Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-4482 for the Prevention of COVID-19 (Laboratory-confirmed SARS-CoV-2 Infection With Symptoms) in Adults Residing With a Person With COVID-19
NCT number:	NCT04939428
Document Date:	16-Oct-2022

Title Page

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Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-4482 for the Prevention of COVID-19 (Laboratory-confirmed SARS-CoV-2 Infection With Symptoms) in Adults Residing With a Person With COVID-19.

Protocol Number: 013-05

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):

EudraCT	2021-000904-39
IND	155588

Approval Date: 16 October 2022

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 5	16-OCT-2022	The rationale for this amendment is 1) to update the anti-SARS-CoV-2 neutralizing antibody testing method and 2) to allow use of qualitative OP swab data, under extenuating circumstances where NP swab data are not available, for baseline viral status categorization (ie, to establish whether they are in the primary analysis population, mITT-VN) and for clinical outcome assessment.
Amendment 4	15-MAY-2022	The rationale for this amendment is 1) to update the interim analysis to remove the assessment of early efficacy; only safety and futility will be assessed at the interim analysis 2) to revise the power calculation and sample size as a result of removing the assessment of early efficacy at the interim analysis and 3) to correct errors mistakenly introduced in the prior amendment in the third secondary objective and second exploratory objective.
Amendment 3	05-APR-2022	The rationale for this amendment is 1) to add as a secondary objective and associated hypothesis for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants regardless of SARS-CoV-2 results (detectable or undetectable) in baseline NP swabs, and 2) to align male contraception requirements across the study with the requirements in the US EUA Fact Sheet for MOV even if not required locally.
Amendment 2	07-JAN-2022	The primary rationale for this amendment was to revise the primary efficacy objective to include only those participants with undetectable SARS-CoV-2 in baseline nasopharyngeal swabs, and to update the interim analysis to include an assessment of early efficacy. These changes required an increase in the sample size (from 1332 to 1500) and an update of the timing of the interim analysis.

Document	Date of Issue	Overall Rationale
Amendment 1	23-AUG-2021	The key reasons for this amendment are to 1) make the evaluation of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline nasopharyngeal (NP) swabs a key secondary endpoint; 2) align the windows (5-days) for COVID-19 symptoms and SARS-CoV-2 testing in the index; and 3) to collect symptom diaries in all participants through Day 29.
Original Protocol	14-JUN-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

The rationale for this amendment is 1) to update the anti-SARS-CoV-2 neutralizing antibody testing method and 2) to allow use of qualitative OP swab data, under extenuating circumstances where NP swab data are not available, for baseline viral status categorization (ie, to establish whether they are in the primary analysis population, mITT-VN) and for clinical outcome assessment.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
8.8 Anti-SARS-CoV-2 Antibody Serology Testing	Updated the anti-SARS-CoV-2 neutralizing antibody testing method.	The assay to be used to test for SARS-CoV-2 neutralization antibodies has been revised due to technical and timing issues with the original method. The updated assay is a validated assay which works by a method similar to the original method (a spike-protein pseudotyped VSV neutralization assay) and has an additional luciferase reporter system that enables higher throughput.
8.2.5 SARS-CoV-2 RT-PCR Assay 9.5.1 Efficacy Analysis Populations	Added a statement to allow for OP swab results to be used for baseline qualitative virology testing in the absence of NP swab results.	Clarified that in some instances, only OP swab results may be available. In light of good concordance between OP and NP swab results observed in prior studies, use of OP swab results is an acceptable alternative to support efficacy endpoints including the primary outcome assessment and baseline viral status. NP swabs remain the required procedure, and OP results will only be used in the event that NP swab results are not available.

Section # and Name	Description of Change	Brief Rationale
10.5.2 Contraception Requirements	Added that tubal occlusion includes tubal ligation.	To clarify that tubal ligation is considered a contraception method, not a sterilization method as per company guidance.
Throughout Document	Minor formatting, editorial, and typographical changes were made throughout the document.	To ensure clarity and accuracy.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-4482 for the Prevention of COVID-19 (Laboratory-confirmed SARS-CoV-2 Infection With Symptoms) in Adults Residing With a Person With COVID-19.

Short Title: MK-4482 Phase 3 Study for Prevention of COVID-19 in Adults

Acronym: N/A
MOVe-AHEAD

Hypotheses, Objectives, and Endpoints:

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

Objectives will be evaluated in participants ≥18 years of age who do not have confirmed or suspected COVID-19 at the time of screening and randomization and are residing with an individual (of any age) with COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms), defined as the index case.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of molnupiravir (MOV) compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline nasopharyngeal (NP) swabs. • *Hypothesis: MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline NP swabs.*	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate the safety and tolerability of MOV compared with placebo.	• Adverse events • Adverse events leading to discontinuation of study intervention

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants regardless of SARS-CoV-2 results in baseline NP swabs. • Hypothesis: MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in all participants regardless of SARS-CoV-2 results in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 29 in participants with undetectable SARS-CoV-2 in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate prevention of viral transmission through Day 14 for MOV compared with placebo in participants with undetectable SARS-CoV-2 in baseline NP swabs.	• SARS-CoV-2 RNA
• To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with detectable SARS-CoV-2 in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Prophylaxis of COVID-19 in adults
Population	Participants ≥18 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo-controlled
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 9 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:

Participants in this study are adult household contacts of index cases. Approximately 1376 participants will be randomized in a 1:1 ratio to receive either blinded MOV or blinded placebo. Index cases will not be randomized to receive intervention in the study.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td>Group 1</td><td>MOV (MK-4482)</td><td>800 mg</td><td>Q12H</td><td>Oral</td><td>5 days (10 doses total)</td><td>Test Product</td></tr>
<tr><td>Group 2</td><td>Matching Placebo</td><td>0 mg</td><td>Q12H</td><td>Oral</td><td>5 days (10 doses total)</td><td>Placebo</td></tr>
<tr><td colspan="7">Admin.=administration; MOV=molnupiravir; Q12H=once every 12 hours</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2 groups (1 active and 1 control)</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will be in the study for ~35 days from the time the participant provides documented informed consent through the final contact. Participants will be randomized on Day 1 and receive 10 doses of assigned blinded study intervention (administered Q12H). Participants will be followed through Day 29 after randomization.</td></tr>
</table>

Study Governance Committees:

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

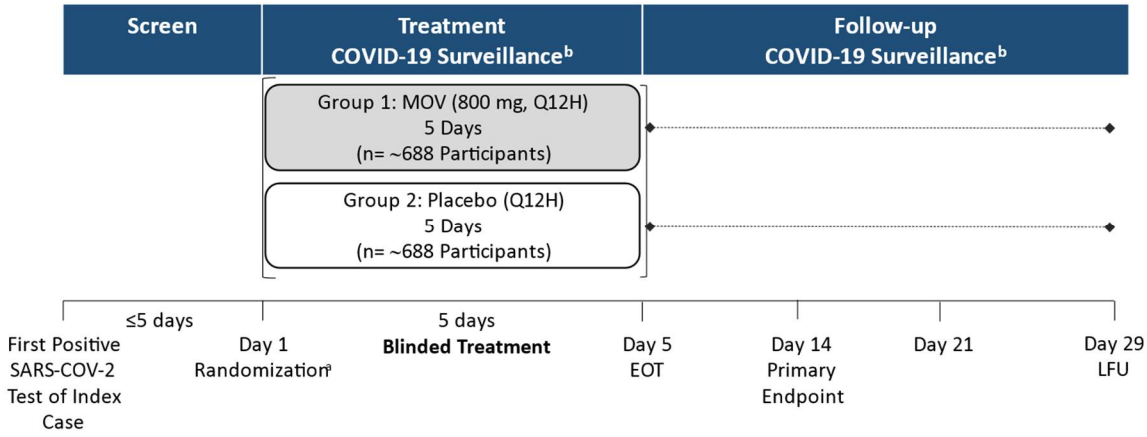
Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 MK-4482-013 Study Design



COVID-19=coronavirus infectious disease 2019; EOT=end of treatment; LFU=Late Follow-up Visit; MOV=molnupiravir; Q12H=administered once every 12 hours; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

[a] Eligible participants (household contacts of index cases) who do not have confirmed or suspected COVID-19 at the time of screening and randomization will be randomized within 5 days of both the time of sample collection for the index case's first detectable SARS-CoV-2 test result and time of onset of the index case's COVID-19 symptoms. Index cases will not be randomized to receive study intervention; however, these individuals will be requested to provide documented informed consent/assent to allow for the collection of information related to COVID-19.

[b] Active surveillance will be conducted in this study for onset of symptoms attributable to COVID-19. Participants will be instructed to contact study personnel if they develop 1 or more symptoms of suspected COVID-19 (listed in the Symptom Diary) at any time through Day 29. If a participant reports qualifying symptoms of suspected COVID-19, a COVID-19 Confirmation Visit should be scheduled to occur as soon as possible, but within 3 days of symptom onset.

1.3 Schedule of Activities

1.3.1 Schedule of Activities for Randomized Participants

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Administrative Procedures								
Informed Consent	X							Documented informed consent must be provided. See Section 8.1.1.
Informed Consent for Future Biomedical Research	X							Participation in Future Biomedical Research is optional. See Section 8.1.1.2.
Register Study Visit in IRT	X	X						
Inclusion/Exclusion Criteria	X	X						Participants must not have confirmed or suspected COVID-19 at the time of screening and randomization.
Participant Identification Card	X	X						Add randomization number to the card at randomization.
Medical History	X	X						Includes prior medical history of COVID-19. See Section 8.1.4 for all reporting criteria.

Study Period:	**Screening**	**Intervention**		**Follow-up**				**Notes**
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	Record the following: • Prior or concomitant COVID-19 vaccine. • Concomitant COVID-19 medication for participants with laboratory-confirmed COVID-19. See Section 8.1.5 for all reporting criteria.
Study Intervention Randomization		X						
Dispense Study Intervention and Participant Study Supplies		X						Includes Study Medication Diary and Symptom Diary.
MOV or Placebo Administration		<=== X ===>						• All efforts should be made to administer the first dose on Day 1 (randomization). • Administration of the first dose must be within 24 hours after randomization.
Completion of Study Medication Diary		<=== X ===>						Complete Study Medication Diary daily.
Reminder for Study Medication Diary Completion		<=== X ===>						Reminders from site personnel should be performed daily during the treatment period.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Study Medication Reconciliation			X	X				Study medication reconciliation is required at the Day 14 visit if EOT is completed after the Day 5 visit.
Study Staff Review and Collection of Study Medication Diary			X	X				Study Medication Diary will be collected after the last dose of study intervention (either Day 5 or Day 14 visit, if EOT is completed after the Day 5 visit).
Efficacy Procedures								
Completion of Symptom Diary		<========== X==========>					X	Complete daily from Day 1 (predose) through Day 29 to confirm the presence/absence and severity of targeted COVID-19 symptoms. See Section 8.2.1.
Reminders for Symptom Diary Completion		<====== X======>			X	X		Reminders from site personnel should be performed: • Daily during treatment period and every other day from EOT through Day 14 to a participant or 1 participant who represents the household. • Weekly after Day 14. See Section 8.2.1.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Investigator Assessed Signs		X	X	X		X	X	Investigator or designee will assess the participant's ability to undertake personal usual activities (ie, activities of daily living) and assess shortness of breath at rest and with exertion.
Study Staff Review and Collection of Symptom Diary		X	X	X	X	X	X	• Completed pages of Symptom Diary will be collected at clinic visits. • Symptom Diaries completed after Day 29 will be returned to the site as allowed per local guidelines.
Monitoring for Symptoms for COVID-19		X	X	X	X	X		Participants should be reminded at all visits to contact the site if they develop symptoms of suspected COVID-19.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
NP Swabs[f] for Viral Testing/Quantification		X	X	X		X	X	• NP swabs at the Day 1, Day 5, Day 14, and Day 29 visits should be collected from all participants. • NP swabs for confirmation of COVID-19 should be collected from all participants who develop qualifying symptoms of COVID-19 through Day 29. • NP swab must be collected by site personnel or medically qualified designee. • If an additional sample is collected for testing per local guidelines, the swab sample for central laboratory testing should be collected first.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Prophylaxis Outcome Assessment				X		X	X	Assess for all participants whether a clinical success (no laboratory-confirmed COVID-19), failure (laboratory-confirmed COVID-19), or indeterminate. At the COVID-19 Confirmation Visit, assess only for participants who develop laboratory-confirmed COVID-19 with symptoms. See Section 8.2.6.
Hospitalization Status			X	X	X	X		Collect from all participants.
Survival Status						X		Collect from all participants.
Health care Utilization for COVID-19			X	X	X	X	X	Collect only from participants with laboratory-confirmed COVID-19.
Assessment for Severity of COVID-19 (NIAID Scale)			X	X	X	X	X	Collect only from participants with laboratory-confirmed COVID-19.
EuroQoL EQ-5D-5L Questionnaire		X	X	X		X		Collect from all participants.
Safety Procedures								
Directed Physical Examination	X	X	X				X	Including height and weight at screening only
Vital Signs	X	X	X	X			X	Heart rate, blood pressure, respiratory rate, temperature.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Blood Collection for Local Laboratory Evaluation	X [g]							
Blood Collection for Central Laboratory Evaluation[h] (Hematology and Chemistry)		X	X	X				Any laboratory test with a result considered abnormal and clinically significant should be repeated until the result returns to normal or baseline, or a new baseline is established, as determined by the investigator. See Section 8.3.3.
Pregnancy Test (WOCBP only)	X [g, h]			X				Pregnancy test at screening may be a urine or serum test. If it is a urine test, it should be sensitive enough to detect 25 mIU/mL hCG. Day 14 (Visit 4) test must be a serum pregnancy test.
Confirm Contraception Requirements (WOCBP and Male Participants)	X	X	X	X	X	X	X	
Pregnancy Follow-up						X		Request pregnancy status of female participant or female partner of male participants. See Section 8.3.5.
AE/SAE Review	X	X	X	X	X	X	x	AEs, SAEs, and other reportable events (eg, pregnancy) will be reported according to Section 8.4.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit
Pharmacodynamics/ Biomarkers								
Anti-SARS-CoV-2 Antibody Serology Testing[i]		X		X		X		Collect predose at the Day 1 visit from enrolled participants only.
Blood (DNA) for Future Biomedical Research		X						Collect predose from enrolled participants only. See Section 8.10

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19=coronavirus disease 2019; CRF=case report form; DNA=deoxyribonucleic acid; EOT=end of treatment (day of last study intervention dose); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IRT=intervention randomization system; LFU=Late Follow-Up; MOV=molnupiravir; NIAID=National Institute of Allergy and Infectious Diseases; NP=nasopharyngeal; rand=randomization; RNA=ribonucleic acid; RT-PCR=reverse transcription polymerase chain reaction; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WOCBP=women of childbearing potential.

[a] Eligible participants (household contacts of index cases) who do not have confirmed or suspected COVID-19 at the time of screening and randomization will be randomized within 5 days of both the time of sample collection for the index case's first detectable SARS-CoV-2 test result and time of onset of the index case's COVID-19 symptoms.

[b] Screening and Day 1 (randomization) may occur on the same day. Study assessments should not be duplicated if screening and Day 1 (randomization) are completed on the same day. Blood collection for central laboratory evaluation is still required if local laboratory evaluation is conducted.

[c] Participants should contact study personnel if they develop 1 or more symptoms of suspected COVID-19 (as listed in the Symptom Diary) at any time through Day 29. If a participant reports qualifying symptoms of suspected COVID-19 (see Section 8.2.2), a COVID-19 Confirmation Visit should be scheduled to occur as soon as possible, but within 3 days of symptom onset (see Section 8.2.3). A participant may have more than one COVID-19 Confirmation Visit.

[d] If circumstances do not support a clinic visit, a home visit or visit to an alternate site may be performed, if allowed by local regulations. In the case of a home visit or visit to an alternate site, all indicated study procedures should be completed, including NP swab collection for SARS-CoV-2 RT-PCR testing and blood collections. The procedures may be conducted by site personnel or their medically qualified designee, as applicable.

[e] When a virtual visit is designated, a clinic or home visit/visit to alternate site is not required. The choice to conduct a virtual visit, rather than a clinic or home visit/visit to an alternate site, is at the investigator's discretion.

Study Period:	Screening	Intervention		Follow-up				Notes
Visit Number/Name:	1 [a,b]	2 [a,b]	3	4	5	6	COVID-19 Confirmation Visit [c]	
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Type of Visit	C [d]	C [d]	C [d]	C [d]	V [e]	C [d]	C [d]	C = Clinic Visit V = Virtual Visit

[f] Leftover isolates from NP swab will be stored for future biomedical research if the participant provides documented informed consent; see Section 8.10.

[g] In participants with reported history of HBV or HCV, ALT and AST must be available within 5 days prior to administration of the first dose of study intervention to support determination of eligibility. In WOCBP, a negative local pregnancy test is required within 24 hours prior to administration of the first dose of study intervention per inclusion criteria. All other inclusion/exclusion criteria determination (eg, HIV status) can be based on participant-reported medical history, available medical records, and the most recently available laboratory results for the participant (eg, HIV RNA viral load). See Appendix 7 for country-specific requirements.

[h] Local laboratory assessment of protocol-required safety laboratory assessments (chemistry, hematology, and pregnancy) may be permissible under extenuating circumstances. Sponsor approval must be obtained, and results must be recorded in the appropriate case report form. Blood collection should take place predose at Day 1 visit.

[i] Leftover serum will be stored for future biomedical research if the participant provides documented informed consent; see Section 8.10.

1.3.2 Schedule of Activities for Index Cases

Study Period:	Screening	Intervention	Notes
Visit Number/Name:	1	2	
Scheduled Day (Window)	(≤5 days prior to randomization of participant[s] [a])	Day 1	
Type of Visit	C [b]/V [c]	N/A	C = Clinic Visit V = Virtual Visit
Administrative Procedures			
Informed Consent/Assent	X		Documented informed consent/assent must be provided. See Section 8.1.1.
Register Study Visit in IRT	X		
Study Allocation		X	Each index case will receive an allocation number. They will not be randomized to receive study intervention.
Report Current (and Any Prior) COVID-19 Diagnosis Information and Date of COVID-19 Onset	X		See Section 8.1.2 and Section 8.1.4.
Report Prior COVID-19 Vaccination and All COVID-19 Medications	X		See Section 8.1.5.1.
NP or OP Swabs for Viral Testing/Quantification	X		• Optional NP or OP swab may be collected at the time of screening. *Note: Test is separate from the first detectable SARS-CoV-2 test result required for index cases prior to randomization of participants (Section 5.1).* • NP swab is preferred; however, OP swabs are acceptable for index cases only.

COVID-19=coronavirus disease 2019; IRT=intervention randomization system; N/A=not applicable; NP=nasopharyngeal; OP=oropharyngeal; rand=randomization; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

[a] The participant(s) is the household contact(s) of the index case.

[b] If circumstances do not support a clinic visit, a home visit or visit to an alternate site may be performed, if allowed by local regulations. In the case of a home visit or visit to an alternate site, all indicated study procedures should be completed. The procedures may be conducted by site personnel or their medically qualified designee, as applicable.

[c] For index cases who do not provide documented informed consent/assent for the optional NP or OP swab for viral testing/quantification, a virtual visit may be conducted. Documented informed consent/assent (as indicated in the Schedule of Activities) must be provided for data collection from these individuals.

2 INTRODUCTION

MOV (also known as molnupiravir [rINN] or MK-4482; formerly EIDD-2801) is a novel ribonucleoside analog prodrug with broad-spectrum antiviral activity against a range of RNA viruses, including coronaviruses. MOV is being developed as an oral prophylactic for COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) in initially asymptomatic individuals ≥18 years of age residing with a person with COVID-19 (defined as the index case).

2.1 Study Rationale

COVID-19, a disease resulting from SARS-CoV-2 infection, was declared a global pandemic by the WHO on 11-MAR-2020. Within 4 months of that declaration, there were over 11 million cases of COVID-19 reported globally and more than 500,000 associated deaths [World health Organization 2020]. As of early JUN 2021, more than 170 million confirmed cases of SARS-CoV-2 infection and over 3.5 million COVID-19-related deaths have been reported globally [Johns Hopkins University & Medicine 2021]. SARS-CoV-2 variants of concern (ie, B.1.1.7, B.1.351, or P1) have been associated with gradual increase in the frequency of global COVID-19 cases and hospitalizations observed since late 2020 in Western Europe and South Africa, and early 2021 in the US [Kirby, T. 2021] [Lauring, A. S. 2021]. There is a high unmet medical need for new, effective therapies and prophylactics.

Household contacts living with a SARS-CoV-2-infected individual are at elevated risk of developing COVID-19 due to their extended close proximity with this individual who is shedding virus. Estimates of the secondary attack rate (ie, risk of onset of COVID-19) for household contacts vary widely between individual studies, but 2 meta analyses have generated pooled estimates of approximately 17.1% and 18.1% [Fung, H. F., et al 2020] [Koh, W. C., et al 2020]. This relatively high secondary attack rate, combined with the known risks of poor outcome associated with COVID-19 [Richardson, S., et al 2020], supports the development of drugs for postexposure prophylaxis for close contacts of an index case.

Notably, while asymptomatic index patients have been documented to contribute to SARS-CoV-2 spread, estimates of secondary attack rates for symptomatic individuals are markedly higher than for asymptomatic individuals as demonstrated by a relative risk of 3.23 (95% CI: 1.46, 7.14) [Luo, L., et al 2020] [Koh, W. C., et al 2020]. Data also suggest a higher vulnerability among the elderly population compared with other household members [Madewell, Z. J., et al 2020]. Emerging evidence on secondary attack rates in the transmission of SARS-CoV-2 infection presents a compelling case that asymptomatic and presymptomatic individuals are the major drivers of the COVID-19 pandemic and argues for reassessment of public health strategies. Targeted antiviral prophylaxis for household residents of the index case, with the aim to lessen human-to-human transmission, is one prevention strategy that has not been fully explored in reducing the public health burden associated with SARS-CoV-2 infection. For these reasons, the population selected for this study comprises asymptomatic housemates of individuals with COVID-19.

Although multiple vaccines are currently being distributed and a global effort is underway to vaccinate the population as rapidly as possible, chemoprophylaxis is anticipated to remain an ongoing need. Clinical data have suggested very high rates (>90%) of efficacy for at least some of the available vaccines, whereas others have shown lower efficacy rates, particularly for preventing mild disease [Baden, L. R., et al 2021] [Voysey, M., et al 2021] [Polack, F. P., et al 2020]. Additionally, emerging variants are appearing, such as the B.1.351 variant identified in South Africa, which has been shown to be poorly neutralized by antispike monoclonal antibodies and convalescent serum [Wibmer, C. K., et al 2021]. Recent evidence has suggested that vaccine protection may be reduced, perhaps substantially, against this variant [Kustin, T., et al 2021]. Based on its mechanism of action (Section 2.2.1), MOV is expected to remain active against emerging SARS-CoV-2 spike protein variants capable of evading monoclonal antibodies and vaccine-induced immunity. Therefore, MOV may be an effective means to prevent illness after exposure to SARS-CoV-2, including SARS-CoV-2 variants with spike gene mutations for which current vaccines may not provide protection.

MOV is a novel drug candidate with demonstrated activity against SARS-CoV-2 in vitro, efficacy against coronaviruses in animal models, and a high barrier to viral resistance. MOV has been generally safe and well tolerated to date in completed and ongoing clinical studies for treatment of COVID-19 in adults. In this study, the safety and efficacy of MOV for prophylaxis against COVID-19 in participants residing in the same household with individuals with COVID-19 will be evaluated.

2.2 Background

Refer to the IB for detailed background information on MOV.

2.2.1 Pharmaceutical and Therapeutic Background

MOV is a novel, broadly active, direct-acting antiviral that has been shown to inhibit replication of viral pathogens from multiple RNA virus families in vitro, including the highly pathogenic coronaviruses (SARS-CoV-2, MERS-CoV), as well as influenza virus, RSV, filoviruses, flaviviruses, chikungunya virus, and alphaviruses. The prodrug is orally administered and rapidly absorbed in the gut where it is hydrolyzed to the parent nucleoside analog β-D-N^4-hydroxycytidine (NHC), which is widely distributed to tissues (including lungs and brain) and metabolized to the pharmacologically active triphosphate form (NHC-TP). The NHC-TP is incorporated into the viral RNA by the viral RNA polymerase, leading to an inhibition of viral replication by error catastrophe. Viral error catastrophe, a concept that is predicated on increasing the viral mutation rate beyond a biologically tolerable threshold, results in impairment of viral fitness leading to viral extinction. This mechanism is distinct from that of remdesivir where its incorporation into nascent RNA results in premature termination of RNA synthesis, halting growth of the RNA strand after a few more nucleotides are added [Gordon, C. J., et al 2020].

NHC has demonstrated a high barrier to the development of resistance in vitro that is anticipated to slow or prevent emergence of viral resistance in humans. NHC has also demonstrated in vitro activity against remdesivir-resistant SARS-CoV-2 and a related coronavirus (mouse hepatitis virus) with F476L and V553L mutations in the viral RNA

polymerase (RdRp). Given the unique mechanism of action, NHC is expected to be active against viruses resistant to other antiviral agents as well as emerging SARS-CoV-2 variants of concern with spike protein mutations.

MOV is unlikely to be a victim or perpetrator of CYP-related DDIs based on its anticipated metabolic pathways and lack of CYP inhibition/induction in vitro. A DDI between MOV and remdesivir is also not expected, given these 2 prodrugs are cleaved in distinct locations (gut versus target cells) and the exposure of their active triphosphate metabolites in cells are regulated by different enzymes in 2 distinct nucleotide pathways (pyrimidine versus purine). To evaluate possible interactions of approved antiviral drugs on the activity of MOV, in vitro drug-drug combination studies were performed. SARS-CoV-2 infected Vero cells were treated with NHC (MOV parent) in combination with other antiviral drugs including remdesivir, tenofovir, lamivudine, emtricitabine, abacavir, nelfinavir, ribavirin, sofosbuvir, and hydroxychloroquine, and antiviral activity and cellular toxicity were assessed. Results demonstrated no significant interaction (synergistic or antagonistic) of any drug tested on the antiviral activity or toxicity profile of NHC in this culture system.

2.2.2 Preclinical and Clinical Studies

Refer to the IB for information on preclinical and clinical studies conducted with MOV.

2.2.3 Clinical Studies

2.2.3.1 Completed Clinical Studies

The following clinical studies are either complete or clinically complete; further details are provided in the IB.

- MK-4482-004 (EIDD-2801-1001; NCT04392219) was a Phase 1, randomized, double-blind, placebo-controlled SAD/MAD study to evaluate the safety, tolerability, and PK of MOV in healthy adult male and female (nonchildbearing potential) participants [Painter, W. P., et al 2021]. This study is complete; a total of 130 healthy participants were enrolled, of whom 100 received at least 1 dose of MOV orally (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). MOV was generally well tolerated. No deaths or SAEs were reported. One participant discontinued from study treatment after receiving MOV 800 mg Q12H for 3 days (6 doses) due to an AE of mild rash, considered related to study treatment by the investigator. No clinically meaningful hematological laboratory test result abnormalities were observed. Overall, no clinically meaningful trends were observed for changes in clinical laboratory values, vital signs, or ECGs as a function of dose or treatment.

  Results indicate linear PK that is dose-proportional, with single-dose PK exposure predictive of multidose exposure. No accumulation was observed following multiple doses. The nucleoside metabolite (NHC) has a short effective plasma half-life (~1 hour), which results in minimal accumulation after multiple dosing with a longer terminal phase

characterized by a half-life of up to ~19 hours. MOV can be dosed without regard to food; no significant food effect was observed with a single MOV 200-mg dose.

- MK-4482-006 (EIDD-2801-2003; NCT04405570) 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 study is complete. A total 204 participants were randomized; of these participants, 140 received at least 1 dose of MOV (23 in the 200 mg BID group, 62 in the 400 mg BID group, and 55 in the 800 mg BID group) and 62 received placebo. Virology data from this study showed a reduction in recovery of infectious virus in MOV-treated participants compared with placebo recipients at Day 5. MOV was generally well tolerated with a comparable incidence of AEs across the intervention groups. The most frequently reported AEs (>2%) in the MOV groups combined were headache (4.3%), ALT increased (2.9%), insomnia (2.9%), dizziness (2.1%), and AST increased (2.1%). The most frequently reported AEs (>2%) in the placebo group were insomnia (6.5%), headache (4.8%), and ALT increased (3.2%). There were no drug-related AEs leading to study intervention discontinuation, no deaths, no drug-related SAEs, and no drug-related Grade 3 or higher AEs.

- Two Phase 2/3 randomized, double-blind, placebo-controlled studies are now clinically complete in hospitalized (MK-4482-001; MOVe-IN) and nonhospitalized (MK-4482-002; MOVe-OUT) adults with COVID-19 to evaluate the efficacy, safety, and PK of MOV (Q12H for 5 days). Enrollment in Part 1 (Phase 2) of each of these studies has been completed, as well as Part 2 (Phase 3) of study MK-4482-002. A summary of interim data from MK-4482-001 and MK-4482-002 that supports dose selection for MK-4482-013 is provided in Section 4.3.1 of this protocol. Summaries of safety data for MK-4482-001 and MK-4482-002 are provided below.

- MK-4482-001 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. The overall safety profiles observed in P001 were generally comparable for MOV doses and placebo. No trends in AEs or changes in clinical laboratory values were observed as a function of dose or study intervention. The most frequently reported AEs (≥5%) in any MOV group were COVID-19, AST/ALT elevations, constipation, bacterial pneumonia, hyperglycemia, and respiratory failure. The most frequently reported AEs (≥5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased, and respiratory failure. SAEs were reported for 15.4% participants (15.1% participants in the MOV groups combined and 16.0% in the placebo group). One drug-related (as per investigator) SAE (Grade 3 urticaria) was reported for 1 participant (MOV 200 mg). A total of 16 participants had AEs leading to death (6.4% in the MOV groups combined and 2.7% in the placebo group). Most deaths occurred in participants who had severe COVID-19 at baseline (12 of 16), were >60 years of age (13 of 16), had underlying comorbidities (14 of 16), and/or had duration of COVID-19 symptoms >5 days before randomization (12 of 16). None of the deaths were considered drug-related per 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 Part 2.

- MK-4482-002 Part 1: A total of 225 nonhospitalized participants with COVID-19 received at least 1 dose of MOV (74 received at least 1 dose of MOV 800 mg) and 74 participants received placebo in the APaT population. The safety profiles for MOV (all doses) and placebo were comparable. No trends in AEs or changes in clinical laboratory values were observed as a function of dose or study intervention. The most frequently reported AEs (≥5%) were COVID-19 pneumonia in any MOV group and diarrhea and COVID-19 in the placebo group. The percentage of participants with drug-related AEs per the investigator was comparable across all intervention groups. SAEs were reported for 3.6% participants in the MOV combined group and for 5.4% participants in the placebo group. No SAEs were considered drug-related per investigator. Efficacy data are summarized in Section 4.3.1.

- MK-4482-002 Part 2: a total of 1411 nonhospitalized participants with COVID-19 received at least 1 dose of study intervention and were included in the APaT population (710 participants in the MOV group and 701 in the placebo group). The percentage of participants with at least 1 AE was comparable between the MOV and placebo groups (30.4% and 33.0% participants, respectively). The observed percentages of participants with SAEs, SAEs leading to discontinuation of study intervention, and AEs leading to death were lower in the MOV group compared with the placebo group. AEs leading to death were reported for 2 (0.3%) participants in the MOV group and 12 (1.7%) participants in the placebo group. No participant in the MOV group had laboratory values that met the predefined ECI criteria for potential DILI or for platelet count of <50,000 cells/μL). In this study, treatment with MOV was shown to significantly reduce the risk of hospitalization or death through Day 29. These results are described in Section 2.3.

2.2.3.2 Ongoing Clinical Studies

The following clinical studies are ongoing; further details are provided in the IB.

- MK-4482-005 (AGILE-ACCORD CST-2 EIDD-2801) is an ongoing Phase 1/2 randomized, adaptive design study to evaluate the safety, and efficacy of MOV for the treatment of adults with COVID-19. Enrollment in the Phase 1 component of the study is complete; 18 participants were randomized in a 4:2 ratio in 3 dosing cohorts (6 participants each) and received MOV 300, 600 or 800 mg or control (standard of care) Q12H for 5 days. The incidence of AEs in participants who received MOV across the 3 cohorts was low. As of 18-SEP-2021, 114 of 180 participants have been enrolled in the Phase 2 component of the study and received MOV (800 mg) or placebo Q12H for 5 days. Five participants (4.4%) had SAEs (considered related to study intervention by the investigator for 2 participants). No deaths were reported.

- MK-4482-007 (EIDD-2801-2004; NCT04405739) is an ongoing Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of 5 days of MOV in hospitalized adults with COVID-19. As of 18-SEP-2021, 65 of 80 participants were enrolled and received 200 mg or 400 mg MOV or placebo Q12H for 5 days. Ongoing Sponsor review of blinded clinical and laboratory data indicate that MOV is generally well tolerated. No significant safety concerns were observed based on the second interim analysis (n=52). There was 1 AE leading to discontinuation which was considered related to study medication. SAEs were reported for 4.6% of participants; none were considered related to study intervention by the investigator. One participant had an AE leading to death (not related to study intervention per investigator assessment). No participant experienced a Grade 3 elevation of lipase or a platelet count <50,000 cells/μL.

2.3 Benefit/Risk Assessment

MOV has demonstrated activity against SARS-CoV-2 in vitro, efficacy against coronaviruses in animal models, and a high barrier to viral resistance in vitro. Data from Phase 2 studies in participants with COVID-19 have shown that treatment with MOV results in an antiviral effect, including reduction in viral load and in infectious virus as well as a higher percentage of mutations in viral RNA posttreatment consistent with the mechanism of action (ie, viral error catastrophe). An interim analysis (IA4) for study MK-4482-002 evaluated efficacy in 762 nonhospitalized participants with mild to moderate COVID-19, with at least 1 risk factor for severe disease. These results showed that the percentage of participants who were hospitalized or died through Day 29 in the MOV group (7.3%) was statistically significantly lower than in the placebo group (14.1%). Treatment with MOV resulted in a 6.8 percentage point reduction [95% CI: -11.3, -2.4; p=0.0012] in the risk of hospitalization or death through Day 29 compared with placebo (approximately 50% relative risk reduction). MOV met the protocol-defined criterion (one-sided p-value boundary <0.0092 at the IA4 timepoint) for demonstration of superiority to placebo for the primary efficacy endpoint. All 8 participants who died through Day 29 were in the placebo group and were hospitalized prior to their death. No participants in the MOV group died. In adults with mild to moderate COVID-19, treatment with MOV 800 mg Q12H for 5 days is superior to placebo in reducing hospitalization or death within 29 days of initiating study intervention. The study was stopped due to early efficacy at the interim analysis, but additional participants already enrolled were followed up to completion. An efficacy analysis that included the full randomized population (N=1408) was supportive of the earlier results, with the percentage of participants who were hospitalized or died through Day 29 in the MOV group being lower than in the placebo group (6.8% vs 9.7%, difference -3.0%, 95% CI: -5.9, -0.1; p=0.0218). Of the 10 participants who died through Day 29, 9 were in the placebo group versus 1 in the MOV group.

As noted in Section 2.1, individuals living with a person with COVID-19 are at elevated risk of becoming infected with SARS-CoV-2 and developing symptoms, which can range from mild to severe or even life-threatening disease. Although this study is designed to evaluate efficacy for prevention of COVID-19 and no clinical benefit can be guaranteed, preclinical and clinical data support the hypothesis that a short prophylactic regimen of MOV may

provide benefit to asymptomatic household members by reducing their likelihood of developing COVID-19.

The integrated assessment of the mutagenic and genotoxic potential of MOV detailed in the IB indicates that MOV is not mutagenic or genotoxic in in vivo mammalian systems. Based on the totality of the genotoxicity data, MOV is of low risk of genotoxicity in clinical use. MOV was devoid of effects on CNS, respiratory, or cardiovascular functions in well-characterized safety pharmacology models. Key target organs of toxicity identified in the GLP repeat-dose toxicity studies were limited to bone marrow in dogs only, and bone and cartilage in rats only.

In a 28-day repeat-dose toxicity study of MOV in dogs, mild hematologic toxicity was noted after Day 7 at exposures with a NOAEL (6 mg/kg/day) 0.13-fold the anticipated clinical exposure of the 800 mg Q12H dose. These changes were fully reversible. No clinically significant abnormalities in hematological laboratory tests as a function of either dose or treatment were observed in available unblinded data from the clinical development program for MOV. For the treatment and prevention of COVID-19 in clinical studies, MOV duration is limited to 5 days.

In a 3-month toxicity study in rats, increased thickness of physeal and epiphyseal cartilage was observed, with the exposure at the lowest observed effect level of 500 mg/kg/day being approximately 5.4-fold above the 800 mg Q12H clinical exposure. These findings do not represent a risk for adult humans 18 years of age or older because physeal/epiphyseal growth cartilage in growing rats is not present in adult humans.

No bone findings were observed in rats dosed for 1 month up to 500 mg/kg/day (female/male ~4/8-fold above the 800 mg Q12H dose), dogs dosed for up to 14 days at 50 mg/kg/day (1.6-fold above the human AUC exposure at 800 mg Q12H), or rasH2 wild-type mice dosed at 2000 mg/kg/day (18-fold above the human AUC exposure at 800 mg Q12H).

EFD studies in rats with MOV demonstrated test article-related postimplantation losses; fetal abnormalities (malformations and variations) and evidence of growth delay at 1000 mg/kg/day (7.5-fold relative to the human AUC exposure at 800 mg Q12H); and reduced fetal growth at 500 mg/kg/day (2.9-fold relative to human AUC exposure at 800 mg Q12H). In the definitive EFD study in rabbits, MOV-related developmental toxicity occurred at 750 mg/kg/day (18-fold relative to the human AUC exposure at 800 mg Q12H) and was limited to reduced mean fetal body weights. In WOCBP, a sensitive test will be used to rule out pregnancy prior to study enrollment, and adherence to highly effective contraceptive measures will be required for 4 days (5 plasma half-lives of NHC) after receiving the last dose of study intervention.

A total of 1393 adults received at least 1 dose of MOV in P002 (Parts 1 and 2), P006, P001, and P004. Of these, 917 participants received at least 1 dose of MOV 800 mg in a dosing regimen of Q12H for 5 days. MOV (800 mg Q12H for 5 days) was generally well tolerated with no major safety concerns identified. There was no evidence of hematologic toxicity for MOV doses ranging between 200 mg and 800 mg Q12H for 5 days based on laboratory evaluations.

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the IB and informed consent documents. It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation because clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Given the antiviral activity of MOV, the anticipated short duration of treatment (5 days), and the totality of available preclinical and clinical data, MOV is considered to have a benefit/risk profile that supports further clinical development as a potential prophylactic for laboratory-confirmed COVID-19.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Objectives will be evaluated in participants ≥18 years of age who do not have confirmed or suspected COVID-19 at the time of screening and randomization and are residing with an individual (of any age) with COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms), defined as the index case.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of molnupiravir (MOV) compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline nasopharyngeal (NP) swabs. • *Hypothesis: MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline NP swabs.*	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate the safety and tolerability of MOV compared with placebo.	• Adverse events • Adverse events leading to discontinuation of study intervention

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants regardless of SARS-CoV-2 results in baseline NP swabs. • Hypothesis: MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in all participants regardless of SARS-CoV-2 results in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 29 in participants with undetectable SARS-CoV-2 in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate prevention of viral transmission through Day 14 for MOV compared with placebo in participants with undetectable SARS-CoV-2 in baseline NP swabs.	• SARS-CoV-2 RNA
• To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with detectable SARS-CoV-2 in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)

Objectives	Endpoints
Exploratory	
• To evaluate the efficacy of MOV compared with placebo for the prevention and laboratory-confirmed COVID-19 through Day 29 in participants regardless of SARS-CoV-2 results in baseline NP swabs.	• COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
• To evaluate the prevention of viral transmission through Day 29 for MOV compared with placebo in participants with undetectable SARS-CoV-2 in baseline NP swabs.	• SARS-CoV-2 RNA
• To evaluate the development of anti-SARS-CoV-2 antibodies through Day 29 in MOV recipients compared with placebo in baseline seronegative participants with undetectable SARS-CoV-2 RNA in baseline NP swabs.	• Anti-SARS-CoV-2 antibodies
• To evaluate the severity of laboratory-confirmed COVID-19 through Day 29 for MOV recipients compared with placebo recipients.	• NIAID ordinal scale criteria for COVID-19 severity
• For participants who develop laboratory-confirmed COVID-19 on or before Day 14, to describe the severity and/or presence of COVID-19 symptoms for MOV recipients compared with placebo recipients through resolution of symptoms or Day 29, whichever is first.	• Participant-reported symptoms severity (for specified COVID-19 symptoms)
• For participants with detectable SARS-CoV-2 in NP swabs at baseline, to evaluate the antiviral activity of MOV compared with placebo as assessed by the change from baseline in SARS-CoV-2 RNA titer and percentage of participants with undetectable SARS-CoV-2 RNA in NP swabs at Day 14.	• Quantitative SARS-CoV-2 RNA

Objectives	Endpoints
• For participants who develop laboratory-confirmed COVID-19 on or before Day 14, to evaluate the effect of MOV on viral RNA mutation rate and detection of treatment-emergent sequence variants as assessed by comparison of viral gene sequencing in virus isolated at baseline and post-baseline in samples with evaluable SARS-CoV-2 RNA.	• Viral RNA Sequences
• For participants who develop laboratory-confirmed COVID-19 on or before Day 14, to evaluate the prevention or reduction of health care utilization related to COVID-19 through Day 29 for MOV recipients compared with placebo recipients.	• Medically attended COVID-19
• To evaluate the impact of MOV on generic health-related quality-of-life through Day 29 in participants who do not have confirmed or suspected COVID-19 at the time of screening and randomization and are residing with an individual with COVID-19.	• EuroQoL Five Dimension Questionnaire (EQ-5D-5L) score

4 STUDY DESIGN

4.1 Overall Design

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.

This is a Phase 3, randomized, placebo-controlled, double-blind, multi-site study (MOVe-AHEAD) to evaluate the efficacy and safety of MOV to prevent COVID-19 in participants ≥18 years of age residing with an individual (no age requirement) with COVID-19 (defined as the index case). Eligible participants who do not have confirmed or suspected COVID-19 at the time of screening and randomization will be randomized within 5 days of both the time of sample collection for the index case's first detectable (ie, positive) SARS-CoV-2 test result and time of onset of the index case's COVID-19 symptoms.

All index cases will be requested to provide documented informed consent/assent for the collection of specific data regarding the diagnosis and time of onset of COVID-19 as well as

demographics, history of prior COVID-19 vaccination, and medication for COVID-19 at the time of screening. Index cases will not be randomized to receive study intervention nor have any study specific assessments or procedures conducted other than an NP or OP swab collected at the time of screening for viral testing/quantification and SARS-CoV-2 genome sequencing for genetic lineage identification. This NP or OP swab is not required for participation of the household contacts; however, it is highly encouraged for complete virologic assessment.

Approximately 1376 participants will be randomized in a 1:1 ratio to receive blinded MOV (800 mg) or blinded placebo by oral administration Q12H (±2 hours) for 5 days (Figure 1). The primary objective of the study will be assessed in participants who have undetectable SARS-CoV-2 in NP swabs at baseline. Assuming approximately 80% of the 1376 participants will have no detectable SARS-CoV-2 at baseline (see Section 4.2.3), approximately 1100 participants will have undetectable SARS-CoV-2 at baseline.

Randomization will be stratified by 1) age category (≤60 vs >60 years) and 2) household size (≤3 vs >3 household residents; all residents, including the index case, are counted regardless of whether they are participating in the study.

All participants will be provided with a Study Medication Diary in which dose administration will be recorded daily for 5 days.

Active surveillance will be conducted in this study for onset of symptoms attributable to COVID-19 as follows:

- Participants will monitor themselves for new onset or marked worsening of symptoms attributable to COVID-19 through the duration of the study. Participants should be reminded by study personnel at weekly visits indicated in the SoA (Section 1.3.1) to actively monitor for symptoms.

- Participants will receive a Symptom Diary in which the presence/absence and severity of a solicited list of symptoms attributable to COVID-19 should be recorded daily through Day 29 (see Section 8.2.1).

- Participants will be instructed to contact study personnel if they develop 1 or more symptoms of suspected COVID-19 (listed in the Symptom Diary) at any time through Day 29. If a participant reports qualifying symptoms of suspected COVID-19 (see Section 8.2.2), a COVID-19 Confirmation Visit that includes NP swab collection for RT-PCR testing at the central laboratory should be scheduled, to occur as soon as possible, but within 3 days of symptom onset (see Section 8.2.3).

Participants with an onset of symptoms of COVID-19 during the study may receive standard of care treatment for COVID-19, as appropriate, in addition to study intervention (Section 6.5). Treatment with MOV, should it become approved for use in the participant's jurisdiction and available for administration, is not permitted for any participant in this study. (This restriction pertains to participants receiving study intervention, not index cases.)

The following will also be collected from participants at time points indicated in the SoA (Section 1.3.1):

- Any hospitalizations, for all participants. In the event of hospitalization, all evaluations outlined in the SoA (Section 1.3.1) should be performed as feasible.
- Survival status, for all participants.
- Health care utilization (ie, medically attended COVID-19) due to COVID-19, for participants with laboratory-confirmed COVID-19. Medically attended COVID-19 refers to COVID-19 for which medical attention is received during an unscheduled, nonroutine visit, such as a telemedicine visit, emergency room visit, an in-person physician office visit, an urgent care or emergency department visit, or hospitalization.
- The EQ-5D-5L questionnaire, for all participants at the Day 1, Day 5, Day 14, and Day 29 visits. The EQ-5D-5L is a standardized instrument for measuring health outcome and will be used in this study to assess the impact of MOV on participant general health status.

All AEs, SAEs, and other reportable events (eg, ECI and pregnancy) will be reported according to the time period and procedures specified in Section 8.4 and Appendix 3.

Interim Analyses

This study will include an interim analysis when approximately 55% (or approximately 600 across the MOV and placebo groups) of the participants with undetectable SARS-CoV-2 in baseline NP swabs have either completed the Day 14 visit or discontinued from the study prior to the Day 14 visit. See Section 9.7 for details of the interim analysis. An eDMC will review the data at this interim analysis. A description of the structure and function of the eDMC, along with the timing and content of the interim analysis and any other study data review, is provided in the eDMC charter. Information regarding the composition of the eDMC is provided in Appendix 1.

4.2 Scientific Rationale for Study Design

Antivirals for prevention of COVID-19 are urgently needed during this unprecedented global pandemic. This randomized, placebo-controlled, double-blind, superiority study is designed to evaluate the efficacy and safety of MOV compared with placebo for the prevention of COVID-19 in household contacts of an individual with COVID-19, in accordance with available regulatory guidance [Food and Drug Administration 2021].

The primary outcome is assessed through Day 14 to allow for a sufficient duration to reliably assess the efficacy of 5 days of MOV for prophylaxis of COVID-19. This duration of the primary outcome assessment is considered appropriate to capture important clinically relevant efficacy endpoints (eg, laboratory-confirmed COVID-19), as the reported duration of the SARS-CoV-2 incubation period is 2 to 14 days [Guan, W., et al 2020] [Li, Q., et al 2020] [Lauer, S. A., et al 2020].

AEs, SAEs, and other reportable safety events will be monitored according to Section 8.4. Final Per-Protocol laboratory assessments occur on Day 14 (9 days after the last dose of study intervention), which allows for the resolution of any abnormal laboratory values identified at the EOT (Day 5). The follow-up time period for the evaluation of safety adequately assesses treatment-emergent AEs, as there is no preclinical or clinical evidence suggesting delayed toxicity for MOV.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint for the study, COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms), was selected in accordance with the US FDA guidance on development of drug and biological products for treatment or prevention of COVID-19 [Food and Drug Administration 2021]. Development of symptomatic disease represents a clinically meaningful endpoint for participants since it demonstrates the onset of deleterious effects they can directly perceive. A COVID-19 case for the study is defined as a participant with qualifying symptoms of COVID-19 with onset through Day 14 (for the primary endpoint) and SARS-CoV-2 detected by central laboratory RT-PCR testing from a sample collected at the COVID-19 Confirmation Visit. Laboratory-confirmed COVID-19 with onset through Day 29 will also be assessed as an exploratory endpoint. The onset of COVID-19 is determined by the day of onset of symptoms, rather than the day of the COVID-19 Confirmation Visit. Therefore, the day of onset of COVID-19 symptoms supports the primary endpoint, even if the day of the COVID-19 Confirmation Visit is later than Day 14. The qualifying symptoms of COVID-19 are provided in Section 8.2.2.

The study will evaluate SARS-CoV-2 RNA as a secondary endpoint through Day 14 (and as an exploratory endpoint through Day 29) to assess the impact of MOV on preventing viral transmission in participants with undetectable SARS-CoV-2 in baseline NP swabs. Viral transmission, even in the absence of symptoms, represents an important outcome with regards to infection control. This is best evaluated via RT-PCR detection of SARS-CoV-2 RNA since nucleic acid amplification offers the most sensitive method for assessment of viral transmission. For this reason, SARS-CoV-2 RNA has been selected as the appropriate endpoint.

For participants with laboratory-confirmed COVID-19, the severity of disease will be assessed using the NIAID ordinal scale for COVID-19 severity [Beigel, J. H., et al 2020]; see Section 8.2.10. The severity endpoint (exploratory) is included since it is conceivable that prophylactic treatment may be more effective at preventing onset of more severe disease than preventing the onset of symptomatic disease of any severity, particularly as some participants will enter the study with a detectable test for SARS-CoV-2 at baseline that is identified postrandomization. While most severity scales include criteria (eg, oxygen saturation criteria) that are not readily ascertained in an outpatient population living at home, the criteria for severe disease described in the NIAID ordinal scale include hospitalization as a basic criterion for moderate to severe disease, with an additional set of criteria (eg, supplemental oxygen requirements) to further delineate severity. These features of the NIAID ordinal scale

criteria for defining disease severity are readily applicable to a population that is mostly outpatient.

In addition to severity of disease, severity of symptoms will be collected from participants in the Symptom Diary to examine potential differences between prophylaxis with MOV or placebo, since prophylaxis may be more effective in preventing severe symptoms than in preventing the onset of any symptoms at all.

4.2.1.2 Safety Endpoints

Safety evaluations include AE collection, physical examinations (including vital signs), and laboratory tests (hematology and chemistry) performed per the SoA (Section 1.3). AEs will be evaluated and assessed according to the guidelines in Section 8.4 and Appendix 3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

In the 28-day toxicity study of MOV at 17 mg/kg/day (0.4-fold relative to the clinical NHC exposure at 800 mg Q12H) administered to dogs, reversible hematologic changes consistent with bone marrow toxicity were noted on Day 7, which progressed to more severe pancytopenia after 14 to 21 days of continuous exposure. No clinically significant abnormalities in hematological laboratory tests as a function of either dose or treatment were observed in available unblinded data from the clinical development program for MOV. However, based on preclinical findings, participants in this study will be monitored for any signs of bone marrow toxicity, including monitoring of CBC and platelets after initiating study intervention.

In preclinical studies, elevated liver enzymes were noted in rats at 61-fold (female) and 91-fold (male) over the clinical NHC exposure at 800 mg Q12H and dogs at 19-fold over the clinical NHC exposure at 800 mg Q12H. No clinically significant abnormalities in liver parameters as a function of either dose or treatment were observed in available unblinded data from the clinical development program for MOV. However, elevated LFTs meeting criteria for potential DILI will be considered an ECI and closely monitored.

4.2.1.3 Virology Endpoints

The proposed exploratory virologic endpoints are aimed at assessing the antiviral activity of MOV as well as evaluating the rate of viral mutagenesis with respect to MOV treatment. Reducing SARS-CoV-2 viral load or eradicating the virus is essential to recovery and has important implications for transmission and infection control strategies. As a direct-acting antiviral, the inclusion of an exploratory endpoint evaluating the change in viral RNA titer from baseline after treatment with MOV is meaningful and consistent with the mechanism of action. Note that after randomization, some participants may be identified to have been detectable for SARS-CoV-2 at baseline; analyzing a transition to viral positivity is only meaningful in the subset of the population that is undetectable at baseline. For participants who are virus-detectable at baseline, viral quantitation can only be used to demonstrate and compare changes in viral titer after treatment.

In addition to a means of assessing the rate of viral mutagenesis, viral genome sequencing will be used to identify SARS-CoV-2 genetic lineage. Since initial identification of the original SARS-CoV-2 genotype, multiple viral variants of concern have been identified and continue to circulate worldwide. SARS-CoV-2 genotype data may be used to assess the impact of viral genotype on MOV efficacy. In addition, viral sequence data may be used to identify treatment-emergent variants that could potentially impact vaccine or antiviral drug efficacy and to further characterize the mechanism of action (viral error catastrophe) of MOV.

4.2.1.4 Serology Endpoints

Although samples for virologic testing are collected at baseline and multiple timepoints post-baseline, there is potential, especially in the case of asymptomatic infection, that transient infections with SARS-CoV-2 may occur in between planned sampling timepoints. These infections can be inferred from development of antibodies toward SARS-CoV-2. For this reason, in addition to virologic endpoints, an exploratory serologic endpoint is included.

4.2.1.5 Health Care Utilization and Health Outcomes

Health care utilization and health outcomes will be measured as exploratory endpoints in this study. Health care utilization information (ie, medically attended COVID-19, as defined in Section 4.1) will be assessed both as an indirect marker of severity (with hospitalization as part of the criteria in the NIAID ordinal scale for severity assessment in Section 8.2.10), and for a potential reduction in health care resource utilization from prophylaxis to asymptomatic individuals at high risk of acquiring COVID-19.

The EuroQoL EQ-5D-5L is a validated, standardized, 5-item health-state questionnaire applicable to a wide range of health conditions and treatments and used to assess health outcomes [The EuroQol Group 1990] [Brooks, R. 1995] [Herdman, M., et al 2011]. The 5 health-state dimensions include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The recall period is today. The EuroQoL EQ-5D-5L also includes a graded (0 to 100) 20 centimeter vertical visual analog scale (EQ VAS) on which subjects rate their current general state of health, from “the worst health you can imagine” to “the best health you can imagine.” The EuroQoL EQ-5D-5L provides a simple descriptive profile and a single index value for health status that can be used to develop health utilities or ”quality adjusted life years” for health economic analyses.

4.2.1.6 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented

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

4.2.2 Rationale for the Use of Comparator/Placebo

This study will be placebo-controlled to avoid bias in the collection/evaluation of data during study conduct and to assess whether any observed effects are treatment-related or an impact of study participation. Participants who develop symptoms attributable to COVID-19 may receive standard of care treatment (as specified in Section 6.5), as appropriate, in addition to study intervention (blinded MOV or matching placebo).

There are currently no agents approved for the prevention of COVID-19 to serve as an active comparator; therefore, placebo will be used.

4.2.3 Rationale for the Selected Participant Population

Household contacts living with a SARS-CoV-2-infected individual will comprise the participant population in this study. As noted in Section 2.1, household contacts are at elevated risk of developing COVID-19 due to their extended close proximity with this individual who is shedding virus and therefore, are potential candidates for prophylaxis with MOV.

In this study, a household is defined as a unit with shared living space(s) with no more than 10 inhabitants (ie, large communal living arrangements such as dormitories, hostels, barracks, and long-term care facilities do not qualify as households). There is no requirement that the household residents share a familial relationship.

The primary endpoint is analyzed in those without detectable SARS-CoV-2 virus at baseline (ie, the Day 1 NP swab; those with detectable virus prior to randomization are ineligible). Recent data from a study of household prophylaxis with casirivimab and imdevimab [O'Brien, M. P., et al 2021] showed that COVID-19 incidence rates are substantially higher in the population that has detectable virus via PCR at baseline than in the population that does not have detectable virus at baseline. The viral status is not known at the time of randomization due to the duration required for RT-PCR testing. Since randomization cannot therefore be stratified to assure balance between the arms, the 2 populations will be analyzed both separately and together for onset of disease. It is assumed that up to 20% of the enrolled population may have detectable virus at baseline, in consideration of the virus-positive (or viral status unknown) percentage (16.5%) reported by O'Brien [O'Brien, M. P., et al 2021] and a conservative adjustment to 20% based on the higher infectivity of more recently reported viral variants.

4.2.4 Rationale for Collection of Racial, Ethnic, and Gender Identity Data

The differential effect on the safety and efficacy based on any demographic parameter, including race, ethnicity, or gender identity, cannot be predicted when evaluating a new investigational drug. Therefore, it is important to collect race, ethnicity, and gender identity data to ensure that there is not a differential effect based on these parameters. These data will also provide assurance that the results observed in the clinical study will be representative of the drug's use in a broader patient population, including transgender people whose gender identities and/or expressions differ from the sex assigned to them at birth. Also, subgroup analyses on race and ethnicity will be performed to better understand how these parameters may influence clinical outcome and toxicity.

4.2.5 Rationale for Selected Stratification Factors

Household size has a recognized influence on secondary attack rate. Multiple studies have demonstrated a decreasing secondary attack rate observed with increasing household size [Grijalva, C. G., et al 2020] [Li, F., et al 2021] [Wu, J., et al 2020]. There is some variability between studies in whether there is an inflection point in the household size and at what household size that inflection point is; however, most show that secondary attack rates drop from 30 to 50% or more between small, 2-person households and larger households of 4 or more. Therefore, a household size of 3 has been selected as the threshold in this study for stratifying the randomization (ie, ≤3 or >3 people).

Advancing age has been noted as a risk factor for COVID-19 incidence as well as severity [Li, F., et al 2021] [Luo, L., et al 2020] [Wu, J., et al 2020], with individuals over 55 or 60 years of age having markedly higher (at least 70% higher) likelihood of acquiring COVID-19 in household or close contact settings with infected individuals than younger adults. For this reason, participant age has been selected as a second stratification variable (ie, ≤60 years or >60 years).

4.3 Justification for Dose

4.3.1 Rationale for Dose

The MOV dose for this Phase 3 study (800 mg MOV Q12H for 5 days) was selected based on interim data from other studies evaluating MOV for treatment as well as the totality of available safety, virology, PK, and clinical data from the MOV program.

The eDMC review of unblinded interim data from MK-4482-001 and MK-4482-002 concluded that there were no safety signals seen at any dose, and no dose-limiting toxicity was observed at the highest dose (800 mg). Furthermore, MOV has been generally well tolerated in other studies in the MOV program at all doses studied with no dose-limiting toxicity observed at the highest dose (800 mg).

Virology data from completed dose-ranging studies in the MOV program (MK-4482-001, MK-4482-002, and MK-4482-006) show that treatment with MOV reduces the SARS-CoV-2 viral load compared with placebo (based on change from baseline, slope of decline, and

greater percentage of participants with a viral load below the limit of quantitation within 15 or 29 days) in nonhospitalized participants enrolled in MK-4482-002 and participants with symptom onset ≤5 days in both MK-4482-001 and MK-4482-002. The exposure-response analyses for various virologic endpoints based on MK-4482-001 and MK-4482-002 suggest that the 800 mg Q12H dose provides a larger magnitude of virologic effect compared with 200 mg and 400 mg Q12H and is near the plateau of the dose response curve. In addition, consistent with the proposed mechanism of action of MOV of viral error catastrophe, the highest percentage of mutations in viral RNA posttreatment at Day 5 were observed in the 800 mg Q12H intervention group from MK-4482-001 and MK-4482-002.

Evaluation of the primary clinical efficacy endpoint for the Phase 2 portion of MK-4482-002 showed that 11 of 299 participants were hospitalized through Day 29 (including 1 participant treated with placebo who died); ~3% of participants in the MOV intervention groups were hospitalized or died through Day 29 (compared with ~5% in the placebo group). Notably, an exposure-response analyses for the endpoint of hospitalization suggested a trend of an increased clinical effect at MOV 800 mg Q12H dose over placebo or lower MOV doses.

Based on the totality of the observed safety profile and virologic data in the MOV program, and trends in clinical efficacy in MK-4482-002, the 800 mg Q12H dose was selected as the dose for further evaluation in Phase 3.

The expectation of both treatment and prophylaxis of COVID-19 using an antiviral is to prevent propagation of the virus; thus, the dose level to be used for both indications is proposed as the dose selected for treatment of symptomatic disease.

4.3.2 Rationale for Dosing Duration

A 5-day duration of dosing of MOV is currently under evaluation for the treatment of COVID-19 in adults in clinical studies. The planned treatment regimen of 5 days in these studies is consistent with other acute antiviral treatments such as oseltamivir for influenza and is supported by nonclinical and clinical safety data for MOV. A 5-day duration is proposed in MK-4482-013 for prophylaxis of household contacts.

In the 28-day toxicity study of MOV at 17 mg/kg/day (0.4-fold relative to the clinical NHC exposure at 800 mg Q12H) administered to dogs, reversible hematology changes consistent with bone marrow toxicity became apparent on Day 7 with increasing severity from Day 14 onward. In a Phase 1 clinical study (MK-4482-004), dosing of MOV up to 800 mg Q12H for 5.5 days was generally well tolerated by healthy participants. No clinically meaningful trends were observed for changes in clinical laboratory values, vital signs, or ECGs as a function of dose or treatment. Specifically, there were no clinically significant abnormalities observed in the hematological laboratory tests. Furthermore, unblinded data obtained from participants treated in the Phase 2 program indicate that MOV has been generally well tolerated across all doses studied. Overall, preclinical and Phase 1 and 2 clinical observations to date support a ~5-day dosing duration for treatment with MOV.

A 5-day duration of dosing of MOV for prophylaxis in household contacts of an individual with COVID-19 is further supported from data evaluating viral shedding and symptom onset

after SARS-CoV-2 infection. Estimates of the duration of viral shedding (and likely infectiousness) have varied widely, and estimation is complicated by the methods used to detect and measure viral load. The most facile method is quantitative RT-PCR; however, it is recognized that the presence of viral nucleic acid does not correspond directly to presence of infectious virus, although high quantities of viral RNA generally correlate with a higher likelihood of viable virus [Wolfel, R., et al 2020]. In mild to moderate cases of COVID-19, 1 small study that evaluated viable virus in 9 patients showed that viral shedding concluded within 8 days after the onset of symptoms [Wolfel, R., et al 2020]. Other studies evaluating viral RNA loads showed a dramatic drop within the first 5 days after onset of symptoms [Kim, S. E., et al 2020], while others showed a more prolonged course [Vetter, P., et al 2020] [Yilmaz, A., et al 2021]. A study of COVID-19 infected health care workers, which evaluated shedding from symptom onset and 14 days thereafter, found that only 1 of 118 of these health care workers was still shedding viable virus 14 days after symptom onset. Of note, these studies provide no indication of changes in relative infectiousness with time. While virus is still detectable in some cases for more than a week past the onset of symptoms, viral RNA titers drop by multiple logs over that time frame and thus may be present in insufficient quantities to be effectively transmitted.

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/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent/assent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male and female participants ≥18 years of age will be enrolled in this study.

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 a household contact of an index case. An index case is a person with documented COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms case) and must have:

    a) A first detectable SARS-CoV-2 test result from a sample collected ≤5 days prior to randomization of the participant(s), **AND**

    b) At least 1 of the following symptoms attributable to COVID-19: fever ≥38.0ºC, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, or loss of smell, with symptom onset no earlier than 5 days prior to randomization of the participant(s).

    Note:

    - *To be considered a household contact, the individual must be currently residing with an index case and expect to continue residing with the index case through the duration of the study. Thus, the index case should not be hospitalized at the time of randomization.*

    - *For the SARS-CoV-2 test for the index case, molecular or antigen tests that detect viral RNA or protein are allowed if authorized for use in the country. Serological tests that detect host antibodies generated in response to recent or prior infection are not allowed.*

    - *A household may have more than one individual with documented COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms); however, the individual with the earliest evidence of COVID-19 (onset of symptoms or detectable SARS-CoV-2 test) is considered the "Index case." If this criterion does not distinguish a single index (ie, more than one individual developed COVID-19 on the same day), either individual can consent to participate as the index. As noted in Exclusion Criterion 1, other individuals within the household with suspected or confirmed COVID-19 cannot be considered household contacts and are ineligible to participate in the study.*

2. The participant does not have confirmed or suspected COVID-19.

3. The participant is willing and able to take oral medication.

Demographics

4. The participant is male or female ≥18 years of age, at the time of providing documented informed consent.

Male Participants

5. Male participants must agree to be abstinent from penile-vaginal intercourse OR agree to use a highly effective contraceptive method while receiving study drug and for at least 3 months after the last dose of study drug.

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:

- Is not a WOCBP

  OR

- Is 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 4 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 (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4.

  Note: If using a urine pregnancy test, it should be sensitive enough to measure 25 mIU/mL hCG.

  - Has had her medical history, menstrual history, and recent sexual activity reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- If contraceptives are interrupted in case of standard of care management of COVID-19 and resumed at a later time point, such as at hospital discharge, then abstinence must be practiced for the defined period of back-up contraception per the contraceptive product labeling. After this period, contraceptive use must adhere to Appendix 5.

Informed Consent

7. The participant's index case (or legally acceptable representative of the index case) has provided documented informed consent/assent for the collection of COVID-19 documentation requirements.

   Note: There is no age requirement for index cases, and they may be less than 18 years of age. Index cases will be offered optional SARS-CoV-2 testing. An index case who opts in for this additional test must have had prior documented, laboratory-confirmed COVID-19 for eligibility of the household contacts (see Inclusion Criterion #1). Informed consent/assent for SARS-CoV-2 testing will be documented.

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

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 prior history of laboratory-confirmed SARS-CoV-2 infection (with or without symptoms), within 6 months prior to randomization.

2. The participant has either of the following conditions:

   - HIV with a recent viral load >50 copies/mL (regardless of CD4 count) or an AIDS-defining illness in the past 6 months

     Note: Participants with HIV may only be enrolled if on a stable antiretroviral therapy regimen.

3. The participant has a history of HBV or HCV infection with any of the following:

   - Cirrhosis
   - End-stage liver disease
   - Hepatocellular carcinoma

- AST and/or ALT >3X upper limit of normal at screening

4. The participant has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.

5. The participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments including, but not limited to participants with conditions that could limit gastrointestinal absorption of capsule contents.

Prior/Concomitant Therapy

6. The participant has received, is taking, or is anticipated to require any prohibited therapies as outlined in Section 6.5.

7. The participant has received a COVID-19 vaccine with the first dose 7 days or more prior to randomization.

Prior/Concurrent Clinical Study Experience

8. The participant is unwilling to abstain from participating in another interventional clinical study through Day 29 with an investigational compound or device, including those for COVID-19 therapeutics.

Diagnostic Assessments

Not applicable.

Other Exclusions

9. The participant is living in a household of more than 10 people.

10. 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

There are no lifestyle restrictions for the study.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (study intervention[s] provided by the Sponsor) will be packaged to support enrollment. 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 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Experimental	MOV (MK-4482)	Drug	Capsule	200 mg	800 mg	Oral	Q12H (+/-2 hours) for 5 days (10 doses total)	Test Product	IMP	Central
Group 2	Placebo Comparator	Matching Placebo	Drug	Capsule	0 mg	N/A	Oral	Q12H (+/-2 hours) for 5 days (10 doses total)	Placebo	IMP	Central

Admin=administration; AxMP=Auxiliary Medical Product; EEA=European Economic Area; IMP=investigational medicinal product; MOV=molnupiravir; N/A=not applicable; NIMP=noninvestigational medicinal product; Q12H=every 12 hours.

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.

Note: Participants will be randomized 1:1 to receive either blinded MOV (Group 1) or blinded placebo (Group 2).

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

Refer to Section 8.1.9 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 randomized in a 1:1 ratio to either MOV (800 mg, Group 1) or placebo (Group 2). Randomization will occur centrally using an IRT system.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Age category (≤60 vs >60 years)
2. Household size (≤3 vs >3 household residents. All residents, including the index case, are counted regardless of whether they are participating in the study.)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MOV and placebo capsules are identical in appearance and will be packaged identically so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by review of a Study Medication Diary during the site visits and documented in the source documents and CRF.

A record of the number of capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

6.5 Concomitant Therapy

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

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

Prior and concomitant therapies listed as prohibited in Table 2 are not permitted for the specific time frames listed. Table 2 is not comprehensive, and the investigator should use their medical judgment when assessing whether a participant's prior and concomitant therapy(ies) are prohibited. The Sponsor Clinical Director or designee should be contacted if there are any questions about a therapy not listed or regarding potential DDIs with a specific treatment that the participant may plan to receive. Of note, if a participant is hospitalized during the study, other medications intended as treatment for COVID-19 are permitted.

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

There are no restrictions for treatment of the index cases for this study as they will not receive intervention provided by this study. Index cases may receive treatment outside this study.

Table 2 Prohibited and Allowed Therapies for Participating Household Contacts

COVID-19 Vaccines	• COVID-19 vaccines are prohibited with the first dose 7 days or more prior to randomization and from the time of randomization through Day 14.
COVID-19 Monoclonal Antibodies	• Monoclonal antibodies are prohibited for prevention of SARS-CoV-2 infection at any time prior to randomization and through Day 29. Note: This includes approved, authorized, or investigational anti-SARS-CoV-2 monoclonal antibodies, COVID-19 convalescent plasma, or other anti-SARS-CoV-2 biologic products with a long (eg, >1 week) half-life. • Monoclonal antibodies are permitted as rescue treatment for participants who develop COVID-19 in accordance with local standard of care.
COVID-19 Therapeutics	• Sponsor-designated[a] treatment or preventative agents targeting SARS-CoV-2 should not be used in asymptomatic participants. • Standard of care treatment for COVID-19 is permitted as rescue treatment for participants who develop COVID-19 (eg, remdesivir, corticosteroids, etc). • Treatment with MOV, if approved for use in the participant's jurisdiction and available for administration, is not permitted.
Non-COVID-19 Investigational Agents	All non-COVID-19 investigational agents including devices are prohibited within 30 days prior to randomization and through Day 29.

COVID-19=coronavirus disease 2019; MOV=molnupiravir; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

[a] Refer to the *MK-4482-013 Sponsor-Designated Treatment or Preventative Agents Targeting SARS-CoV-2* document.

6.5.1 Rescue Medications and Supportive Care

Standard of care for COVID-19 is permitted as rescue treatment for participants who develop COVID-19 (eg, remdesivir, corticosteroids, etc). Monoclonal antibodies are permitted as rescue treatment for participants who develop COVID-19 in accordance with local standard of care.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification of MOV or placebo is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.12). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

This section is not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3.1 and Section 8.11.2. unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the

investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant is no longer able to take oral medication or becomes intubated prior to completion of study intervention.
- The participant receives concomitant treatment with MOV that is provided outside this study (see Section 6.5).
- A female participant becomes pregnant.

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

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

7.2 Participant Withdrawal From the Study

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

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

Hospitalization and survival status at Day 29 are required for all randomized participants and should still be reported for participants who withdraw from the study where it is permitted by local guidelines. Site personnel should attempt to obtain information regarding vital status (including date last known to be alive, hospitalization, date of death, primary cause of death, and COVID-19 contribution to death) as outlined in Section 8.2.8.

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 8.1.11 and 8.11.3. 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 amount of blood collected from each participant for clinical laboratory assessments over the duration of the study is approximately 33.0 mL (Appendix 2, Table 12).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

Potential participants who will be requested to provide documented informed consent/assent are index cases and household contacts of each index case, as per study eligibility requirements described in Section 5.1. The informed consent/assent activities are described in Section 1.3.

For the information provided in Section 8.1.1 and Section 8.1.1.1, the term "participant" refers to index cases and household contacts of each index case.

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent/assent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR (only household contacts will participate in 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/assent is in place.

8.1.1.1 General Informed Consent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent 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/assent discussion.

A copy of the signed and dated informed consent/assent 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/assent form or addendum to the original consent/assent form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

Informed consent/assent 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.

Index cases will not participate in FBR in this study.

8.1.1.3 Consent/Assent for Data Collection and Viral Testing/Quantification for Index Cases

The investigator or medically qualified designee will explain the collection of data and optional swab collection for viral testing/quantification to all index cases and/or their legally acceptable representative, answer all of their questions, and obtain documented informed consent/assent before performing the collection of data or swab from the index case. The COVID-19 data include COVID-19 diagnostic test information (Section 8.1.2), date of onset for prior and current COVID-19 diagnoses (Section 8.1.4), prior COVID-19 vaccine information (Section 8.1.5.1), and medication for COVID-19 at the time of screening (Section 8.1.5.1). The NP or OP swab collection and viral testing/quantification are described in Section 1.3.2 and Section 8.2.4. A copy of the signed informed consent/assent will be given to the index case and/or the index case's legally acceptable representative.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria (Section 5.1 and Section 5.2) will be reviewed by the investigator, who is a qualified physician, to ensure that a participant qualifies for the study.

The first detectable SARS-CoV-2 test result for the index case must be from a sample collected within 5 days prior to randomization of the potential participant(s) in the study. The index case's SARS-CoV-2 test result must be confirmed for the participant(s) to be eligible for the study. Data pertaining to the index case's SARS-CoV-2 sample and test must be entered into the eCRF including date specimen collected, sample type (eg, NP swab), test method (eg, RT-PCR), and result (detectable result is required).

For participants with reported history of HBV or HCV, ALT and AST must be available from within 5 days prior to randomization to support determination of eligibility. In WOCBP, a negative local urine or serum pregnancy test is required within 24 hours prior to the first dose of study intervention per inclusion criteria.

All other inclusion/exclusion criteria determination (eg, HIV status) can be based on participant-reported medical history, available medical records, and the most recently

available laboratory results for the participant (eg, HIV RNA viral load or CD4 count). See Appendix 7 for country-specific requirements.

8.1.3 Participant Identification Card

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

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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 as follows:

- Participants will provide any prior medical history of COVID-19, background or concomitant conditions, drug allergies and/or surgical procedures within the last 12 months. Medical history for the following conditions will also be collected separately on the Medical History Pre-Specified Conditions eCRF: chronic kidney disease, chronic obstructive pulmonary disease, obesity, active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality), congestive cardiac failure, coronary artery disease, cardiomyopathies, and diabetes mellitus (Appendix 8).

- All index cases will provide information pertaining to COVID-19 diagnostic test (as described in Section 8.1.2) and date of COVID-19 onset for the current COVID-19 diagnosis, as well as any prior COVID-19 diagnosis.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior medications taken by participants as follows:

- Participants will provide prior medications taken within 30 days before the first dose of study intervention and prior COVID-19 vaccine, regardless of the time period.

- All index cases will be asked to provide all medications being taken for COVID-19 (at the time of screening) and any prior COVID-19 vaccine.

8.1.5.2 Concomitant Medications

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

In addition, the following concomitant medications and vaccines will be recorded on the appropriate eCRF:

- Medication(s) for the treatment of COVID-19. This includes all supportive therapies (eg, antipyretic and anti-inflammatory agents) to manage COVID-19 symptoms. See Section 6.5 for prohibited and allowed therapies.

- COVID-19 vaccine(s) at any time during the study. Note: COVID-19 vaccine(s) are prohibited from the time of randomization through Day 14; see Section 6.5.

Treatment with MOV, if approved for use in the participant's jurisdiction and available for administration, is not permitted for any participant in this study. (This restriction pertains to participants receiving study intervention, not index cases.)

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.

Participants may be rescreened. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.2.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after intervention 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.

Index cases will not be randomized to receive study intervention, but will receive an allocation number for the collection of data and optional NP or OP swab.

8.1.8 Participant Study Supplies

On Day 1 of the study, participants will receive bottles of study intervention and the following study supplies:

- Copy of informed consent
- Information about the study
- Instructions on study procedures and how to take study intervention
- Participant identification card with study contact information
- Instructions on what to do if participants develop symptoms of COVID-19 or become hospitalized
- Study Medication Diary (see Section 8.1.10)
- Symptom Diary (see Section 8.2.1)
- EuroQoL EQ-5D-5L questionnaire (see Section 8.2.11)

8.1.9 Study Intervention Administration

Study intervention will be provided as per Table 1 and dispensed through the IRT system at the Day 1 (randomization) visit. Study intervention and the Study Medication Diary will be dispensed according to the pharmacy manual for at home administration. Study intervention will be self-administered by the participants according to the study intervention period in the SoA (Section 1.3.1) and timing described in Section 8.1.9.1.

8.1.9.1 Timing of Dose Administration

Participants will take the appropriate number of capsules of study intervention (as described in the study intervention administration instructions) Q12H (±2 hours) for 5 days. Study intervention may be administered without regard to food.

As outlined in the SoA (Section 1.3.1), all efforts should be made to administer the first dose of study intervention on Day 1, but administration of the first dose must be within 24 hours of randomization; therefore, it is possible that dosing may not begin until Day 2. Thus, the final dose could occur on the evening of Day 6, if dosing initiated in the morning; or the morning of Day 7, if dosing initiated in the evening.

For all doses, the timing of dose administration should be recorded in the Study Medication Diary.

If a participant misses a dose of the study intervention, then the following guidance should be followed:

- If ≤10 hours from the time the missed dose should have been taken, the missed dose should be taken, and a Q12H dosing schedule resumed. Each subsequent dose should be taken 12 hours after its preceding dose.

- If >10 hours from the time the missed dose should have been taken, the missed dose should be skipped, and Q12H dosing schedule resumed. In this case, the subsequent dose should be taken 12 hours after the time that the missed dose should have been taken (which would be 24 hours after the last dose consumed). The participant should not double the next dose to compensate for what has been missed.

8.1.10 Study Medication Diary

A paper Study Medication Diary will be provided for the documentation of doses of study intervention and assessment of compliance. Participants should complete the Study Medication Diary for each dose taken. If the participant is (in the judgment of the investigator) unable to complete the diary, information regarding study intervention administration may be recorded by a legally acceptable representative or other close contact who witnesses administration of the study intervention.

To further support compliance with completion of the Study Medication Diary by the participant, the study staff should provide daily telephone or other reminders (eg, email, text messages) during the treatment period (see SoA, Section 1.3.1).

The Study Medication Diary will be reviewed in conjunction with capsule counts by study staff with each participant at the visits described in the SoA, Section 1.3.1, to ensure compliance with completion and consistency with capsule counts. Capsule counts will be performed by study staff (expected versus actual) for each study intervention bottle according to the pharmacy manual.

The Study Medication Diary will be collected as soon as possible after the last dose (ie, 10th dose) of study intervention. If the EOT visit is performed prior to the last dose of study intervention, the Study Medication Diary should be collected no later than the Day 14 visit. The study intervention data as recorded in the participant's Study Medication Diary will be entered in the eCRF.

In the event of hospitalization, the Study Medication Diary will be completed by the participant as feasible. If the participant is unable to complete the diary during hospitalization, the individual administering the study intervention (eg, study or nonstudy staff) will collect information corresponding to study intervention administration in the participant's Study Medication Diary or other source notes (documentation should be maintained as part of participant records at the site).

8.1.11 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits after EOT as outlined in the SoA (Section 1.3.1) and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Day 29 visit (or the EOT visit if withdrawing prior to completion of the treatment period or the Day 14 visit if withdrawing after the EOT visit and prior to the Day 14 visit; see Section 8.11.3) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

Hospitalization and survival status at Day 29 are required for all randomized participants and should still be reported for participants who withdraw from the study where permitted by local guidelines.

8.1.11.1 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.

8.1.12 Participant Blinding/Unblinding

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

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

him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade 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 should continue to be monitored in the study.

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

8.1.13 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Completing the Symptom Diary and Monitoring for Symptoms of COVID-19

Completing the Symptom Diary

Participants will self-report COVID-19 symptoms daily, if any, using a paper Symptom Diary. The Symptom Diary contains 15 targeted COVID-19 symptoms for which 13 will be assessed for absence/presence as well as severity (mild, moderate, or severe). Two other symptoms (loss of taste and loss of smell) will be assessed for absence/presence only. The recall period is "during the past 24 hours."

Targeted symptoms for COVID-19 assessed in the Symptom Diary include:

- Cough
- Sore throat
- Nasal congestion (stuffy nose)
- Runny nose
- Shortness of breath or difficulty breathing
- Muscle or body aches
- Fatigue (tiredness)
- Feeling hot or feverish
- Chills
- Headache
- Nausea
- Vomiting
- Diarrhea
- Loss of taste
- Loss of smell

The Symptom Diary will be completed by participants as follows:

- Participants will begin to complete the Symptom Diary on Day 1 (the same day as randomization), prior to the first dose of study intervention. Completion of the Day 1 Symptom Diary will be observed at the site (or a home visit, or visit to an alternate site) and documented, including time of participant completion, by study staff/qualified health care provider.
- After Day 1, participants should complete the Symptom Diary daily at approximately the same time every day through Day 29, recording the absence/presence of each symptom and highest severity (mild, moderate, or severe) for 13 of the 15 symptoms during the past 24 hours.

If the participant is able to comprehend the Symptom Diary questions (in the judgment of the investigator), but is unable to record their responses on the diary on their own per investigator judgment, collection of COVID-19 symptom data by study staff via an in-person

or virtual (eg, telephone) participant interview using a Sponsor-provided interviewer script should be implemented.

In the event of hospitalization, the Symptom Diary should be completed during hospitalization if possible. If the participant is unable to record their responses on the diary on their own, the Sponsor-provided interviewer script should be implemented by study staff. Completion of the diary should be resumed by the participant after discharge per the SoA, Section 1.3.1.

The Symptom Diary will be reviewed by study staff with each participant at the visits described in the SoA (Section 1.3.1) to ensure compliance with completion. To further support compliance with completion by the participant, the study staff should provide the following reminders for Symptom Diary completion:

- Daily telephone or other reminders (eg, email, text messages) during the treatment period and every other day from EOT through Day 14 to a participant or 1 participant who represents multiple participants from the same household.

- After Day 14, weekly telephone or other reminders (eg, email, text messages).

The Symptom Diary will be collected per the SoA, Section 1.3.1, and the diary data will be recorded in the eCRF.

In addition to the participant-recorded symptoms, the Investigator or designee will assess the participant's ability to undertake personal usual activities (ie, activities of daily living) and assess shortness of breath at rest and with exertion at scheduled visits per the SoA, Section 1.3.1.

All participants should be reminded at weekly visits (as specified in the SoA, Section 1.3.1) to contact the site if they develop symptoms of suspected COVID-19 (through Day 29) for assessment at a COVID-19 Confirmation Visit.

Monitoring for Qualifying Symptoms of COVID-19

Participants will be instructed to contact study personnel if they develop 1 or more symptoms of suspected COVID-19 (listed above and in the Symptom Diary) at any time through Day 29. If a participant reports qualifying symptoms of suspected COVID-19 (described in Section 8.2.2) at any time during the study, a COVID-19 Confirmation Visit that includes NP swab collection for RT-PCR testing at the central laboratory should be scheduled, to occur as soon as possible, but within 3 days of symptom onset (see Section 8.2.3).

8.2.2 Qualifying Symptoms of Suspected COVID-19

To identify suspected cases of COVID-19, prespecified symptoms as well as time criteria will be elicited from participants. Any participant who presents with a new onset or marked worsening of any one of the 15 targeted COVID-19 symptoms listed in the Symptom Diary (described in Section 8.2.1) persisting or recurring over a period of at least 24 hours (except

the symptoms of feeling hot or feverish, cough, shortness of breath, loss of taste, or loss of smell, which can be present for any duration) should be assessed by the investigator or medically qualified designee at a COVID-19 Confirmation Visit (see Section 8.2.3).

8.2.3 Scheduling Requirements and Procedures at a COVID-19 Confirmation Visit

The COVID-19 Confirmation Visit should be scheduled to occur as soon as possible, but within 3 days of symptom onset. If the 3-day window is exceeded, then the Confirmation Visit should be scheduled to be conducted as soon as possible. Every attempt should be made to assess the participant. If circumstances do not support a clinic visit, a home visit or visit to an alternate study site may be used, if allowed by local regulations. In the case of a home visit or visit to an alternate study site, all indicated study procedures should be performed, including NP swab collection (Section 8.2.4) for SARS-CoV-2 RT-PCR testing at the central laboratory. A participant may have more than one COVID-19 Confirmation Visit.

The COVID-19 Confirmation Visit must be performed by the investigator or medically qualified designee.

The following procedures are to be performed at a COVID-19 Confirmation Visit in any setting (eg, clinic, home, or alternate site visit) to assess the participant for COVID-19:

1. Confirm the presence or absence of symptoms of COVID-19. All COVID-19 symptoms that prompted the COVID-19 Confirmation Visit and/or are observed during the visit will be recorded on the appropriate eCRF.

2. An NP swab will be collected from the participant for central laboratory RT-PCR testing (see Section 8.2.4). If an additional sample is collected for local testing per local guidelines, the NP swab for central laboratory testing should be collected first.

3. A directed physical examination, vital signs measurement (including heart rate, blood pressure, respiratory rate, and temperature), and SpO2 (if device to measure SpO2 is available) to assess the participant's symptoms and severity of COVID-19.

4. Assess the participant for severity of COVID-19. See Section 8.2.10 for COVID-19 severity criteria.

5. Determine if further triage or clinical evaluation is needed, consistent with standard of care and local guidelines, and in conjunction with the participant's primary physician (if applicable).

6. The COVID-19 Confirmation Visit may be performed separately from the scheduled study visits in the SoA (Section 1.3.1) per the scheduling requirements described above. However, if a scheduled visit (Section 1.3.1) overlaps with the COVID-19 Confirmation Visit, all applicable procedures can be performed at the same visit.

If a participant was assessed for COVID-19 symptoms in a nonstudy outpatient or inpatient clinical setting (eg, outpatient clinic, Emergency Department, urgent care center, or hospital),

attempts should be made to obtain medical records from the outpatient facility or hospital for review by the investigator (or medically qualified designee). Relevant information (COVID-19 symptoms, local COVID-19 testing results, etc) should be recorded on the appropriate eCRF.

Study sites will follow infection control practices for encounters with participants presenting with suspected COVID-19 per local guidelines.

8.2.4 Nasopharyngeal Swab Collection for Viral Testing/Quantification

Study site personnel or their medically qualified designee will collect the NP swabs from participants and NP or OP swabs from index cases.

Swabs will be collected and tested as follows:

- For participants, NP swabs will be collected at the Day 1, Day 5, Day 14, and Day 29 study visits and at a COVID-19 Confirmation Visit (see below). At study entry (Day 1), the samples should be collected prior to the first dose of study intervention. Qualitative and quantitative SARS-CoV-2 RT-PCR testing at the central laboratory and SARS-CoV-2 genome sequencing for genetic lineage identification will be performed on the NP swabs. Testing for coinfection with other respiratory pathogens is also planned for the NP swabs collected from participants.

- For index cases, NP or OP swabs may be collected at screening (see Section 1.3.2). NP swabs are preferred; however, OP swabs are also acceptable for index cases only. This swab is separate from the sample for the first detectable SARS-CoV-2 test required for the index case prior to randomization of the participant(s) in the study (see Section 5.1). The swab is not required for study participation of household contacts; however, it is highly encouraged for complete virologic assessment. Qualitative and quantitative SARS-CoV-2 RT-PCR testing at the central laboratory and SARS-CoV-2 genome sequencing for genetic lineage identification will be performed on the NP or OP swabs collected at screening.

The swabs for collecting NP and OP samples will be provided by the central laboratory. The NP and OP swab sample collection, storage, and shipment instructions are provided in the laboratory manual.

Nasopharyngeal Swab Collection at a COVID-19 Confirmation Visit

NP swab samples should be collected from participants by study site personnel or their medically qualified designee within the time requirements for the COVID-19 Confirmation Visit (see Section 8.2.3). If an additional sample is collected for testing per local guidelines, the swab sample for central laboratory testing should be collected first.

If it is not possible to conduct the COVID-19 Confirmation Visit at the study site, as described in Section 8.2.3, the investigator may designate staff caring for the participant in an alternate nonstudy outpatient or inpatient clinical setting to obtain the samples.

The following procedures should be followed for obtaining an NP swab sample during a nonstudy outpatient or inpatient visit in a clinical setting (eg, outpatient clinic, Emergency Department, urgent care center, or hospital) other than the study site:

1. If a participant first visits a nonstudy outpatient or inpatient clinical setting other than the study site and is confirmed to have symptoms of COVID-19, the study staff should make every effort to obtain an NP sample using the study-supplied swab, as permitted, and the site should send this sample to the central laboratory for analysis.

2. If site staff are not permitted to access the outpatient facility or hospital to obtain an NP sample, they should coordinate with providers caring for the participant to use the study-supplied NP swab or equivalent to collect the sample for central laboratory testing, if possible.

3. If it is not possible to collect the NP swab sample with study-supplied NP swabs for central laboratory testing, the local SARS-CoV-2 test result should be collected.

4. If an NP sample cannot be collected at a nonstudy outpatient or inpatient clinical setting other than the study site, the sample should be collected using the study-supplied swab as soon as possible postvisit or postdischarge. The local SARS-CoV-2 test result and medical records should also be obtained from the outpatient facility or hospital.

8.2.5 SARS-CoV-2 RT-PCR Assay

NP swab samples collected from participants and NP or OP swab samples collected from index cases (Section 8.2.4) will be tested for the presence of SARS-CoV-2 RNA using the Roche Cobas SARS-CoV-2 PCR assay, which has been approved under EUA, at the central laboratory. This is a qualitative dual target assay that specifically amplifies a region in the SARS-CoV-2 ORF1 a/b as well as a conserved region in the E-gene for pan Sarbecovirus detection. The lower limit of detection for this assay is 1.8×10^3 NDU/mL (RNA NAAT detectable units/mL). In addition, a second research-use only PCR assay, developed at Q-squared Genomics Laboratories, will be used to quantify SARS-CoV-2 RNA titers in NP samples. The SARS-CoV-2 Viral Load Quantitation Assay utilizes the MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit on the KingFisher system and reagents from the TaqPath™ COVID-19 Combo Kit to amplify 2 unique regions in the ORF1ab, N protein, and S protein genes. The lower limit of quantification is 500 RNA copies/mL and the upper limit of quantification is 500,000,000 RNA copies/mL.

Central laboratory RT-PCR assay results from NP swabs will be used for the analysis of efficacy. If extenuating circumstances impact the ability to use the central laboratory, results from a local laboratory will be used if available. If only OP swabs are available, the RT-PCR results will be used to support clinical endpoints and establish baseline viral status (ie, to establish whether they are in the primary analysis population, mITT-VN) but will not be used to assess virologic endpoints.

8.2.6 Assessment of Prophylaxis Outcome

The clinical outcome of prophylaxis will be assessed at the Day 14 and Day 29 visits for all participants and at the COVID-19 Confirmation Visit for participants who develop laboratory-confirmed COVID-19 with symptoms (see Section 1.3.1). Assessments should be made according to the following definitions:

Term	Definition
Clinical Success	The participant does not develop laboratory-confirmed COVID-19 with onset within the window of interest (ie, symptom onset on or before Day 14 for the Visit 4 assessment; and on or before Day 29 for Visit 6 assessment). Note: Participants who remain asymptomatic through Day 14 (or Day 29, for the Day 29 endpoint) are also considered clinical successes regardless of SARS-CoV-2 results (positive, negative, or missing).
Clinical Failure	The participant develops laboratory-confirmed COVID-19 with onset within the window of interest (ie, symptom onset on or before Day 14 for the Visit 4 assessment; and on or before Day 29 for Visit 6 assessment). The date of onset is considered the date of onset of symptoms. *Note: An assessment of "Clinical Failure" on or before Day 14/Visit 4 will also be carried forward to the Day 29/Visit 6 assessment.*
Indeterminate	The outcome is indeterminate if any of the following apply: • The participant is lost to follow-up during or has discontinued from the study prior to the window of interest (ie, prior to Visit 4 or Visit 6 for the outcome assessments conducted at those visits). *Note: This definition does not apply to participants who developed laboratory-confirmed COVID-19 with symptoms prior to leaving the study. For those participants, prophylaxis outcome should be assessed as "Clinical Failure" per the definition above.* • Death unrelated to COVID-19. • The participant is symptomatic and missing the required viral test for confirmation of COVID-19. *Note: A virus-detectable NP swab collected within +/-5 days of symptom onset is considered to be within an acceptable window to confirm onset of COVID-19. A virus-undetectable NP swab that is collected within 5 days after symptom onset is considered to be within an acceptable window to rule out COVID-19.* *NP swabs collected outside these windows are considered missing.* • There are other extenuating circumstances that preclude classification as a clinical success or failure, such as: - The participant receives Sponsor-designated treatment or preventative agents targeting SARS-CoV-2 for reasons other than rescue treatment for participants who develop COVID-19; see Section 6.5.

Term	Definition
	- Clinical observations and diagnostic tests cannot distinguish COVID-19 from another confirmed diagnosis (eg, influenza like symptoms with detectable results for both influenza and SARS-CoV-2 diagnostic tests).

8.2.7 Hospitalization

Hospitalization status will be assessed for all participants as outlined in the SoA (Section 1.3.1). Hospitalization is defined as ≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic. The date and time of hospital admission, date and time of discharge, and primary reason for hospitalization (including if the admission is related to COVID-19) will be recorded. The Sponsor must be notified within 24 hours of site's awareness of a participant's hospitalization.

Participants who report worsening illness from any cause during the study may be referred to their health care provider or a medical facility. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, ie, hospitalization or death.

For any participants who become hospitalized during the study, all study procedures outlined in the SoA (Section 1.3.1), including study intervention administration (if applicable), should be continued if possible. If the hospitalized participant has not completed study intervention and is unable to swallow the capsules or is intubated during hospitalization, then study intervention should be discontinued (Section 7.1).

It is recognized that use of nonstudy personnel may be necessary for some procedures in the study. In such cases, documentation of these responsibilities and source documentation of study intervention administration must be maintained in the site's source documentation as appropriate. If in-person visits are not permitted by the institution in which the participant is hospitalized, a virtual visit (eg, telehealth, telephone) may be performed to collect data per the SoA (Section 1.3.1) that does not require in-person collection. Every attempt should be made to obtain equivalent data from hospital records.

In addition to information regarding hospitalization details, available pertinent information will be collected, including assessment of participant self-reported COVID-19 symptoms (eg, based on Symptom Diary via self-recording or Sponsor-provided interview script, if completed), local COVID-19 testing results, vital signs, supplemental oxygenation use, ventilation procedures, concomitant medications and AEs, including death.

In addition, every effort should also be made for a visit to be scheduled after discharge from the hospital, provided that the visit is within 28 days of initiation of dosing.

8.2.8 Survival Status

Survival status (ie, whether the participant is alive or deceased) will be assessed for participants per the SoA (Section 1.3.1).

Site personnel should attempt to obtain information regarding vital status (including date last known to be alive, hospitalization, date of death, primary cause of death, and COVID-19 contribution to death) from the participant or other sources (eg, family members, other designated secondary contacts, hospital the participant stated they would most likely go to, clinic/hospital/medical records, and local or national databases).

Information about death should be entered in the eCRF within 24 hours of a site becoming aware of a death.

8.2.9 Health Care Utilization for COVID-19

Medically attended COVID-19 (as defined in Section 4.1) will be collected for participants with laboratory-confirmed COVID-19 per the SoA (Section 1.3.1) and entered on the appropriate eCRF. The investigator or qualified designee will assess participant reports to determine if COVID-19 required medical care per the protocol definition of medically attended COVID-19.

8.2.10 Assessment for Severity of COVID-19

The severity of COVID-19 will be assessed for participants who develop laboratory-confirmed COVID-19 at study visits specified in the SoA and the COVID-19 Confirmation Visit (Section 1.3.1). COVID-19 severity assessments will be performed using the NIAID ordinal scale criteria for COVID-19 severity [Beigel, J. H., et al 2020], as follows:

1. Not hospitalized and no limitations of activities
2. Not hospitalized with limitation of activities, home oxygen requirement, or both
3. Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control or other nonmedical reasons)
4. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related to COVID-19 or to other medical conditions)
5. Hospitalized, requiring any supplemental oxygen
6. Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices
7. Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8. Death

The participant's worst severity experienced since the prior visit should be entered on the appropriate eCRF.

8.2.11 EuroQoL EQ-5D-5L Questionnaire

A quality-of-life assessment will be conducted using the paper EuroQoL EQ-5D-5L questionnaire (as described in Section 4.2.1.5) for participants at study visits specified in the SoA (Section 1.3.1). The questionnaire should be self-administered by participants. If a participant is unable to record responses on the questionnaire on their own, the Sponsor-provided EQ-5D-5L Interviewer Administered Script should be implemented by study staff. If a validated Interviewer Administered Script is unavailable in a language understood by a participant who is unable to record responses on the questionnaire on their own, the quality-of-life assessment does not need to be performed. The EuroQoL EQ-5D-5L questionnaire assessments should be entered on the appropriate eCRF.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided in the subsections that follow.

Planned time points for all safety assessments are provided in the SoA. The volume of blood to be drawn for clinical laboratory assessments over the course of the study is provided in Appendix 2, Table 12.

8.3.1 Physical Examinations

A directed physical examination will be conducted at the screening visit by a nurse or other qualified health care provider. Height and weight will also be collected and recorded. A nurse or other qualified health care provider will also conduct directed physical examinations targeted at the participant's symptoms/complaints at visits indicated in the SoA (Section 1.3.1). Details of the physical examinations will be provided to the investigator or medically qualified designee (consistent with local requirements) for review and assessment per institutional standard.

8.3.2 Vital Signs

Body temperature, heart rate, respiratory rate, and blood pressure will be assessed. Vital sign measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

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

8.3.4 Pregnancy Testing

Pregnancy testing requirements for study inclusion are described in Section 5.1. Pregnancy testing should be conducted at screening (may use either serum or urine test; if using a urine test, the test should be sensitive enough to measure 25 mIU/mL hCG) and on Day 14 (serum), approximately 9 days after the last dose of study intervention.

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

8.3.5 Pregnancy Follow-up

Pregnancy status (eg, estimated date of conception and delivery date) for female participants of childbearing potential and, female partners of male participants will be collected at the Day 29 (LFU) visit (Section 1.3.1). Collection of pregnancy data for female partners of male participants is not required if the male participant is confirmed to be azoospermic (vasectomized or secondary to medical cause) as documented in medical history.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

For participating household contacts, all AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention.

From the time of intervention randomization, through 14 days after cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

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

For participating index cases, all AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before allocation, must be reported by the investigator if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention.

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 (index or household contact) has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

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

Table 3 Reporting 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	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	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	Not applicable	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor as described in Section 8.4.1.

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 lead to an elective termination of a pregnancy will be reported as an SAE for the fetus.

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

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

Certain efficacy endpoints including hospitalizations and mortality must be collected throughout the study (ie, during both treatment and follow-up periods). From the time of randomization through 14 days after cessation of study intervention, these events must be reported as described in Section 8.4.1. New hospitalizations and/or deaths that occur after 14 days after cessation of treatment must continue to be assessed for seriousness and causality. However, they must only be reported to the Sponsor within 24 hours as new SAEs if there is evidence to suggest a causal relationship between the study intervention and the SAE.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. 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).

8.5 Treatment of Overdose

In this study, an overdose is the receipt of any number of capsules greater than the number of capsules to be taken as outlined in the pharmacy manual.

No specific information is available on the treatment of 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.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Virologic, clinical efficacy, and clinical safety endpoints (Section 3) will be summarized. For assessment of antiviral activity of MOV, baseline and postdose virologic information (eg, viral RNA) from NP swabs of participants will be measured at prespecified timepoints in the SoA (Section 1.3.1). For each participant, the baseline measurement is defined as the measurement obtained predose on the first day of dosing.

8.8 Anti-SARS-CoV-2 Antibody Serology Testing

Participants will have serologic testing performed for the presence of anti-SARS-CoV-2 nucleocapsid (N) protein and neutralizing antibodies in serum at time points indicated in the SoA (Section 1.3.1).

Anti-nucleocapsid antibodies will be measured at the central laboratory using the Roche Elecsys Anti-SARS-CoV-2 test that is currently available under EUA. This assay is a qualitative test yielding a positive versus negative result for anti-nucleocapsid antibodies.

Anti-SARS-CoV-2 neutralizing antibody titers will be measured at a centralized testing laboratory using a VSV pseudotype containing a luciferase reporter and bearing a cytoplasmic domain-truncated SARS-CoV-2 spike protein. This assay, validated at Nexelis Laval Canada (a Q^2 Solutions Company), measures the ability of antibodies in serum to neutralize infection of a VSV reporter virus pseudotyped with the SARS-CoV-2 spike protein [Bewley, K. R., et al 2021].

8.9 Biomarkers

Biomarkers will not be evaluated in this study.

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:

- DNA for future research
- Leftover isolates from NP swab for viral testing/quantification stored for future research
- Leftover serum from anti-SARS-CoV-2 antibody serology testing stored for future research

8.11 Visit Requirements

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

8.11.1 Infection Prevention Procedures

Each site will follow their institutional procedures and/or local requirements to protect study staff and other patients from infectious exposure to SARS-CoV-2. These procedures may include, but are not limited to:

- Provision of PPE to site staff, participants, and legally acceptable representatives
- Performing home visits, visits to alternate sites, or virtual visits (as allowed per the SoA)
- Designating special entry points for study participants for clinic visits

8.11.2 Types of Study Visits

8.11.2.1 Screening/Rescreening Visits

Screening

Screening of potential participants and index cases will occur within 5 days prior to randomization of the participants. The sample for the first detectable SARS-CoV-2 test for the index case must have been collected within 5 days prior to randomization of the participants. In addition, COVID-19 symptom onset for the index case may be no earlier than 5 days prior to randomization of the participants.

Prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Participants are expected to enroll as soon as possible after eligibility is confirmed.

Rescreening

Participants are allowed to rescreen 1 time. Rescreening procedures must be completed within 5 days from the time of sample collection for the first detectable SARS-CoV-2 test result of the index case and also within 5 days from the time of onset of symptoms for the index case. The following assessments must be repeated for participants who are rescreened:

- Vital signs and directed physical examination
- Review medical history and prior/concomitant medications for new information
- Local laboratory assessments for inclusion/exclusion (results within 5 days prior to randomization may be used for eligibility)
- Urine or serum β-hCG (pregnancy testing for WOCBP)

- Review of AEs

If the informed consent form has been updated, participants should be reconsented before rescreening. If no updates have been made, the informed consent from the original screening period should be reviewed with the participant and a verbal reconsent to continue in the study should be documented.

8.11.2.2 Clinic Visits, Home Visits, or Visits to an Alternate Site

If circumstances do not support a clinic visit, a home visit by the site personnel or a qualified health care provider (eg, home health care company, visiting nurse, etc) or a visit to an alternate site may be appropriate to perform study assessments and procedures per the SoA (where available and when permitted by local regulations and IRB/IEC). All study procedures indicated in the SoAs (Section 1.3.1 and Section 1.3.2) should be completed. The documentation from the visit will be provided to the investigator or medically qualified designee (consistent with local requirements) for review and assessment per institutional standards.

Every attempt should be made to assess the participant for a COVID-19 Confirmation Visit. See Section 8.2.3 for scheduling and visit requirements for a COVID-19 Confirmation Visit.

Refer to the procedure manual and/or the Investigator Trial File Binder (or equivalent) for additional details.

8.11.2.3 Virtual Visits

For participants, the investigator or designee may conduct a virtual visit (eg, by telehealth, telephone, webcast, videoconference, etc) for the Day 21 visit. When a virtual visit is listed in the SoA (Section 1.3.1), a clinic or home visit is not required. The choice to conduct a virtual visit, rather than a clinic or home visit/visit to an alternate site, is at the investigator's discretion. All study procedures indicated in the SoA (Section 1.3.1) should be completed.

For index cases who do not provide documented informed consent/assent for the optional NP or OP swab for viral testing/quantification, a virtual visit may be conducted for screening (Visit 1) procedures in the SoA (Section 1.3.2).

Identity of each participant and index case should be confirmed according to institutional procedures and/or local guidelines prior to conduct of virtual visits.

8.11.3 Participants Who Discontinue or Withdraw

Participants who discontinue study intervention prior to completion of the treatment period should complete the activities for the EOT visit at the time of discontinuing study intervention. The participant should then be encouraged to complete all the remaining subsequent study visits after EOT as outlined in the SoA (Section 1.3.1). If an active condition requires ongoing monitoring (eg, abnormal laboratory results, AEs, or progression

of COVID-19 symptoms), unscheduled visit(s) may be performed prior to the next study visit on Day 14.

Study activities for participants who withdraw from the study depend on the time of withdrawal, as follows:

- Participants who withdraw from the study prior to completion of the treatment period should complete the activities for the EOT visit at the time of withdrawal.
- Participants who withdraw from the study after the EOT visit, but prior to the Day 14 visit should complete all activities scheduled for the Day 14 visit, including the NP swab collection for RT-PCR testing at the central laboratory, at the time of withdrawal.
- Participants who withdraw from the study after the Day 14 visit should be encouraged to complete all applicable activities scheduled for the Day 29 visit at the time of withdrawal.

This visit at the time of study withdrawal should be conducted at the clinic or as a home visit if possible. If circumstances do not support an in-person visit, a virtual visit may be used; in this case, laboratory or other in-person measures would not be collected. Return of participant diaries and reconciliation of any study intervention should be coordinated if relevant. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

Both hospitalization and survival status at Day 29 are required for all randomized participants and should still be reported for participants who withdraw from the study where permitted by local guidelines.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If after the study has begun, but prior to any unblinding/final database lock, changes are made to the primary hypothesis, or the statistical methods related to this hypothesis, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, medical resource utilization outcomes and research plasma samples) are beyond the scope of this document or will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-4482 for the Prevention of COVID-19 (Laboratory-confirmed SARS-CoV-2 Infection With Symptoms) in Adults Residing With a Person With COVID-19.
Treatment Assignment	Approximately 1376 participants (regardless of SARS-CoV-2 results in baseline NP swabs) will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either MOV or placebo, Q12H for 5 days. • MOV 800 mg (n~688) • Placebo (n~688)
Analysis Populations	**Efficacy**: mITT **Safety**: APaT
Primary Endpoint(s)	**Efficacy**: Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 14. **Safety**: AEs, and AEs leading to discontinuation of study intervention.
Secondary Endpoints	1. Percentage of participants (regardless of SARS-CoV-2 results in baseline NP swabs) developing COVID-19 through Day 14 2. Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 29. 3. Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs having viral transmission through Day 14. 4. Percentage of participants with detectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 14
Statistical Methods for Key Efficacy Analyses	The primary objective and hypothesis, superiority of MOV compared with placebo with respect to the percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 14, will be evaluated using a 2-sided 95% CI. The CI will be calculated based on the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with Cochran-Mantel-Haenszel weights (stratified by age and household size).
Statistical Methods for Key Safety Analyses	95% CIs (Tier 2 endpoints) will be provided for between treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	One IA will be performed to evaluate safety and futility with respect to the primary efficacy hypothesis. Results will be reviewed by an eDMC. A summary of the IA is provided below. Further details are provided in Section 9.7. • Timing: To be conducted when approximately 55% of the participants with undetectable SARS-CoV-2 in baseline NP swabs have either completed the Day 14 visit or discontinued from the study prior to the Day 14 visit. • Testing: The primary efficacy hypothesis will be tested.
Multiplicity	A gatekeeping strategy will be used to control the overall FWER associated with the primary and secondary analyses. The following efficacy hypotheses will be tested sequentially at a one-sided 2.49% Type I error rate at final analyses: 1. Primary efficacy hypothesis (H1) testing superiority of MOV compared with placebo in participants with undetectable SARS-CoV-2 in baseline NP swabs through Day 14 2. Secondary hypothesis (H2) testing superiority of MOV compared with placebo in participants regardless of SARS-CoV-2 results in baseline NP swabs through Day 14 The primary hypothesis (H1) will be tested first. The secondary hypothesis (H2) will be tested only if H1 is rejected. If H1 fails to reach statistical significance, then H2 will not be tested. Although there is no plan to stop the study early for efficacy at the interim analysis, a small statistical penalty (α=0.0001) will be applied for this interim analysis. The final analysis will be conducted at 0.0249 alpha-level to preserve the type I error level.
Sample Size and Power	The study will enroll approximately 1376 participants (regardless of SARS-CoV-2 results in baseline NP swabs; approximately 688 each in MOV 800 mg and in the placebo group). Assuming approximately 20% of the 1376 participants will have detectable SARS-CoV-2 at baseline [O'Brien, M. P., et al 2021], this will result in approximately 1100 participants with undetectable SARS-CoV-2 at baseline. The primary objective will be assessed on the approximately 1100 participants with undetectable SARS-CoV-2 in baseline NP swabs. Assume: • A background secondary attack rate of 8% and an underlying treatment difference (MOV minus placebo) in percentage of participants developing COVID-19 through Day 14 of -4.8 percentage points (a 60% relative reduction in attack rate). • At least 10% of the approximately 276 participants with detectable SARS-CoV-2 in baseline NP swabs are randomized to the MOV group.

	The study has at least 90% power to demonstrate that MOV is superior to placebo for prevention of confirmed COVID-19 in household contacts (with undetectable SARS-CoV-2 in baseline NP swabs) of an index case through Day 14 at an overall one-sided 2.5% alpha-level. Details are provided in Section 9.9.1.

9.2 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment.

Blinding issues related to the planned interim analysis are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between treatment differences are listed below.

9.4.1 Efficacy Endpoints

The primary efficacy endpoint is the percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) through Day 14.

The secondary efficacy endpoints are:

- Percentage of participants (regardless of SARS-CoV-2 results in baseline NP swabs) developing COVID-19 through Day 14
- Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 29
- Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs having viral transmission through Day 14

- Percentage of participants with detectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 14

The exploratory efficacy endpoints are:

- Percentage of participants (regardless of SARS-CoV-2 results in baseline NP swabs) developing COVID-19 through Day 29
- Percentage of participants with detectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 29
- Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs having viral transmission through Day 29
- Percentage of baseline seronegative participants with undetectable SARS-CoV-2 in baseline NP swabs developing anti-SARS-CoV-2 antibodies through Day 29
- Severity of laboratory-confirmed COVID-19 through Day 29 using NIAID ordinal scale criteria
- Participant-reported symptoms severity (for specified COVID-19 symptoms) in participants who develop laboratory-confirmed COVID-19 on or before Day 14
- Change from baseline in SARS-CoV-2 RNA titer and percentage of participants with undetectable SARS-CoV-2 RNA in NP swabs at Day 14 in participants with detectable SARS-CoV-2 in NP swabs at baseline
- Viral RNA mutation rate and detection of treatment-emergent sequence variants as assessed by comparison of viral gene sequencing at baseline and postbaseline in participants who develop laboratory-confirmed COVID-19 on or before Day 14
- Percentage of participants who develop laboratory-confirmed COVID-19 on or before Day 14 utilizing health care related to COVID-19 through Day 29
- Generic health-related quality-of-life in participants through Day 29 via EuroQoL Five Dimension Questionnaire (EQ-5D-5L)

9.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

PDLC in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a baseline and postrandomization on-treatment measurement to be included. Participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study intervention) will be classified as to whether or not they fall outside the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria will be adapted from the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, JUL-2017, version 2.1. A listing of the participants who meet the criteria will also be provided.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The mITT will serve as the primary population for the analysis of efficacy data in this study. The mITT consists of all randomized participants who received at least 1 dose of study intervention. The primary objective will be assessed in the mITT-VN population, which consists of the subset of the participants in the mITT with undetectable SARS-CoV-2 in baseline NP swabs (ie, virus negative/undetectable at baseline). The mITT-VP population, consisting of the subset of the participants in the mITT with detectable SARS-CoV-2 in baseline NP swabs (ie, virus-positive/detectable at baseline) will be used in some of the exploratory analyses. Under certain extenuating circumstances (Section 8.2.5), eg, when only qualitative OP swab results are available from the central laboratory, qualitative OP swab results can be used to derive the baseline viral status.

A supportive analysis using the Per-Protocol population will be performed for the primary efficacy endpoint. The Per-Protocol population excludes participants from the mITT due to deviations from the protocol that may substantially affect the results of the primary efficacy endpoints. Participants with prophylaxis outcomes of "indeterminate" (Section 8.2.6) will be excluded from the Per-Protocol population. Moreover, participants who took <80% of the required doses will be excluded from the Per-Protocol population.

The final determination on protocol deviations, and thereby the composition of the Per-Protocol population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

Due to the conflict in Ukraine, participants in Ukraine who were randomized in FEB-2022 with incomplete data for the primary endpoint (ie, no clinical outcome assessment on Day 14) will be excluded from the efficacy analyses in the mITT population.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the intervention group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the

intervention group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the intervention group corresponding to the study intervention actually received.

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

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP. Methods related to analyses of biomarkers and other exploratory samples (Section 8.10) will be described separately.

Efficacy results that will be deemed to be statistically significant after consideration of the type I error control strategy are discussed in Section 9.8 and a description of the interim analysis is in 9.7. Statistical testing and inference for safety analyses are described in Section 9.6.2.

9.6.1 Statistical Methods for Efficacy Analyses

For the evaluation of the primary hypothesis, the superiority of MOV compared with placebo with respect to the percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 14 will be assessed using the stratified Miettinen and Nurminen method with CMH weights [Miettinen, O. and Nurminen, M. 1985]. Stratification factors include age and household size as specified in Section 6.3.2. The primary hypothesis will be addressed by testing the null hypothesis $p_t \geq p_c$ versus the alternative hypothesis $p_t < p_c$, where p_t and p_c refer to event rates in MOV and placebo groups in participants with undetectable SARS-CoV-2 in baseline NP swabs, respectively. The null hypothesis will be rejected if the 1-sided p-value is less than 0.0249 (see Section 9.8 for alpha adjustment) and the superiority of MOV relative to placebo will be demonstrated for the primary endpoint.

For the analysis of this primary endpoint in the mITT-VN population, the following Table shows how to handle the indeterminate clinical outcomes of prophylaxis presented in Section 8.2.6 (Table 4).

Table 4 Imputation for Indeterminate Prophylaxis Outcomes

Indeterminate Prophylaxis Outcomes	Imputation
Lost to follow-up during or discontinued from the study prior to the window of interest (ie, prior to Visit 4 or Visit 6 for the outcome assessments conducted at those visits). This does not include participants who were already determined to be clinical failures prior to being lost to follow-up or discontinued.	Considered a case of COVID-19
Death unrelated to COVID-19	Considered a case of COVID-19
Missing the required viral test for confirmation of COVID-19 (see also Section 8.2.6 for details around acceptable windows)	Considered a case of COVID-19
Other extenuating circumstances that preclude classification as a clinical success or failure (such as the participant receives another agent for the prevention of COVID-19)	Considered a case of COVID-19
Participants in Ukraine who were randomized in FEB-2022 without clinical outcome assessment on Day 14 will be excluded from the efficacy analysis.	

Moreover, a participant without a Day 14 clinical outcome assessment, but assessed as a clinical success through Day 29 will be treated as a clinical success through Day 14. A participant without a Day 29 clinical outcome assessment, but assessed as a clinical failure through Day 14 will be treated as a clinical failure through Day 29. If a participant discontinued from the study prior to the Day 14 or the Day 29 visit, but was assessed as a clinical failure from the COVID-19 Confirmation Visit, then the clinical failure should be carried forward to the Day 14 and/or the Day 29 visit after the COVID-19 Confirmation Visit. All other missing clinical outcome assessments will be imputed as clinical failures.

For the evaluation of the secondary hypothesis, the superiority of MOV compared with placebo with respect to the percentage of participants (regardless of SARS-CoV-2 results in baseline NP swabs) developing COVID-19 by Day 14 will be assessed using the same method in the primary hypothesis, ie, the stratified Miettinen and Nurminen method with CMH weights [Miettinen, O. and Nurminen, M. 1985] (stratified by age and household size as described in Section 6.3.2, and SARS-CoV-2 status in baseline NP swab). The secondary hypothesis will be evaluated by testing the null hypothesis $p_{ts} \geq p_{cs}$ versus the alternative hypothesis $p_{ts} < p_{cs}$, where p_{ts} and p_{cs} refer to event rates (percentages of participants developing COVID-19 by Day 14) in MOV and placebo groups, respectively. The null hypothesis will be rejected if the 1-sided p-value is less than 0.0249 (see Section 9.8 for alpha adjustment) and the superiority of MOV relative to placebo will be concluded for this secondary endpoint.

The efficacy of MOV compared with placebo for the prevention of COVID-19 with respect to the percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 29 will be evaluated. The difference in percentages between treatment groups (MOV minus placebo) and the associated 95% CI will be

calculated using the stratified Miettinen and Nurminen method with CMH weights [Miettinen, O. and Nurminen, M. 1985] (stratified by age and household size as described in Section 6.3.2).

For the evaluation of the prevention of viral transmission using MOV compared with placebo through Day 14 among participants with undetectable SARS-CoV-2 in NP swabs at baseline, the percentage of participants in the 2 intervention groups who have positive/detectable SARS-CoV-2 RNA through Day 14 will also be compared using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] (stratified by age and household size as described in Section 6.3.2).

The efficacy of MOV compared with placebo for the prevention of COVID-19 with respect to the percentage of participants with detectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 14 will be evaluated. The difference in percentages between treatment groups (MOV minus placebo) and the associated 95% CI will be calculated using the Miettinen and Nurminen method with CMH weights [Miettinen, O. and Nurminen, M. 1985].

A detailed analysis strategy for key efficacy endpoints is listed in Table 5.

Table 5 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 14	P	Stratified M&N method with CMH weights[b]	mITT-VN	As described in 9.6.1
Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 14	S	Stratified M&N method with CMH weights[b]	PP	Observed data only
Secondary				
Percentage of participants (regardless of SARS-CoV-2 results in baseline NP swabs) developing COVID-19 by Day 14	P	Stratified M&N method with CMH weights[b]	mITT	As described in 9.6.1
Percentage of participants (regardless of SARS-CoV-2 results in baseline NP swabs) developing COVID-19 by Day 14	S	Stratified M&N method with CMH weights[b]	PP	Observed data only

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 29	P	Stratified M&N method with CMH weights[b]	mITT-VN	As described in 9.6.1
Percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 29	S	Stratified M&N method with CMH weights[b]	PP	Observed data only
Percentage of participants who develop positive/detectable SARS-CoV-2 through Day 14 among those with undetectable SARS-CoV-2 in NP swabs at baseline	P	Stratified M&N method with CMH weights[b]	mITT-VN	M=C[c]
Percentage of participants who develop positive/detectable SARS-CoV-2 through Day 14 among those with undetectable SARS-CoV-2 in NP swabs at baseline	S	Stratified M&N method with CMH weights[b]	PP	Observed data only
Percentage of participants with detectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 14	P	Stratified M&N method with CMH weights[b]	mITT-VN	As described in 9.6.1
Percentage of participants with detectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 14	S	Stratified M&N method with CMH weights[b]	PP	Observed data only

C=case of COVID-19; CMH=Cochran-Mantel-Haenszel; M=missing; M&N=Miettinen and Nurminen; mITT-VN=modified intent-to-treat population with undetectable SARS-CoV-2 in baseline NP swabs; NP=nasopharyngeal; PP=per-protocol.

[a] P=Primary approach; S=Supportive approach.

[b] Miettinen and Nurminen method with CMH weights stratified by age and household size.

[c] M=C is Missing considered as a case of COVID-19.

Participants in Ukraine who were randomized in FEB 2022 without clinical outcome assessment on Day 14 will be excluded from the efficacy analysis.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

The analysis of safety results for participants will follow a tiered approach (Table 6). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet PDLCs in laboratory will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Safety parameters or adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. No a priori clinical events of concern have been identified for this study.

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the percentage of participants with events (via the unstratified Miettinen and Nurminen method (1985) [Miettinen, O. and Nurminen, M. 1985]).

Because many 95% confidence intervals for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

ECIs identified in Section 8.4.7 are considered Tier 2 events, as well as the broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE, which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints. In addition, individual AEs observed in ≥1% of participants in any intervention group will be categorized as a Tier 2 event. Events reported less frequently than in 1% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful differences.

Safety endpoints that are not Tier 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in Table format.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison[a]	Descriptive Statistics
Tier 2	ECIs	X	X
	Any AE	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥1% of participants in one of the intervention groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <1% of participants in all of the intervention groups)		X
	Change from Baseline Results in selected laboratory test results		X

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

[a] 95% CIs will be based on the method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

9.6.3 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

Study enrollment is likely to be ongoing at the time of the interim analysis. Blinding to treatment assignment will be maintained at all investigational sites. The results of the interim analysis will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An eDMC will serve as the primary reviewer of the interim data and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level to act on these

recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional details for this interim analysis and any other study data review will be provided in the eDMC Charter.

Results from the interim analysis will be provided to the eDMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

This study will include an interim analysis when approximately 55% (or approximately 600 across the MOV and the placebo groups) of the participants with undetectable SARS-CoV-2 in baseline NP swabs have either completed the Day 14 visit or discontinued from the study prior to the Day 14 visit. The purpose of this interim analysis is to review safety and allow for early stopping in the case of futility. There is no plan to stop the study early for efficacy. However, a small statistical penalty (α=0.0001) will be applied for this interim analysis using a Haybittle-Peto type adjustment [Haybittle, J. L. 1971] [Peto, R, et al 1976]. The final analysis will be conducted at a 0.0249 alpha-level to preserve the overall type I error level.

The allocation of the approximately 1100 participants with undetectable SARS-CoV-2 in baseline NP swabs randomized to the 2 intervention groups may not be in a 1:1 ratio, since SARS-CoV-2 in baseline NP swabs will not be available before randomization so that the number of participants in each group may vary. As an example, the case when approximately 660 participants with undetectable SARS-CoV-2 in baseline NP swabs and approximately 440 participants with undetectable SARS-CoV-2 in baseline NP swabs are randomized to MOV and placebo groups, respectively, will be discussed in this section.

The Gamma family spending function with γ = -4 will be used to set the futility boundary for the primary endpoint as a guide for the eDMC to control overall type I error rate of 0.025, one-sided. Assuming the information fraction of 55%, the nonbinding futility boundary expressed on the risk difference (MOV minus placebo) is -0.0049. The boundary crossing probabilities for futility are 59.8% under H0 and 1.4% under H1 (risk difference of -0.048). Power assessments for additional scenarios where the number of participants with undetectable SARS-CoV-2 in baseline NP swabs may be different from the scenario described above are presented in Section 9.9.1.

9.8 Multiplicity

Two main objectives will be evaluated in this study. A gatekeeping procedure that controls the overall FWER associated with the primary and secondary analyses will be used. The primary hypothesis (H1) is that MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 in participants with undetectable SARS-CoV-2 in baseline NP swabs through Day 14. As stated in Section 9.6.1, the null hypothesis $p_t \geq p_c$ will be tested versus the alternative hypothesis $p_t < p_c$. The secondary hypothesis (H2) is that MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 in participants regardless of SARS-CoV-2 results in baseline NP swabs through Day 14. As stated in Section 9.6.1, this will be evaluated by testing the null hypothesis $p_{ts} \geq p_{cs}$ versus the alternative hypothesis $p_{ts} < p_{cs}$.

As stated in Section 9.7, although there is no plan to stop the study early for efficacy, a small statistical penalty (α=0.0001) will be applied for this interim analysis using a Haybittle-Peto type adjustment [Haybittle, J. L. 1971] [Peto, R, et al 1976]. The final analysis will be conducted at a 0.0249 alpha-level to preserve the overall type I error level.

Testing begins with the primary hypothesis (H1). The secondary hypothesis (H2) will be tested only if H1 is rejected. Both tests will be performed at the same one-sided 2.49% alpha-level. If H1 fails to reach statistical significance, then H2 will not be tested. In this way, the overall one-sided 2.5% type I error rate is controlled.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power Calculations for Efficacy Analyses (Primary Objective)

The study will enroll approximately 1376 participants (regardless of SARS-CoV-2 results in baseline NP swabs) in a 1:1 ratio to MOV and placebo groups. Assuming approximately 80% of the 1376 participants will have undetectable SARS-CoV-2 at baseline (see Section 4.2.3), approximately 1100 participants will have undetectable SARS-CoV-2 at baseline and 276 participants will have detectable SARS-CoV-2 at baseline.

The primary endpoint of this study is the percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 through Day 14. Thus, the primary analysis population consists of the approximately 1100 participants with undetectable SARS-CoV-2 at baseline, which is a subset of the 1376 participants randomized that is based on a factor (SARS-CoV-2 results in baseline NP swabs) that will not be available before randomization.

Moreover, because this factor cannot be used for stratification at randomization, the allocation of the participants with undetectable SARS-CoV-2 in baseline NP swabs randomized to the 2 intervention groups may not be in a 1:1 ratio. If at least 10% of the approximately 276 participants with detectable SARS-CoV-2 in baseline NP swabs are randomized to the MOV group, the study has at least 90% power to demonstrate the superiority of MOV over placebo for participants with undetectable SARS-CoV-2 in baseline NP swabs at an overall one-sided 2.5% alpha-level. The power and sample size calculation for the primary objective were computed using EAST and based on the following assumptions:

- The percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs is assumed to be 80% among the 1376 participants (see Section 4.2.3), resulting in approximately 1100 participants with undetectable SARS-CoV-2 in baseline NP swabs.

- The background secondary attack rate, in the absence of MOV, for participants with undetectable SARS-CoV-2 in baseline NP swabs, is assumed to be ~8% [Regeneron Pharmaceuticals, Inc. 2021].

- MOV is assumed to reduce the background secondary attack rate for participants with undetectable SARS-CoV-2 in baseline NP swabs by 60%, resulting in a secondary attack rate of ~3.2% in the MOV group.

- A futility interim analysis at 55% information as outlined in Section 9.7. The Haybittle-Peto type adjustment [Haybittle, J. L. 1971] [Peto, R, et al 1976] with a small amount of alpha (α=0.0001) will be applied to this interim analysis.

Some selected power and sample size calculations are presented in Table 7, including the extreme cases where all participants with detectable SARS-CoV-2 in baseline NP swabs are either in the MOV or the placebo group, and some less-extreme scenarios:

1. In the scenario where the approximately 276 participants with detectable SARS-CoV-2 in baseline NP swabs are balanced between the 2 intervention groups (allocation ratio of 1), approximately 550 participants with undetectable SARS-CoV-2 in baseline NP swabs would be randomized to each group.

2. In the scenario where the approximately 276 participants are all randomized to the MOV group, there would be approximately 412 participants with undetectable SARS-CoV-2 in baseline NP swabs in this group versus approximately 688 in the placebo group, with an allocation ratio (MOV versus placebo) of 0.6.

3. In the scenario where the approximately 276 participants are all randomized to the placebo group, there would be approximately 688 participants with undetectable SARS-CoV-2 in baseline NP swabs in the MOV group versus approximately 412 in the placebo group with an allocation ratio of 1.67.

4. Two additional scenarios with allocation ratios of 1.5 and 0.85 are also provided.

All scenarios are based on a total sample size of 1100 participants with undetectable SARS-CoV-2 in baseline NP swabs and an overall one-sided, 2.5% alpha-level.

Table 7 Power Analysis to Assess the Primary Objective in Participants With Undetectable SARS-CoV-2 in Baseline NP Swabs; N=1100 Participants, Overall Alpha=0.025, One-sided

Sample Size	Allocation Ratio	Sample Size in MOV	Sample Size in Placebo	Power (%)
1100	1.67	688	412	89
1100	1.5	660	440	90
1100	1	550	550	93
1100	0.85	505	595	94
1100	0.6	412	688	94
MOV=molnupiravir; NP=nasopharyngeal				

As shown in Table 7, the power in the first scenario (the extreme case where all approximately 276 participants with detectable SARS-CoV-2 in baseline NP swabs are in the placebo group) is approximately 89%. In scenarios where at least 10% of the participants with detectable SARS-CoV-2 in baseline NP swabs are in the MOV group, there is at least 90% power.

Moreover, as long as the event rate reduction is at least 54%, the study has over 80% power in the most extreme scenario (when all participants with detectable SARS-CoV-2 in baseline NP swabs, expected to be approximately 276, are in the placebo group).

9.9.2 Sample Size and Power Calculations for Efficacy Analyses (Secondary Objective)

The secondary endpoint associated with a hypothesis of this study is the percentage of participants developing COVID-19 through Day 14, regardless of SARS-CoV-2 results in baseline NP swabs. The related analysis population will consist of participants in the mITT population (see Section 9.5.1), approximately 1376 participants.

The power and sample size calculation for the secondary objective were computed using EAST and based on the following assumptions in addition to the assumptions listed in the previous section:

- The percentage of participants with detectable SARS-CoV-2 in baseline NP swabs is assumed to be 20% among the 1376 participants (see Section 4.2.3), resulting in approximately 276 participants with detectable SARS-CoV-2 in baseline NP swabs.

- The background secondary attack rate, in the absence of MOV, for participants with detectable SARS-CoV-2 in baseline NP swabs, is assumed to be ~40% based on the secondary attack rate calculated for the virus-positive participants in the REGEN-COV™ prophylaxis study [O'Brien, M. P., et al 2021] [Food and Drug Administration 2021].

- The secondary attack rate for participants in the MOV group with detectable SARS-CoV-2 in baseline NP swabs is ~28% (with a risk reduction of 30% relative to the placebo group based on the reduction observed with REGEN-COV™ in this population) [O'Brien, M. P., et al 2021] [Food and Drug Administration 2021].

Since the SARS-CoV-2 viral status at baseline will not be available before randomization, there is a potential imbalance in the 2 study intervention groups for participants with undetectable and detectable SARS-CoV-2 in baseline NP swabs. This also leads to different potential allocation ratios of participants with undetectable versus detectable SARS-CoV-2 in baseline NP swabs in the 2 study intervention groups. Assessment of power for this comparison is presented under 3 selected scenarios in Table 8:

- Scenario with more participants with detectable SARS-CoV-2 in baseline NP swabs in the MOV group (as listed in Table 7). There are approximately 188 participants with detectable SARS-CoV-2 in baseline NP swabs and 500 participants with undetectable SARS-CoV-2 in baseline NP swabs randomized to the MOV group. Approximately 88

participants with detectable SARS-CoV-2 in baseline NP swabs and 600 participants with undetectable SARS-CoV-2 in baseline NP swabs are randomized to the placebo group.

- Equal allocation scenario: There are approximately 138 participants with detectable SARS-CoV-2 in baseline NP swabs and 550 participants with undetectable SARS-CoV-2 in baseline NP swabs randomized to in each of the 2 intervention groups.

- Scenario with more participants with detectable SARS-CoV-2 in baseline NP swabs in the placebo group (as listed in Table 7 and described in Section 9.7). There are approximately 28 participants with detectable SARS-CoV-2 in baseline NP swabs and 660 participants with undetectable SARS-CoV-2 in baseline NP swabs randomized to the MOV group. Approximately 248 participants with detectable SARS-CoV-2 in baseline NP swabs and 440 participants with undetectable SARS-CoV-2 in baseline NP swabs are randomized to the placebo group.

All scenarios below are based on a total sample size of 1376 participants and an overall one-sided, 2.5% alpha-level.

Table 8 Power Analysis to Assess the Secondary Objective Participants; N=1376 Overall Alpha=0.025, One-Sided

Sample Size	Sample Size						Power (%)
	V-		V+		Total		
	MOV	Placebo	MOV	Placebo	MOV	Placebo	
1376	500	600	188	88	688	688	24
1376	550	550	138	138	688	688	95
1376	660	440	28	248	688	688	>99

MOV=molnupiravir; NP=nasopharyngeal; V- = undetectable SARS-CoV-2 in baseline NP swabs; V+ = detectable SARS-CoV-2 in baseline NP swabs

As shown in Table 8, the power for the secondary objective analysis is greater than 90% in second and third scenarios, given the stated assumptions. There is substantially less power in the first scenario where there is a marked and unfavorable imbalance in randomization of the participants with detectable SARS-CoV-2 in NP swabs, causing the difference in the overall secondary attack rates between the 2 intervention groups to be smaller.

9.9.3 Sample Size and Power Calculations for Safety Analyses

There will be approximately 1376 participants in total (approximately 688 participants in each intervention group) included for the analysis of safety endpoints.

Table 9 demonstrates the difference in the percentage of participants with an AE (MOV minus placebo) that can be ruled out with different power levels and 95% confidence when there are approximately 688 participants in each intervention group. The underlying percentage of participants with the AE is assumed to be the same for the 2 intervention

groups. For example, for an AE that occurs in 10% of participants in both groups, the study has 80% power to show with 95% confidence that the true difference between the treatment groups is no more than 5.0% percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 9 Difference in Percentage of Participants With AEs (MOV Minus Placebo) That Can be Ruled Out With 688 Participants in Each Group

Target Power	Underlying Percentage of Participants With AE			
	1%	5%	10%	20%
80	2.2%	3.8%	5.0%	6.4%
85	2.4%	4.1%	5.4%	6.8%
90	2.6%	4.5%	5.9%	7.4%

AE=adverse event; CI=confidence interval; MOV=molnupiravir.

Note: The upper bound of the 2-sided 95% CI (Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]) for the difference in percentages of participants with AEs (MOV minus placebo) assuming the percentages are the same.

The probability of observing at least 1 of a particular type of AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population. If the underlying percentage of participants with a particular AE is 0.1%, there is 49.8% chance of observing at least 1 AE among 688 participants in an intervention group. If no AE of that type is observed among the 688 participants in an intervention group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <0.6% (1 of approximately every 189 participants). The estimate of, and the upper bound of the 95% CI for, the underlying percentage of participants with an AE given various hypothetical observed numbers of participants with the AE within each treatment group are provided in Table 10. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934].

Table 10 Percentage of Participants with AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs (688 Participants per Group)

Hypothetical Numbers of Participants with AEs	Percentage	95% Upper Confidence Bound[a]
0	0.0%	0.5%
14	2.0%	3.4%
40	5.8%	7.8%
55	8.0%	10.3%
69	10.0%	12.5%

AE=adverse event; CI=confidence interval

[a] Based on the 2-tailed exact CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. 1934]).

9.10 Subgroup Analyses

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

- Baseline SARS-CoV-2 NP swab result (undetectable, detectable)
- Baseline serology result for anti-SARS-CoV-2 antibodies (positive, negative)
- Age category (≤60, >60 years)
- Household size (≤3, >3 household residents)
- Sex (female, male)
- Race (American Indian or Alaska Native, Asian, Black or African American, White)
- Geographic region (North America, Europe, Asia Pacific, Latin America, Africa)

9.11 Compliance (Medication Adherence)

Compliance will be calculated based on capsule counts. For a participant who is followed up for the entire study treatment period, the "Number of Capsules Should be Taken" is the total number of capsules that should be taken from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinues from the study treatment, the "Number of Capsules Should be Taken" is the total Number of Capsules should be taken from randomization to the date of the last dose of study intervention. The "Number of Capsules Taken" will be based on data reported in the eCRF.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Capsules Taken}}{\text{Number of Capsules Should be Taken}} \text{ X } 100$$

Summary statistics will be provided on percent compliance by treatment group for the mITT.

9.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, median, standard deviation) for the "Number of Capsules Taken" by treatment group.

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

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.5 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 11 will be performed by the central laboratory. (Note: Local laboratory assessment of protocol-required safety laboratory assessments [chemistry, hematology, and pregnancy] may be permissible under extenuating circumstances. Sponsor approval must be obtained, and results must be recorded in the appropriate eCRF).

- Documentation of the index's first detectable SARS-CoV-2 local laboratory test result from a sample collected within 5 days prior to randomization of the potential participant(s) in the study is required.

- Other local laboratory results are only required if the central laboratory results are not available in time for participant management, or for either study intervention administration and/or response evaluation. If a collection of a local sample is required, it is important that the sample for central analysis is obtained first (eg, NP swab). Additionally, if the local laboratory results are used for participant management, or to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.

- 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.

- The investigator (or medically qualified designee) must document their review of each laboratory safety report (eg, hematology, chemistry, pregnancy).

- Laboratory/analyte results that could unblind the participant's intervention group will not be reported to blinded site and Sponsor personnel. These laboratory results include, but may not be limited to virology results with the exception of screening results and error reports.

Table 11 Protocol-required Clinical Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH RDW	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Calculation of: Neutrophil/lymphocyte ratio Absolute Neutrophil Count
Chemistry	BUN	Chloride	AST/SGOT
	Albumin	Calcium	ALT/SGPT
	Creatinine	Phosphorous	Alkaline phosphatase
	Glucose (nonfasting)	Amylase	GGT
	Potassium	Lipase	LDH
	Bicarbonate	Total Protein	Total bilirubin (and direct bilirubin if total bilirubin is elevated above the ULN)
	Sodium	Magnesium	
	CK		
Pregnancy Testing	• Urine or Serum hCG pregnancy test (as needed for WOCBP)		
Serology	• SARS-CoV-2 Antibodies		
Virology	• SARS-CoV-2 RNA (RT-PCR; qualitative and quantitative) from NP swab samples • SARS-CoV-2 Gene Sequencing		
Other Laboratory Assessments	• Testing for other respiratory pathogens is planned from NP swab samples.		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatine kinase; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; NP=nasopharyngeal; RBC=red blood cell; RDW=red cell distribution width; RNA=ribonucleic acid; RT-PCR=reverse transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential.

Table 12 Approximate Whole Blood Volumes (mL) for Clinical Laboratory Assessments

Study Period:	Screening	Intervention		Follow-up			COVID-19 Confirmation Visit	Total Blood Volume
Visit Number/Name:	1	2	3	4	5	6		
Scheduled Day (Window)	(≤5 days prior to rand)	Day 1	Day 5 (+ 2 days) EOT	Day 14 (+3 days)	Day 21 (+3 days)	Day 29 (+3 days) LFU		
Laboratory Assessment								
Chemistry[a] (Day 14 includes serum pregnancy)	Per Local Requirements	2.5	2.5	2.5	N/A	N/A	N/A	10.0
Hematology[a]	N/A	2.0	2.0	2.0	N/A	N/A	N/A	8.0
Anti-SARS-CoV-2 Antibody Serology Testing	N/A	5.0	N/A	5.0	N/A	5.0	N/A	15.0
Total	N/A	9.5	4.5	9.5	N/A	5.0	N/A	33.0

COVID-19=coronavirus infectious disease 2019; EOT=end of treatment (day of last study intervention dose); LFU=Late Follow-Up; N/A=not applicable; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

[a] Where local safety laboratories are permitted on days other than screening (see Appendix 2), volumes will be per local requirements.

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."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE which changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.

  - Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.

  - Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.

  - Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

  - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

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

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

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

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

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion (tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. **Highly Effective Contraceptive Methods That Are User Dependent[d] (must be used in combination with a barrier method)** • Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable • Progestogen-only hormonal contraception[b] - Oral - Injectable Barrier methods to be used with user dependent hormonal methods above (male condoms are preferred method) • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. [d] Failure rate of <1% per year when used consistently and correctly (and not in combination with barrier method). Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). Note: The following are not acceptable methods of contraception alone or in combination: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.10 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.

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirements for Argentina

Section 1.3.1 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 8.1.2 Inclusion/Exclusion Criteria

HBV, HCV, and HIV testing at screening is mandatory.

10.7.2 Country-specific Requirements for France

Section 1.3.1 Schedule of Activities

Footnote g: In France and associated territories, the following laboratory results must also be available for all participants within 5 days prior to administration of the first dose of study intervention to support determination of eligibility: serum creatinine, platelets, and absolute neutrophil count.

Section 8.1.2 Inclusion/Exclusion Criteria

For participants enrolled in France and associated territories, participants with any of the following conditions are excluded:

- A neutrophilic granulocyte absolute count <500/mm^3
- A platelet count <100,000/µL or received a platelet transfusion in the 5 days prior to randomization
- On dialysis or has reduced eGFR <30 mL/min/1.73 m^2 by the MDRD equation (Appendix 9):

  eGFR (mL/min/1.73 m^2) = 175 × $(SCr)^{-1.154}$ × $(age)^{-0.203}$ × 0.742 [if female] × 1.212 [if African American]

10.8 Appendix 8: Individuals at Increased Risk for Severe Illness from COVID-19

Individuals with at least 1 of the following characteristics or underlying medical conditions are at increased risk for severe illness from COVID-19, as adapted from the US CDC [Centers for Disease Control and Prevention 2020] [Centers for Disease Control and Prevention 2021] [Centers for Disease Control and Prevention 2020] [Centers for Disease Control and Prevention 2021] and the WHO [World Health Organization 2020]:

- Age >60 years
- Active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality [eg, basal cell carcinomas])
- Chronic kidney disease (excluding participants on dialysis or has reduced eGFR <30 mL/min/1.73 m^2; See Section 5.2)
- Chronic obstructive pulmonary disease
- Obesity (body mass index* of 30 or higher)
- Serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies
- Diabetes mellitus

* Body mass index = weight (kg)/[height (m)]^2

10.9 Appendix 9: Calculation of eGFR

Modification of Diet in Renal Disease Study (MDRD) equation

eGFR (mL/min/1.73 m^2) = 175 × $(SCr)^{-1.154}$ × $(age)^{-0.203}$ × 0.742 [if female] × 1.212 [if African American]

Notes:

- eGFR = estimated glomerular filtration rate
- SCr = standardized serum creatinine
- Age = years

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APaT	all-participants-as-treated
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CD4	cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTFG	clinical trial facilitation group
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EAST	software platform for the statistical design, simulation and monitoring of clinical trials
ECG	electrocardiogram
ECI	event of clinical interest
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
EEA	European Economic Area
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	executive oversight committee
EOT	end of treatment
EUA	emergency use authorization
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FWER	family wise error rate
GCP	good clinical practice
GLP	good laboratory practice
H1	hypothesis 1
H2	hypothesis 2
HBV	hepatitis B virus
hCG	human chorionic gonadotropin

Abbreviation	Expanded Term
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
IRT	intervention randomization system
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhoea method
LFT	liver function test
LFU	late follow-up
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MERS	Middle East respiratory syndrome
mITT	modified intent-to-treat
mITT-VN	subset of modified intent-to-treat population with undetectable SARS-CoV-2 in baseline nasal swabs
mITT-VP	subset of modified intent-to-treat population with detectable SARS-CoV-2 in baseline nasal swabs
MOV	Molnupiravir (MK-4482)
N/A	not applicable
NCT	National Clinical Trial
NEJM	New England Journal of Medicine
NHC	β-D-N^4-hydroxycytidine
NHC-TP	N-hydroxycytidine pharmacologically active triphosphate
NIAID	National Institute of Allergy and Infectious Diseases
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect-level
NP	nasopharyngeal
NSAE	nonserious adverse event
OP	oropharyngeal
PCR	polymerase chain reaction
PDLC	predefined limit of change
PK	pharmacokinetic
PPE	personal protective equipment
PRO	patient reported outcome
Q12H	administered once every 12 hours
RBC	red blood cell
RdRp	RNA-dependent RNA polymerase
RDW	red cell distribution width
rINN	recommended International Nonproprietary Name
RNA	ribonucleic acid
RSV	respiratory syncytial virus

Abbreviation	Expanded Term
RT-PCR	reverse transcription polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	standardized serum creatinine
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SpO_2	oxygen saturation
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
VSV	vesicular stomatitis virus
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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