/migraine or prophylactic treatment for migraine is an exclusion. PI discretion may also be based on for example IMP vs. non IMP study.

8. The participant has a physician diagnosed mild Irritable Bowel Syndrome not requiring regular treatment can be included at the discretion of the PI.

9. The participant has an estimated CrCl ≤60 mL/min based on the MDRD Equation.

MDRD Equation:

eGFR (mL/min/1.73 m^2) =
175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if black or African American])

At the discretion of the investigator a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

Participants who have an eGFR or measured CrCl of up to 10% below of either 80 mL/min (for CrCl) or 80 mL/min/1.73m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

Prior/Concomitant Therapy

10. The participant uses or anticipated use during the conduct of the study of concomitant medications (prescription and/or non-prescription), including vitamins or herbal and dietary supplements within the specified windows, unless in the opinion of the study physician/PI, the medication will not interfere with the study procedures or compromise participant safety. Specifically, the following are excluded:

    a) Herbal supplements within 7 days prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first).

    b) Chronically used medications, vitamins or dietary supplements, including any medications known to be potent inducers or inhibitors of CYP450 enzymes, within 21 days prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first).

    c) Over the counter medications (eg, paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first) has exceeded the maximum permissible 24-hour dose (eg, ≥4 g paracetamol over the preceding week)

    d) Systemic anti-viral administration within 4 weeks of Viral Challenge/first dosing with IMP (whichever occurs first).

11. The participant 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 intervention, 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

12. The participant has evidence of receipt of vaccine within the 4 weeks prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first).

13. The participant intends to receive any vaccine(s) before the last day of follow-up. (Note: no travel restrictions will apply after the Day 28 follow-up visit.)

14. The participant has received of any investigational drug within 3 months (or 5 half-lives, whichever is greater) prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first).

15. The participant has received 3 or more investigational drugs within the previous 12 months prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first).

16. The participant has had a prior inoculation with a virus from the same virus family as the challenge virus.

17. The participant has a prior participation in another human viral challenge study with a respiratory virus in the preceding 3 months, taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study.

Diagnostic Assessments

18. The participant has a presence of fever, defined as participant presenting with a temperature reading of ≥37.9°C on Day -3/Day -2, Day -1, and/or pre-Challenge on Day 0.

19. The participant has any of the following: QTc interval >450 msec, a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), uncorrected hypokalemia or hypomagnesemia, or is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

20. The participant is under the age of legal consent.

21. The participant has smoked ≥10 pack years at any time (10 pack years is equivalent to one pack of 20 cigarettes a day for 10 years).

22. The participant has a recent history or presence of alcohol addiction, or excessive use of alcohol (weekly intake in excess of 28 units alcohol; 1 unit being a half glass of beer, a small glass of wine or a measure of spirits), or excessive consumption of xanthine containing substances (eg, daily intake in excess of 5 cups of caffeinated drinks, eg, coffee, tea, cola).

23. The participant 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.

24. The participant has a confirmed positive test for drugs of abuse and cotinine on first study visit. One repeat test allowed at PI discretion

25. The participant has a lifetime history of anaphylaxis and/or a lifetime history of severe allergic reaction. Significant intolerance to any food or drug in the last 12 months, as assessed by the PI.

26. The participant has venous access deemed inadequate for the phlebotomy and cannulation demands of the study.

27. The participant has any significant abnormality altering the anatomy of the nose in a substantial way or nasopharynx that may interfere with the aims of the study and, in particular, any of the nasal assessments or viral challenge. History of nasal polyps is

allowed, but large nasal polyps causing current and significant symptoms and/or requiring regular treatments in the last month is exclusionary).

28. The participant has any clinically significant history of epistaxis (large nosebleeds) within the last 3 months of the first study visit and/or history of being hospitalized due to epistaxis on any previous occasion.

29. The participant has had any nasal or sinus surgery within 3 months of the first study visit.

30. The participant has a forced expiratory volume in 1 second <80%.

31. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

32. The participant is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Participants will fast from all food and drinks, except water, for at least 8 hours before administration of the AM dose on study Day 4 and Day 7, after which rich PK sampling will take place. Water will be restricted 1 hour before and 1 hour after study intervention administration but will otherwise be provided ad libitum. Participants will fast from all food and drinks, except water, between administration of the AM dose on study Day 4 and Day 7 and the first scheduled meal.

On days with sparse PK sampling (ie, trough samples), while domiciled in the clinic or at home, meals and snacks will be unrestricted in caloric content, composition and timing.

Each study intervention administration will be taken with 250 mL water. Additional water, if needed, is allowed.

5.3.1.2 Fruit Juice Restrictions

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

On Day 4 and Day 7, participants will refrain from the consumption of all fruit juices 24 hours before the AM study intervention administration until after drug administration.

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

The consumption of caffeine or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) should be limited to no more than 6 units per day (1 unit = 120 mg of caffeine) from 48 hours prior to quarantine admission and during quarantine.

5.3.2.2 Alcohol Restrictions

Participants will not be allowed to consume alcohol from 72 hours prior to study intervention and 72 hours prior to quarantine admission, and while in the clinic unit.

5.3.2.3 Tobacco Restrictions

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

Participants must not smoke or use tobacco or nicotine containing products for 72 hours prior to and during quarantine. Participants that are current smokers may be enrolled in the study if, in the opinion of the PI/investigator, cessation of smoking during quarantine will not lead to withdrawal symptoms which could interfere with the accurate recording on the symptom diary card.

5.3.3 Activity Restrictions

Participants must refrain from strenuous exercise for 48 hours prior to and during quarantine and for at least 48 hours prior to each clinic visit (unless it is within the usual activity of the participant) and participants are advised to avoid any new strenuous activities for 1 week prior to clinic visits such as weightlifting or running to avoid potential spurious elevation of clinical laboratory safety parameters.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen-failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

For individuals who do not meet the criteria for participation in this study (screen failure), the PI/investigator will decide whether the participant should be permanently excluded from the study or invited back for repeat assessments (i.e., repeat clinical laboratory test) if the initial screening assessments are still within the allowed screening windows or rescreening for a later quarantine, as appropriate.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

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.

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 (MOV 200-mg capsules and matched placebo capsules) 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 before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2. Table 3 depicts the study administration schedule.

Table 2 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Active	Experimental	MK-4482	Drug	Capsule	200 mg	800 mg	Oral	Prophylaxis: MK-4482 800 mg Q12H x 5 days (10 doses) D-1 to D4 Triggered dosing: 800 mg Q12H x 5 days (10 doses) D2/D5 to D6/D10	Experimental	IMP	Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Capsule	Not applicable	Not applicable	Oral	Matched Placebo Arm: PBO Q12H x 11 days Prophylaxis: PBO Q12H D4 to D10 Triggered Dosing: PBO Q12H x 6 days total, before and after active MK-4482	Placebo	IMP	Sponsor
Virus Inocula-tion	Not applicable	RSV A Memphis 37b virus	Virus (Challeng e Agent)	N/A	Approximately 4 Log10 PFU*	Approximately 4 Log10 PFU*	Intranasal	Single Administration	Challenge Agent	N/A	Site (hVIVO)

AM=ante meridiem (before midday); D=day; EEA =European Economic Area; IMP=investigational medicinal product; N/A=not applicable; NIMP=noninvestigational medicinal product; PBO=placebo; PCR=polymerase chain reaction; PFU=plaque-forming unit; PM=post meridiem (after midday); Q12H=every 12 hours; RSV=respiratory syncytial virus.

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

Prophylaxis dose Active MK-4482 begins on PM of D -1 and continues for a total of 10 doses over a 5-day period. Dosing with PBO is provided on the remaining days following Active MK-4482.

Triggered dose Active MK-4482 begins 12 hours following detection of RSV infection on nasal wash PCR, as early as D2 PM, and continues for a total of 10 doses over a 5-day period. If RSV infection is not detected by D5 AM, the participant is assigned to begin dosing Active MK-4482 on D5 PM for a total of 10 doses over a 5-day period. Dosing with PBO is provided on the remaining days before and after Active MK-4482 to span D-1 to D10.

The challenge virus will be prepared to have an inoculum concentration of between 3.5 Log10 PFU/mL and 5 Log10 PFU/mL. The details will be outlined in the Analytical Plan).

Table 3 Study Administration Schedule

Panel	Treatment Arm	Admission	Prophylactic Dosing	Inoculation		Triggered Dosing (earliest)			Triggered Dosing (Latest)							Discharge
	Treatment Day	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12
A	Prophylactic Dosing		1	2	3	4	5	6	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo		
B	Triggered Dosing – start Day 2		Placebo	Placebo	Placebo	1	2	3	4	5*	Placebo	Placebo	Placebo	Placebo		
	Triggered Dosing – start Day 3		Placebo	Placebo	Placebo	Placebo	1	2	3	4	5*	Placebo	Placebo	Placebo		
	Triggered Dosing – start Day 4		Placebo	Placebo	Placebo	Placebo	Placebo	1	2	3	4	5*	Placebo	Placebo		
	Triggered Dosing – start Day 5		Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	1	2	3	4	5*	Placebo		
C	Matched Placebo		Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo		

Dosing will occur Q12H.
Dosing on Day -1 will occur in the PM for all participants.
Participants in Panel B may begin triggered dosing with MK-4482 either in the AM or PM following positive testing for RSV on nasal wash, beginning as early as Day 2 PM and continuing for a total of 10 doses (800 mg Q12H x 5 days). As such, participants who begin triggered dosing in the PM will complete their 10 doses in the AM of the next day (*).
For participants in Panel B who remain negative on PCR testing for RSV on the morning of Day 5, triggered Dosing with MK-4482 is initiated on Day 5 PM and will continue x 10 doses (800 mg Q12H x 5 days) to complete on the morning of Day 10.
The last dose of placebo or active will occur for all subjects in all panels on Day 10 in the AM to maintain blinding.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

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 shown in Table 4.

Table 4 Sample Allocation Schedule of Participants to Treatment

Panel	Panel Description	Number of Participants	Treatment
A	Prophylactic Dosing	35	800-mg MOV Q12H for 5 days (10 doses) starting on Day -1 then matching PBO Q12H for 6 days from Day 4 through Day 10 am
B	Triggered Dosing	35	Matching PBO starting on Day -1 Q12H until seropositive then 800-mg MOV Q12H for 5 days (10 doses).[a,b] Then, matching PBO Q12H through Day 10 am (if needed)
C	Matched Placebo	35	Matching PBO Q12H for 11 days

am=ante meridiem (before midday); MOV=molnupiravir; PBO=placebo; Q12H=every 12 hours

[a] If participant's serostatus does not convert by Day 5, MOV dosing will automatically commence.

[b] PBO administered on alternate days to maintain participant blinding.

6.3.2 Stratification

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

6.3.3 Blinding

A double-blinding technique will be used. MK-4482 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the time periods specified by this protocol. 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 restrictions for concomitant therapy or vaccination:

- Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood within the 3 months prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first) or planned during the 3 months after the final visit.

- Chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune-modifying drug within 6 months prior to dose administration and through poststudy visit (Day 28).

- Medication or product (prescription or over-the-counter) for symptoms of nasal congestion or respiratory tract infection during the impatient quarantine visit.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

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

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

The suggested doses may be adjusted downward at the discretion of the sponsor based upon newly available safety, tolerability, and/or PK data from this study or other studies within the program.

6.6.1 Stopping Rules

The following stopping rules will be used 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. To continue the study (on joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

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

2. Any unexpected virus-related SAE or unexpected virus-related AEs of clinical concerns have been reported following Human Viral Inoculation (expectedness will be assessed by referring to the inoculation virus dossier).

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

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

6.9 Standard Policies

Not applicable for this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study. As certain data on clinical events beyond study intervention discontinuation may be important to

the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a PCL.

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 Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant 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 UDS at any time during the course of the study prior to the final follow up study visit. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

A participant must be discontinued prior to inoculation but continue to be monitored in the study for any of the following reasons:

- Positive human immunodeficiency virus (HIV), B (HBV), or C (HCV) test within 60 days of inoculation.
- Any clinically significant epistaxis (large nosebleeds) from signing the study-specific consent to admission to quarantine.
- Any nasal or sinus surgery from signing the study-specific to admission to quarantine.
- Presence of fever (≥37.9°C) following admission to the quarantine unit and prior to inoculation.
- History or currently active symptoms suggestive of upper or lower respiratory tract infection within 4 weeks prior quarantine admission.

- Use of herbal supplements within 7 days prior to inoculation unless in the opinion of the PI, the supplements will not interfere with the study procedures or compromise participant safety.

- Use of over the counter medications (eg, paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date of Viral Inoculation has exceeded the maximum permissible 24-hour dose (eg ≥4 g paracetamol over the preceding week), unless in the opinion of the PI, the medication will not interfere with the study procedures or compromise participant safety.

- In the opinion of the investigator, the participant is no longer able to comply with the protocol and requirements of the inpatient stay.

7.2 Participant Withdrawal From the Study

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the 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 volume of blood collected from each participant over the duration of the study (ie, from screening through final follow-up visit) will not exceed ~ 189.2 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. If additional samples are required in excess of this amount, eg, to monitor laboratory abnormalities, these will be taken at the discretion of the PI/investigator

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are

changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The participants will be quarantined from the time the study specific informed consent is signed (Day -2/Day-2) until discharge from the site (Day 12). The investigator or qualified designee will provide the participant with a participant identification card at the time of discharge form the inpatient quarantine. 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 14 days before starting the study.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

In a situation where rerandomization of the participants is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

Study medication will be administered by unblinded study staff, as described in the pharmacy manual.

8.1.8.1 Timing of Dose Administration

Day -1 dose of MOV or placebo will be administered in the PM. All subsequent doses of MOV or placebo will be given in the morning and evening (ie, Q12H) on Days 0 through Day 10 am, at approximately the same time each day.

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 . 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 8.12.5 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 8.5.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.5.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

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

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

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

8.1.11 Domiciling

Participants will report to the CRU on either Day -3 or Day -2 before the scheduled day of study intervention administration on Day -1 and remain in the unit until Day 12. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Participants may leave the unit, for emergency situations or if this is the wish of the participant, during the domiciling period. The CRU will notify the Sponsor and the decision on how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

8.1.12 Calibration of Equipment

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

8.2 Intranasal Administration of the Challenge Virus

The challenge agent used in this study is RSV A Memphis 37b.

The challenge agent stock was manufactured under current GMP. The challenge agent stock has undergone quality testing performed during manufacturing (identity, appearance, sterility, infectivity, and contaminants) according to predetermined specifications, and has subsequently also passed an extensive panel of adventitious agent testing. The challenge agent is stored in a secure -80ºC freezer (normal temperature range -60°C to -90°C).

Inoculum vials containing the challenge agent will be used for intranasal inoculation of each participant. The inoculum will be prepared and/or provided according to the hVIVO AP and administered in accordance with hVIVO SOPs.

All administrations will be made by a member of the study staff and witnessed by a second study staff member. The exact time of challenge agent inoculation will be recorded in the administration log. Accurate records will be kept of when and how much inoculum is prepared and used. The oversight process will be signed off prior to administration of the challenge agent. Any noncompliance or problems with the inoculation will be recorded in the participant's source notes and reported to the PI/investigator.

Following challenge agent inoculation, participants will be closely observed specifically for potential allergic reactions and any AEs for the following 24 hours. Post inoculation, participants will lie flat for 10 minutes then sit up with nose pegs on for 20 minutes. Participants will continue to be monitored throughout the clinical phase of the study.

8.3 Efficacy Assessments

Compliance with the efficacy and safety assessments (along with study treatment use) is essential, and any noncompliance noted by the investigator or designee should result in consultation with the participant on corrective measures needed to ensure compliance.

8.3.1 RSV Symptom Diary Card

Participants will report and assess the severity of any challenge agent-related signs and symptoms 3 times per day during quarantine, at the same time each day (±1 hour), using the hVIVO SDC. This information will be collected using a paper form.

The following symptoms in the 13-item symptom questionnaire will be graded on a scale of 0 to 3 (Grade 0: no symptoms; Grade 1: just noticeable; Grade 2: clearly bothersome from time to time but does not interfere with me doing my normal daily activities; Grade 3: quite bothersome most or all of the time, and it stops me participating in activities); shortness of breath and wheeze have an additional grade, ie, Grade 4: symptoms at rest.

- Runny nose
- Stuffy nose
- Sneezing
- Sore throat
- Earache
- Malaise/tiredness
- Headache
- Muscle and/or joint ache
- Chilliness/feverishness
- Cough
- Chest tightness
- Shortness of breath
- Wheeze

Additional to the categorical SDC, a visual analogue scale diary card using a 100 mm scale, with the same symptoms, will be completed by the participants.

Previous studies with RSV A Memphis 37b have used a 10-item symptom questionnaire. The 10 symptoms out of the 13 listed above will be used for the primary analysis, and excludes the following 3 symptoms that may be additionally explored separately:

- Chilliness/feverishness
- Chest tightness
- Wheeze

8.3.2 Nasal Wash for RSV Virology

During the quarantine period, experienced site staff will collect nasal wash samples from each participant following inoculation with RSV, as specified in the SoA (Section 1.3). Instructions for receipt, storage, and handling/shipment of nasal wash specimen and testing for RSV by PCR and plaque assay are provided in the AP.

Nasal wash samples will be collected twice daily from Day 2 through Day 11. From Study Day 2 to Study Day 11, nasal wash sample collections will occur 12 hours apart ± 1 hour. A single nasal wash sample will be collected on Day 12.

8.3.3 Nasopharyngeal Swab

Nasopharyngeal swabs will be performed to collect samples of epithelial lining fluid for:

- Respiratory pathogen screen

Where required, a rapid viral antigen test will be used to determine the presence of RSV in a nasopharyngeal swab sample taken prior to discharge from the quarantine unit on Day 12. A PCR test may be used as an alternative test for this purpose, details of which will be documented in the AP.

A rapid viral antigen test/PCR test will be performed at the discretion of the PI/investigator and only if indicated for a clinical or other reason

8.4 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.

8.4.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height (recorded at screening only) and weight will also be measured and recorded.

A brief directed physical examination, including nasal exam, will be conducted at the discretion of the investigator by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

BMI

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

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

8.4.2 Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, O_2 saturation, and BP will be assessed.
- BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- VS are to be taken before blood collection for laboratory tests.

8.4.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 5 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements. Note that Screening vital signs only may be conducted in a supine as per site SOP.

Upon admission to the CRU, on Day -1 and Day 28, HR and BP will be triplicate measurements obtained within a 10-minute period and the median of the three measurements will be used to assess for participant eligibility. This may be repeated at the discretion of the study investigator.

The predose (baseline) HR and BP will be triplicate measurements prior to the first dose of MK-4482/placebo only, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-4482/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements except for the Day 28 Poststudy measurement which will be in triplicate.

Participants will continue to rest semirecumbent following the am dose until 4 hours post the am dose on full PK sampling days only except to stand for other study related procedures, if required, per the SoA.

Body Temperature

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

8.4.3 Electrocardiograms

- 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and potentially significant findings.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before 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 for at least 10 minutes before each ECG measurement.

The correction formula to be used for QTc is Fridericia.

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

Predose ECGs will be single measurements obtained within 3 hours before dosing MK-4482/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

During the treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥ 60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

During the treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

Postdose ECG measurements will be single measurements.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

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

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

8.4.4 Clinical Safety Laboratory Assessments

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

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

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4.5 Pregnancy Testing

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Pregnancy testing (urine), as required by local regulation, should be conducted at the poststudy visit.

    Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.4.6 Photograph of Rash

Where possible, photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence in determining etiology and drug relationship.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.5.1 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 participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator under any of the following circumstances:

- if the participant is receiving placebo run-in or other run-in treatment,
- if the event causes the participant to be excluded from the study,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation/randomization through 14 days after 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 the period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

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

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

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:
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

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

8.5.2 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.

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

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

8.5.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.5.5 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.

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

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

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

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

Not applicable for this study.

8.5.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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.

8.6 Treatment of Overdose

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

Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.7 Pharmacokinetics

The decision as to which plasma and/or PBMC samples collected will be measured for evaluation of PK will be collaboratively determined by the Sponsor. If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.7.1 Blood Collection for Plasma NHC and/or Metabolites Assay

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

8.7.2 Blood Collection for PBMC NHC-TP and/or Metabolites Assay

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

8.8 Pharmacodynamics

The virologic endpoints (as described in Sec. 3) will be used to evaluate any pharmacokinetic/ pharmacodynamic relationships for NHC and/or NHC-TP.

8.9 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

8.9.1 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.10 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research

8.11 Health Economics Medical Resource Utilization and Health Economics

This section is not applicable. Health Economics OR Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

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

8.12.1 Screening

Participants will be screened under the hVIVO generic screening process. Participants who fulfill inclusion and exclusion criteria for this study through the hVIVO generic screening process, including being serosuitable within 90 days and having normal or not clinically significant laboratory safety data within 56 days, will be invited for admission to the quarantine unit on Day -3/-2.

Upon admission, inclusion/exclusion will be confirmed prior to randomization. A protocol specific consent form will be signed prior to randomization on Day 1.

8.12.2 Treatment Period

Participants will be randomized and dosed at the study site on Day -1 as set forth in the SoA and Section 6.

On Day -1, after all predose procedures have been completed, participants will be assigned a unique randomization number associated with a specific treatment as defined by a computer-generated allocation schedule.

Participants will be administered study drug as indicated in Section 6. Participants on Day -1 who have an acute illness or fever prior to the administration of study drug may be rescheduled as long as their Day 1 visit falls within the screening window (within 90 days for serosuitability and 56 days for laboratory safety data of the first screening).

8.12.3 Intranasal RSV Inoculation Period

On Day -1, participants will be administered either MK-4482 or placebo. On Day 0, participants will be inoculated with RSV A Memphis 37b strain. Participants will undergo a nasal wash procedure every 12 hours for RSV viral load testing. Approximately 12 hours following a positive PCR test for RSV on the wash sample, participants will begin dosing

with 800-mg MK-4482 every 12 hours for 5 days. A detailed description of the preparation and administration of RSV is provided in the Procedures Manual and/or the AP. The trial site will be responsible for recording the lot number, manufacturer, and expiry date of applicable supplies related to RSV administration.

To reduce the risk of passing the Challenge Virus to others, participants will be asked to avoid contact with vulnerable people for 2 weeks after they leave quarantine. For the purposes of this protocol, a vulnerable individual is as follows:

1. Elderly individuals ≥65-year-old;
2. Children ≤2-years-old;
3. Anyone who lives in a nursing home;
4. Anyone with a low resistance to infection or who takes drugs that lower their resistance;
5. Anyone who is having or is about to have drug treatment for cancer (chemotherapy);
6. Anyone who has chronic obstructive pulmonary disease (COPD), emphysema or other severe lung disease;
7. Anyone who has heart disease such as heart failure; has had a heart attack or heart surgery;
8. Anyone with cerebral palsy, epilepsy, who has seizures or who has had a stroke;
9. Anyone who has had a bone marrow or solid organ transplant;
10. Women who are pregnant or trying to become pregnant

8.12.4 Participants Discontinued From Study Intervention but 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.

8.12.5 Poststudy

Participants will be required to return to clinic approximately 28 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 28 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 28 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.12.6 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for plasma NHC and/or metabolites assay is the critical procedure.

At any postdose time point, the blood sample for NHC and/or metabolites assay 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 before 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.

- Screening 2 procedures: up to additional 4 hours of scheduled time
- Plasma NHC and/or metabolites PK samples collection windows are outlined in Table 6.

PBMC NHC-TP and/or metabolites PK sample collection windows are as outlined in Table 7

Table 6 Pharmacokinetic (Blood for Plasma NHC and/or Metabolites Assay) Collection Windows

Plasma NHC PK Collection	**Collection Window**
Predose (Day -1)	Within 3 hr prior to first dose
Predose (all other days)	Within 30 min prior to the next dose
0 to <1 h	5 min
1 to <12 h	10 min
12 h	15 min
PK collection windows are +/- relative to the AM dose on the respective day, with the exception of the Day -1 sampling, which occurs following the PM dose.	

Table 7 Pharmacokinetic (Blood for PBMC NHC-TP and/or Metabolites Assay) Collection Windows

PBMC NHC-TP PK Collection	Collection Window
Predose (Day -1)	Within 3 hr prior to first dose
Predose (all other days)	Within 30 min prior to the next dose
0 to <1 h	5 min
1 to <12	10 min
12 h	15 min
PK collection windows are +/- relative to the AM dose on the respective day, with the exception of the Day -1 sampling, which occurs following the PM dose.	

- Predose standard safety evaluations: VS and ECG at 3 hours; laboratory safety tests and physical exam at 24 hours
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam
  - Starting Day 1, postdose evaluations may be obtained within +/- 1 hour of the theoretical sampling time
- Study intervention administration (multiple dose studies only): at 30 minutes.

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

This protocol is written with some flexibility to accommodate the inherent dynamic nature of early phase 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.

- Decrease in the dose of the study intervention
- Decrease in the duration of study intervention administration (eg, number of days)
- 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

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available data. These collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) currently outlined in the protocol 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.

- Additional blood or urine samples may be taken for laboratory safety tests or other tests, such as measurement for PK analysis. Any additional urine collections may include continuous, total collections, if necessary. Up to an additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

- Additional noninvasive, painless procedures that are already specified in this protocol may be performed based on newly available data.

- An additional 24 hours residence in the CRU and up to 2 additional outpatient visits per period will be permitted, in the event of a technical failure, and/or if extra blood or urine samples, or extra pharmacodynamic measurements, are needed.

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study. Full detail is in the SAP (Section 9.2 to 9.9). The additional statistical analysis details/data derivations, including exploratory analyses and subgroup analyses may be documented in a sSAP, if applicable.

Method:

Safety

AEs will be tabulated and descriptively summarized. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, 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).

Efficacy

Prophylaxis:

Only Panel A (prophylaxis) and Panel C (placebo) will be included in the model.

PVL (on the log10 scale) of RSV A Memphis 37b determined by viral quantitative culture (plaque assay) between Day 2 and Day 12 am after intranasal inoculation (Day 0) will be analyzed using a linear model with treatment group as a fixed categorical effect. The mean PVL in each group and the differences in mean PVL between MK-4482 and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

Treatment:

Only Panel B (treatment) and Panel C (placebo) will be included in the model. For both panels, only the participants with RSV infection will be included.

VL-AUC (on the log10 scale) determined by viral quantitative culture (plaque assay) from initial triggered administration of MK-4482/placebo, through Day 12 am (inclusive) after viral inoculation (Day 0) will be analyzed using a linear model with treatment group as a fixed categorical effect. The mean VL-AUC in each group and the differences in mean VL-AUC between MK-4482 and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

For both prophylaxis and treatment arm, if the assumptions of a linear model are not met, an alternative method, such as Wilcoxon-Rank-Sum test will be applied.

Power:

105 participants will be randomized and dosed with MK-4482 or placebo. 35 per panel will be administered the intranasal RSV A Memphis 37b inoculation, complete the follow up and sample collection through Day 12 am post inoculation.

The primary hypothesis:

The assumed CV in VL-AUC or PVL as well as infection rate of 61% (based on a single quantitative plaque assay positive from Day 2 to Day 12) were obtained from previous published and unpublished RSV challenge studies conducted by hVIVO (Vendor contracted to perform the study) and all based on log10 pfu /mL. The evaluable sample size is assumed to be 35 per group with expected dropout rate of 2 (~ 5% out of 33).

For prophylaxis, with a sample size of 33 per group, there is ~ 80.9% power to detect a decrease in PVL of 65% (on the log10 scale) in MK-4482 group vs the placebo group assuming a CV in PVL of 0.917 with a 2-sided alpha=0.05 test.

For treatment, with a sample size of 19 that test positive per group, there is ~ 80.5% power to detect a decrease in VL-AUC of 70% (on the log10 scale) in MK-4482 group vs the placebo

group assuming a CV in VL-AUC of 0.767 with a 2-sided alpha=0.05 test. Considering the infection rate of 61%, a sample size of 31 per group will maintain 80% power.

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 Pharmacometrics Department and Translational Medicine Departments 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 CSR.

9.3 Hypotheses/Estimation

To determine if MK-4482 (800 mg Q12 x 5 days) results in a reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to placebo.

Hypothesis (Prophylaxis): MK-4482 (800 mg Q12 x 5 days), when administered to begin prior to intranasal inoculation with respiratory syncytial virus (RSV-A Memphis 37b), reduces the Peak Viral Load (PVL) after viral inoculation compared to placebo.

Hypothesis (Treatment): MK-4482 (800 mg Q12 x 5 days), when administered following infection with respiratory syncytial virus (RSV-A Memphis 37b), reduces the Area Under the Viral-Load-time (VL-AUC) after MK-4482 administration compared to placebo.

9.4 Analysis Endpoints

Primary Endpoints:

Prophylaxis: PVL as defined by the maximum viral load determined by viral quantitative culture (plaque assay) starting from Day 2 up to planned discharge from quarantine (Day 12 am)

Treatment: VL-AUC determined by viral quantitative culture (plaque assay) starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am)

Secondary Endpoints:

Safety:

- Safety data including, but not limited to, occurrence of AEs from initial administration of MK-4482/placebo up to the Day 28 follow-up.
- Occurrence of SAEs from initial administration of MK-4482/placebo up to the Day 28 follow-up.
- Occurrence of serious AEs (SAEs) from initial administration of MK-4482/placebo up to the Day 28 follow-up.

- Occurrence of AEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up.

- Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up.

- Use of concomitant medications from viral challenge (Day 0) up to the Day 28 follow-up.

Prophylaxis:

- VL-AUC determined by viral quantitative culture (plaque assay) starting from Day 2 up to planned discharge from quarantine (Day 12 am)

- VL-AUC determined by qRT-PCR starting from Day 2 up to planned discharge from quarantine (Day 12 am)

- PVL defined by the maximum viral load determined by qRT-PCR starting from Day 2 up to planned discharge from quarantine (Day 12 am)

- Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring starting from Day 2 up to planned discharge from quarantine (Day 12am).

- Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system starting from Day 2 up to planned discharge from quarantine (Day 12am).

- Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system starting from Day 2 up to planned discharge from quarantine (Day 12am).

- Peak daily symptom score: individual maximum daily sum of symptom score starting from Day 2 up to planned discharge from quarantine (Day 12am).

- RT-PCR-confirmed RSV infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 2 up to Day 12.

- Occurrence of at least 1 positive quantitative (≥LLOQ) cell culture measurement in nasal samples, from Day 2 up to Day 12.

- RT-PCR-confirmed symptomatic RSV infection, defined as:
    - RT-PCR-confirmed RSV infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND
    - Symptoms ≥2 at a single time point.
- RT-PCR-confirmed moderately severe symptomatic RSV infection, defined as:
    - RT-PCR-confirmed RSV infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 2 up to Day 12, AND
    - Any symptoms of grade ≥2 at a single time point.
- Culture lab-confirmed symptomatic RSV infection, defined as:
    - Lab-confirmed culturable RSV infection (1 quantifiable [≥LLOQ] cell culture measurement), from Day 2 up to Day 12, AND
    - Symptoms ≥2 at a single time point.

Treatment:

- PVL as defined by the maximum viral load determined by viral quantitative culture (plaque assay) starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am)
- Time (days) to confirmed negative test by viral quantitative culture (plaque assay) measurements starting at initial administration of MK-4482/placebo to first confirmed undetectable (<LLOQ) assessment after peak measure.
- VL-AUC determined by qRT-PCR starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am)
- PVL defined by the maximum viral load determined by qRT-PCR starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12 am).
- Time (days) to confirmed negative test by qRT-PCR starting at initial administration of MK-4482/placebo to first confirmed undetectable (<LLOQ) assessment after peak measure.
- Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring system starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12am).

- Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system starting at initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12am).

- Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12am).

- Peak daily symptom score: individual maximum daily sum of symptom score from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12am).

- Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at initial administration of MK-4482/placebo to time of returning to baseline score.

Pharmacokinetics:

- NHC concentrations in plasma at sampling times. The following plasma NHC pharmacokinetic parameters may also be evaluated: Cmax, Tmax, AUC0-12, and Ctrough.

Exploratory Endpoints:

Note that tertiary objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported.

Prophylaxis:

- Duration of quantifiable RSV qRT-PCR measurements starting from Day 2 up to Day 12am. Duration is defined as the time (days) from first quantifiable detection until first confirmed undetectable (<LLOQ) assessment after peak measure (after which no further virus is detected)

- Duration of quantifiable RSV viral quantitative culture (plaque assay) measurements starting from Day 2 up to Day 12am. Duration is defined as the time (days) from first quantifiable detection until first confirmed undetectable (<LLOQ) assessment after peak measure (after which no further virus is detected)

- Duration (days) of grade 2 symptoms measured from 10 symptoms within the graded daily symptom scoring system starting from Day 2 to planned discharge from quarantine (Day 12am), as measured by time from first occurrence of grade 2 or higher symptoms, to first 24 hours period without grade 2 or more symptoms after the peak total symptom score.

- Time (days) to peak as measured from 10 symptoms within the graded daily symptom scoring system starting from Day 2 to the time of peak daily symptom score.

- Total weight of mucus produced starting from Day 2 up to planned discharge from quarantine (Day 12am).

- Total number of tissues used by participants starting from Day 2 up to planned discharge from quarantine (Day 12am).

Treatment:

- Time (days) to peak as measured from 10 symptoms within the graded daily symptom scoring system starting from initial administration of MK-4482/placebo to the time of peak daily symptom score.

- Total weight of mucus produced starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12am).

- Total number of tissues used by participants starting from initial administration of MK-4482/placebo up to planned discharge from quarantine (Day 12am).

Note for all endpoint analysis:

  - Further sensitivity analysis may be performed on the above viral qRT-PCR-related incidence endpoints where detection by qRT-PCR is reported above the levels of detection in the assay instead of the LLOQ. Details will be provided in the statistical analysis plan (sSAP).

  - All clinical symptom-related endpoints may be further explored, as measured with either the full 13 or a subset of the 13 symptoms within the graded symptom scoring system.

Pharmacokinetics:

- NHC-TP concentrations in PBMCs at sampling times.

Pharmacokinetics/Pharmacodynamics:

- Exposure-response relationship: the relationship between plasma NHC parameters (e.g., AUC, Ctrough) or PBMC NHC-TP concentrations and virological endpoints for treatment and prophylaxis.

9.5 Analysis Populations

Full Analysis Set (FAS) Population

The FAS will serve as the primary population for the evaluation of efficacy. The FAS population consists of all randomized participants who received 1 dose of the correct clinical

material corresponding to the treatment group the participants were randomized into and who received the viral inoculation.

Full Analysis Set – Infected (FAS-I) Population

The FAS-I will serve as the primary population for the treatment portion for the evaluation of efficacy. For the treatment portion, only those that are RSV infected participants in the FAS will be included in the efficacy analysis.

Safety Analysis Population

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 (APaT): The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

PK Analysis Population

Per-Protocol (PP): The Per-Protocol Population consists of 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 Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Safety

AEs will be tabulated and descriptively summarized. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from baseline, 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).

Efficacy

Prophylaxis

Only panel A (prophylaxis) and panel C (placebo) will be included in the model. PVL (on the log10 scale) of RSV A Memphis 37b determined by viral quantitative culture (plaque assay)

between Day 2 and Day 12 am after intranasal inoculation (Day 0) will be analyzed using a linear model with treatment group as a fixed categorical effect. The mean PVL in each group and the differences in mean PVL between MK-4482 and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

Treatment:

Only Panel B (treatment) and Panel C (placebo) will be included in the model. For both panels, only the participants with RSV infection will be included.

VL-AUC (on the log10 scale) determined by viral quantitative culture (plaque assay) from initial triggered administration of MK-4482/placebo, through Day 12 am (inclusive) after viral inoculation (Day 0) will be analyzed using a linear model with treatment group as a fixed categorical effect. The mean VL-AUC in each group and the differences in mean VL-AUC between MK-4482 and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

The primary hypothesis for treatment and prophylaxis will be tested separately. The primary hypothesis will be supported if the upper limit of the two-sided 95% CI for the difference in mean PVL/VL-AUC between MK-4482 and placebo is <0 (indicating a reduction).

The proportion of participants with symptomatic RSV infection between Day 2 and Day 12 am after intranasal inoculation (Day 0) will be computed along with exact 95% CIs for each treatment group. Exact 95% CIs will be computed for the difference in proportions between each MK-4482 dose and placebo [Chan, I. S. F. and Zhang, Z. 1999]. Additionally, the presence of symptomatic RSV infection will be modeled using a 3-parameter sigmoidal (logistic) function with treatment group as a fixed effect. Other discrete efficacy endpoints will be analyzed in a similar manner.

For both prophylaxis and treatment arm, if the assumptions of a linear model are not met, an alternative method, such as Wilcoxon-Rank-Sum test will be applied.

Details for analyses of the numerous secondary and exploratory endpoints will be included in a supplemental statistical analysis plan (sSAP).

Pharmacokinetics

The following (non-model-based) descriptive statistics will be provided for all PK parameters: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

9.7 Interim Analyses

No interim analyses are planned.

9.8 Multiplicity

The study has only 1 primary hypothesis for treatment and prophylaxis arm respectively which will be addressed and preserve the alpha level at 0.05 2-sided; therefore, there is no need for a multiplicity adjustment.

9.9 Sample Size and Power Calculations

105 participants will be randomized and dosed with MK-4482 or placebo. 35 per panel will be administered the intranasal RSV A Memphis 37b inoculation, complete the follow-up and sample collection through Day 12 am post inoculation.

The primary hypothesis:

The assumed CV in VL-AUC or PVL as well as infection rate of 61% (based on a single quantitative plaque assay positive from Day 2 to Day 12) were obtained from previous published and unpublished RSV challenge studies conducted by hVIVO (Vendor contracted to perform the study) and all based on log10 pfu/mL. The evaluable sample size is assumed to be 35 per group with expected dropout rate of 2 (~ 5% out of 33).

For prophylaxis, with a sample size of 33 per group, there is ~80.9% power to detect a decrease in PVL of 65% (on the log10 scale) in MK-4482 group vs. the placebo group assuming a CV in PVL of 0.917 with a 2-sided alpha=0.05 test.

For treatment, with a sample size of 19 that test positive per group, there is ~ 80.5% power to detect a decrease in VL-AUC of 70% (on the log10 scale) in MK-4482 group vs. the placebo group assuming a CV in VL-AUC of 0.767 with a 2-sided alpha=0.05 test. Considering the infection rate of 61%, a sample size of 31 per group will maintain 80% power.

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage

underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on

behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

This section is not applicable.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical 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 trials 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.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasted)	Calcium	Alkaline phosphatase	Cardiac Enzymes (CK and Troponin)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum hCG or urine pregnancy test (as needed for WOCBP)			

Laboratory Assessments	Parameters
Other Screening Tests	• FSH (as needed in WONCBP only) • Serum or urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology HIV antibody, HBsAg, and hepatitis C virus antibody • Breath alcohol test • Coagulation (PT/aPTT) • Cardiac Enzymes (CK and Troponin) • Thyroid Function Test
ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential Notes: Laboratory safety tests (hematology and chemistry) will be performed after approximately 8-hour fast. Screening safety tests, Day -3/-2, and any repeat hematology tests to confirm out of range values do not need to be fasted.	

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

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

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

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

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

Events NOT meeting the AE definition

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

10.3.2 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:

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

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

- 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.

Assessment of causality

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal 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.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[b,c] IUS[b,d] Nonhormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the WOCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
Progestogen-only hormonal contraception[b,c] - Oral - Injectable
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [b] Penile/external condoms must be used in addition to the WOCBP's hormonal contraception. [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin-releasing IUD. Note: Tubal occlusion includes tubal ligation

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

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

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Table

Panels A, B and C	Screening	Treatment and Inoculation Period	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Screening & Admission Laboratory Safety Test (chemistry and hematology)	1	-	-	1	7.0	7.0
Coagulation Testing (PT/aPTT)	1	-	-	1	2.7	2.7
Routine Safety Laboratory Test	-	3	1	4	5.5	20
FSH (for WONCBP only, if applicable)(blood from chemistry sample)	1	-	-	1	-	-
Serum β-hCG for WOCBP only, if applicable)(blood from chemistry sample)	1	-	-	1	-	-
HIV/Hepatitis Screen (at the discretion of the investigator) (blood from chemistry sample)	1	-	-	1	-	-
Blood - Serum Markers Humoral Immunity	1	2	1	4	5	20
Blood for Plasma NHC Assay	-	17	-	17	3	51
Blood for PBMC NHC-TP Assay	-	5	-	5	16	80
Blood for Planned Genetic Analysis	-	1	-	1	8.5	8.5
	Total Blood Volume per Participant[a]					189.2 mL

aPTT=activated partial thromboplastin time; β-hCG=beta human chorionic gonadotropin; FSH=follicle stimulating hormone; HIV-human immunodeficiency virus; NHC=N-hydroxycytidine; NHC-TP=N-hydroxycytidine-triphosphate; PT=prothrombin time; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential;

[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: 12-Lead Electrocardiogram Abnormality Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

	Screen Failure Criteria	**Potentially Significant Postrandomization Findings (clarification on action to take)**
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave. Baseline is defined as Predose Day 1		

10.10 Appendix 10: 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:

    a. The participant may be excluded from the study;

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

    c. 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

    d. 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.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
am	ante meridiem (before midday)
AP	Analytical Plan
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-12	area under the curve from time 0 to 12 hours
BMI	body mass index
BP	blood pressure
CAC	Clinical Adjudication Committee
CCU	cardiac care unit
CFB	Change from baseline
CG	Cockcroft-Gault
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CL	clearance
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
Ctrough	trough concentration
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC50	half-maximal effective concentration
ECG	electrocardiogram s
ECI	event of clinical interest

Abbreviation	Expanded Term
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full Analysis Set
FAS-I	Full Analysis Set -Infected
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplantation
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgB	immunoglobulin B
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LNS	low frequency nucleotide substitutions
LRI	lower respiratory tract illness
MAD	maximum administered dose
MDRD	Modification of Diet in Renal Disease
MERS	Middle East respiratory syndrome

Abbreviation	Expanded Term
MERS-CoV	MERS-associated coronavirus
MOV	Molnupiravir
mRNA	messenger RNA
NCS	not clinically significant
NHC	N-hydroxycytidine
NHC-TP	NHC 5'-triphosphate
NDA	New Drug Application
P	protocol (number)
PBMC	peripheral blood mononuclear cell
PCL	Protocol Clarification Letter
PCR	polymerase chain reaction
PI	primary investigator
PK	pharmacokinetic
po	orally
PP	per-protocol
PRNT	Plaque Reduction Neutralization Tests
PTT	partial thromboplastin time
PVL	peak viral load
Q12H	every 12 hours
qicPCR	qualitative integrative cycler PCR
qRT-PCR	real-time quantitative reverse transcription PCR
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	SARS-associated coronavirus-2
SD	standard deviation
SDC	symptom diary card
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLAB	supplemental laboratory test(s)
SNA	serum neutralizing antibody
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TK	toxicokinetic(s)
Tmax	time to maximum plasma concentration
TSS	total clinical symptoms
t1/2	half life
UDS	urine drug screen

Abbreviation	Expanded Term
ULN	upper limit of normal
VL	viral load
VL-AUC	area under the viral load-time curve
VS	vital signs
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

11 REFERENCES

[Akerlind, B. 1986]	Akerlind B, Norrby E. Occurrence of respiratory syncytial virus subtypes A and B strains in Sweden. J Med Virol. 1986 Jul;19(3):241-7.	[04Q5VC]
[Bloom-Feshbach, K., et al 2013]	Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS One. 2013;8(2):e54445.	[04Q5VR]
[Borchers, A. T., et al 2013]	Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus - a comprehensive review. Clin Rev Allergy Immunol. 2013 Dec;45(3):331-79.	[04Q5W0]
[DeVincenzo, J. P., et al 2010]	DeVincenzo JP, Wilkinson T, Vaishnaw A, Cehelsky J, Meyers R, Nochur S, et al. Viral load drives disease in humans experimentally infected with respiratory syncytial virus. Am J Respir Crit Care Med. 2010;182:1305-14.	[04YKRF]
[DeVincenzo, J., et al 2020]	DeVincenzo J, Tait D, Efthimiou J, Mori J, Kim YI, Thomas E, et al. A randomized, placebo-controlled, respiratory syncytial virus human challenge study of the antiviral efficacy, safety, and pharmacokinetics of RV521, an inhibitor of the RSV-F protein. Antimicrob Agents Chemother. 2020 Feb;64(2):e01884-19.	[083BXW]
[Falsey, A. R. 2000]	Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clin Microbiol Rev. 2000 Jul;13(3):371-84.	[04VR9V]
[Flavell, R. A., et al 1974]	Flavell RA, Sabo DL, Bandle EF, Weissmann C. Site-directed mutagenesis: generation of an extracistronic mutation in bacteriophage Qbeta RNA. J Mol Biol. 1974;89:255-72.	[05JF06]

[Gilca, R., et al 2006]	Gilca R, De Serres G, Tremblay M, Vachon ML, Leblanc E, Bergeron MG, et al. Distribution and clinical impact of human respiratory syncytial virus genotypes in hospitalized children over 2 winter seasons. J Infect Dis. 2006 Jan 1;193(1):54-8.	[04Q7H8]
[Glezen, W. P., et al 1986]	Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. AJDC 1986;140:543-6.	[03PFZR]
[Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. 2021]	Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. J Biol Chem. 2021 Jul;297(1):100770.	[06G33J]
[Hall, C. B. 1981]	Hall CB, Douglas RG Jr. Modes of transmission of respiratory syncytial virus. J Pediatr. 1981 Jul;99(1):100-3.	[04Q7HC]
[Hall, C. B. 2001]	Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001 Jun 21;344(25):1917-28.	[04Q7HH]
[Hall, C. B., et al 2009]	Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360(6):588-98.	[03R4JG]
[Haynes, A. K., et al 2013]	Haynes AK, Manangan AP, Iwane MK, Sturm-Ramirez K, Homaira N, Brooks WA, et al. Respiratory syncytial virus circulation in seven countries with Global Disease Detection Regional Centers. J Infect Dis. 2013 Dec 15;208 Suppl 3:S246-54.	[04Q5K7]
[Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. 2021]	Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol. 2021 Aug 11.	[06G338]

[Lambkin-Williams, R., et al 2018]	Lambkin-Williams R, Noulin N, Mann A, Catchpole A, Gilbert AS. The human viral challenge model: accelerating the evaluation of respiratory antivirals, vaccines and novel diagnostics. Respir Res. 2018;19:123.	[083BXY]
[Mufson, M. A., et al 1988]	Mufson MA, Belshe RB, Orvell C, Norrby E. Respiratory syncytial virus epidemics: variable dominance of subgroups A and B strains among children, 1981-1986. J Infect Dis. 1988 Jan;157(1):143-8.	[04Q7CL]
[National Institutes of Health 2008]	National Institute of Allergy and Infectious Diseases [Internet]. Bethesda (MD): National Institutes of Health (NIH). Respiratory syncytial virus (RSV); 2008 Dec 12 [cited 2022 Apr 1]; [about 7 screens]. Available from: https://www.niaid.nih.gov/diseases-conditions/respiratory-syncytial-virus-rsv.	[0805CT]
[Ohuma, E. O., et al 2012]	Ohuma EO, Okiro EA, Ochola R, Sande CJ, Cane PA, Medley GF. Et al. The natural history of respiratory syncytial virus in a birth cohort: the influence of age and previous infection on reinfection and disease. Am J Epidemiol. 2012 Nov 1;176(9):794-802.	[04Q7CZ]
[Sadoff, J., et al 2021]	Sadoff J, De Paepe E, DeVincenzo J, Gymnopoulou E, Menten J, Murray B, et al. Prevention of respiratory syncytial virus infection in healthy adults by a single immunization of Ad26.RSV.preF in a human challenge study [manuscript]. J Infect Dis. 2021. 31 p.	[083BBN]
[Schmoele-Thoma, B., et al 2022]	Schmoele-Thoma B, Zareba AM, Jiang Q, Maddur MS, Danaf R, Mann A, et al. Vaccine efficacy in adults in a respiratory syncytial virus challenge study. N Engl J Med. 2022 Jun 23;386(25):2377-86.	[083BBP]

[Shi, T., et al 2020]	Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, et al. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. J Infect Dis. 2020;222(Suppl 7):S577-83.	[0805CM]
[Stensballe, L. G., et al 2003]	Stensballe LG, Devasundaram JK, Simoes EAF. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003;22(2):S21-S32.	[03Q539]
[Stevens, M., et al 2018]	Stevens M, Rusch S, DeVincenzo J, Kim YI, Harrison L, Meals EA, et al. Antiviral activity of oral JNJ-53718678 in healthy adult volunteers challenged with respiratory syncytial virus: a placebo-controlled study. J Infect Dis. 2018 Sep 1;218:748-56.	[083BXZ]
[Walsh, E. E. 2012]	Walsh EE, Falsey AR. Respiratory Syncytial Virus infection in adult populations. Infect Disord Drug Targets. 2012;12(2):98-102.	[04W9J9]
[Yoon, J. J., et al 2018]	Yoon JJ, Toots M, Lee S, Lee ME, Ludeke B, Luczo JM, et al. Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses. Antimicrob Agents Chemother. 2018 Aug;62(8):e00766-18.	[05JF0G]