Official Protocol Title:	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19
NCT number:	NCT04575584
Document Date:	17-DEC-2020

Title Page

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Protocol Title: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19

Protocol Number: 001-01

Compound Number: MK-4482

Sponsor Name:

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

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT	2020-003367-26
IND	147734

Approval Date: 17 December 2020

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	17-DEC-2020	To revise the dose selection process before initiation of Part 2 (Phase 3), update the benefit/risk assessment, clarify the primary efficacy endpoint definition, and add a new inclusion criterion and discontinuation criterion
Original Protocol	14-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

To revise the dose selection process before initiation of Part 2 (Phase 3), update the benefit/risk assessment, clarify the primary efficacy endpoint definition, and add a new inclusion criterion and discontinuation criterion.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for Study Design 8.1.8 Study Intervention Administration	References to 'Day 1' and/or 'first dose' were revised to 'randomization' and clarification regarding study day numbering (ie, randomization = Day 1) was provided	To add clarity and consistency
1.2 Schema 5.1 Inclusion Criteria	Clarified that 10-day window for assessment of COVID-19 sign/symptoms does not include the day of randomization	To clarify the timing of symptom onset prior to randomization for study eligibility
1.3 Schedule of Activities	-Included an option for clinic or at-home visit in lieu of virtual visits on Days 2 and 4. Corresponding update in Section 8.11.2.4.	-To increase flexibility for visit scheduling

Section # and Name	Description of Change	Brief Rationale
	-Added a footnote to clarify that LFU visit will occur 7 months after the last dose of study intervention.	-To add clarity
	-Visit Window for LFU visit changed to ±1 Month.	-To increase flexibility for visit scheduling
	-Review of inclusion/exclusion criteria added to Day 1 in SoA and Section 8.1.2	-To add clarity for the timing of certain screening activities in relation to randomization through the IRT system.
	-COVID-19 severity must be based on Day 1 pre randomization values. Corresponding updates to Section 8.1.2.	-To add clarity.
	-Clarified that the first dose of study intervention is preferably administered on Day 1. Corresponding updates in Section 8.1.8.	-To add clarity.
	-Revised note for Serum and Plasma for Exploratory Research to provide the correct cross-reference.	-To correct an error.
	-Added a separate line to the SoA for collection of serum for antibody exploratory research	-To add clarity as a separate laboratory collection kit is needed to collect this sample.
	-Text revised to indicate that discharge readiness will be assessed daily while hospitalized.	-To add clarity.

Section # and Name	Description of Change	Brief Rationale
	-Added a separate line to the SoA for Blood Collection for Local Laboratory Evaluation and revised footnote. Corresponding updates to Section 8.1.2. -Added a separate line in SoA requiring sites to confirm contraception requirements	-To add clarity for local laboratory evaluations during screening. -To add clarity for confirming contraceptive requirements.
1.3 Schedule of Activities 4.2.1.1.3 Secondary endpoints (Ordinal Scales) 8.2.5 (Deleted) National Institutes of Health Stroke Scale 9.4.1.1 Efficacy Endpoints 10.8.1 Pulmonary and Pulmonary +	Removed the use of the NIHSS in assessing stroke-related neurological deficits.	To remove use of NIHSS due to the challenges of implementing the tool at all participating clinical sites.
2 Introduction 4.1 Overall Design	An additional term and abbreviation for MK-4482 were added.	To introduce molnupiravir, and the abbreviation MOV, as the generic name for MK-4482
[redacted]		

Section # and Name	Description of Change	Brief Rationale
[redacted] 5.1 Inclusion Criteria 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.11.4 Late Follow-up (7 month)Visit	Revised inclusion criteria regarding contraception duration and duration of pregnancy follow up for WOCBP from 7 months after the last day of study intervention to 28 days from the start of study intervention.	[redacted]
4.1 Overall Design	Added text to clarify that participants will be contacted 7 months after the last dose of study intervention.	To add clarity and consistency
4.2.1.1.1 Primary Clinical Endpoint 9.4.1.1 Efficacy Endpoints	Clarified events that do not meet the definition of sustained recovery.	To clarify definition of sustained recovery.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	-Clarified use of molecular or antigen tests are allowed if authorized for use in the country. Serological tests that detect host antibodies are not allowed to confirm study eligibility. -Inclusion Criterion #4 added to indicate that participants with mild, moderate, or severe COVID-19 (per Appendix 9) are eligible for study entry.	-To clarify appropriate diagnostic testing that can be used for study eligibility -To add clarity
5.2 Exclusion Criteria 8.1.2 Inclusion/Exclusion Criteria	Revised exclusion criterion related to HBV or HCV infection.	To allow participants with stable and/or well-controlled HBV/HCV participation in the study.
5.2 Exclusion Criteria	Mechanical ventilation criterion edited.	To broaden this criterion since participants with a recent history of mechanical ventilation for any reason (not just due to COVID-19) are a higher risk for re-intubation.
6.1 Study Intervention(s) Administered	Changed the placebo comparator use from experimental to placebo	To add clarity
6.3.1 Intervention Assignment	Added text describing study intervention assignments.	Inadvertently omitted in original protocol.
6.3.2 Stratification	Revised wording of stratification criteria. Repeated text present in Section 4.1 regarding planned sample size.	To add clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
6.4 Study Intervention Compliance	Study intervention compliance requirements clarified.	To allow increased flexibility in the event that local infection-control restrictions do not allow for direct medical supervision of study intervention administration or for confirmation at the time of dosing by a member of the study site staff other than the person administering the study intervention.
6.5 Concomitant Therapy	Updated 'Investigational Agents" to "Non-Covid-19 Investigational Agents" and "medications" to "therapies" in the Prohibited and Allowed Therapies table	To clarify that this row refers to Investigational Agents not intended for COVID-19 treatment and for wording consistency.
7.1 Discontinuation of Study Intervention	-Added criteria for participants who meet liver enzyme ECI criteria -Revised criterion for participants with a platelet count <50,000 µL that repeat confirmatory testing is needed. -Added a discontinuation criterion for participants who become pregnant -Repeated discontinuation text present in Sections 8.6.1 and 8.6.2.	-To align with ECI criteria for participant safety -To align with the ECI criterion -To add criterion for participant and fetal safety -To add clarity and consistency
8.1.8 Study Intervention Administration	Added text describing study intervention administration.	To provide text inadvertently omitted in original protocol

Section # and Name	Description of Change	Brief Rationale
8.1.8.1 Timing of Dose Administration	-Timing of dosing and EOT visit was added -Clarified that if a participant's renal function deteriorates requiring dialysis, discontinuation is not required	-To clarify details regarding the EOT visit requirements -To add clarity
8.1.14 Study Medication Diary	-Added options for recording study intervention in the Study Medication diary. -Included option for collection of the Study Medication Diary at the Day 10 visit if collection at EOT is not feasible. -Clarified capsule count definition. Corresponding updates made in Section 9.11.	-To increase flexibility for appropriate methods of recording study intervention administration -To provide flexibility -To provide clarification that capsule count should be recorded on the eCRF
8.3.1 Physical Examinations	Revised to indicate the height and weight data will be collected (not measured).	To allow increased flexibility for collection of height and weight data.
8.3.3 Electrocardiograms	Revised text to indicate that ECG parameters may be either calculated manually during review by a qualified physician or obtained via an ECG machine that automatically calculates such parameters.	To allow increased flexibility for ECG data collection.
8.6.1 Blood Collection for Measurement of NHC in Plasma	Footnote added to clarify timing of pre-dose samples in Part 2.	To provide text inadvertently omitted from original protocol

Section # and Name	Description of Change	Brief Rationale
8.6.2 Blood Collection for Measurements of NHC-TP in PBMCs	PBMC requirements clarified.	To allow flexibility if PBMC collection is not possible due to infection control restrictions.
8.11.2.2 Hospitalized Visits	Removed text indicating that participants require ≥24 hours of medical care in the hospital.	To clarify specific duration of medical care in the hospital required for study eligibility.
9.1 Statistical Analysis Plan Summary 9.5.1 Efficacy Analysis Populations 9.5.2 Safety Analysis Populations 9.9.3 Sample Size and Power Calculations for Safety Analyses (Part 2)	-Clarified that Part 1 (Phase 2) and Part 2 (Phase 3) efficacy endpoints will be analyzed separately -Clarified that Part 1 (Phase 2) and Part 2 (Phase 3) will be combined for the final analysis of safety endpoints	To provide additional details regarding the analysis of efficacy and safety in Part 1 (Phase2) and Part 2 (Phase 3).

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Analysis Plan Summary 9.7 Interim Analyses	Revised to state that dose evaluation will occur after 300 participants complete EOT, MK-4482-001 and MK-4482-002 combined, during IA1 Modifications made to IA1 and IA2 to indicate that dose selection for Phase 3 will not occur until IA2	To clarify the timing for dose evaluation
9.2 Responsibility for Analyses/In-house Blinding 9.7 Interim Analyses	Clarified that Part 2 of the study will not be initiated until Part 1 of the study is completed	To add clarity
9.4.1.1 Efficacy/Pharmacokinetics Endpoints	Description of WHO 11-point ordinal scale was added	To provide more detail about the significance of the WHO 11-point ordinal scale
9.6.1 Statistical Methods for Efficacy Analyses	-Removed geographic region as stratification factor for the primary analysis. -Text added to describe sensitivity analyses. -Text added to clarify impact of lost to follow up and other discontinuations on primary endpoint.	To clarify primary analysis methodology

Section # and Name	Description of Change	Brief Rationale
9.6.1 Statistical Methods for Efficacy Analyses 9.9.2 Sample Size and Power Calculations for Virology Analyses (Part 1)	-Statistical methods for viral RNA endpoints added -Section added to describe sample size and power calculations for viral RNA endpoints.	To provide additional description for the analyses of virology endpoints
9.6.2 Statistical Methods for Safety Analyses	Updated Tier 3 safety endpoint description	To align table with text
9.7 Interim Analyses	Revised Sponsor siDMC review of IA1 data	To revise purpose of siDMC review of IA1 data
9.10 Subgroup Analyses	-Revised subgroup related to remdesivir use. -Added a subgroup for corticosteroid use at baseline.	-To add clarity -To add a subgroup factor
10.2 Appendix 2: Clinical Laboratory Tests	Updated approximate whole blood volumes and visit windows. Corresponding updates in Section 8.	To revise the specimen collection volumes and to clarify windows for specimen collection time points
10.7 Appendix 7: Country-specific Requirements	Text added to indicate that participants in South Korea whose renal function deteriorates requiring dialysis must be discontinued.	To provide country-specific requirement for South Korea

Section # and Name	Description of Change	Brief Rationale
10.9 Appendix 9: COVID-19 Severity Categorization	Table format was modified. Clarified that participants with new oxygen needs not previously on supplemental oxygen are considered to have severe COVID-19.	To add clarity
Throughout the document	Corrected minor typographical and grammatical errors	To improve clarity and consistency throughout the document.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19

Short Title: MK-4482 Ph 2/3 Study in Hospitalized Adults with COVID-19

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in hospitalized participants ≥18 years of age with COVID-19.

Primary Objectives	Primary Endpoints
- To evaluate the efficacy of MK-4482 compared to placebo as assessed by the rate of sustained recovery from randomization through Day 29. Hypothesis (H1): MK-4482 is superior to placebo as assessed by the rate of sustained recovery through Day 29.	- Time-to-sustained recovery
- To evaluate the safety and tolerability of MK-4482 compared to placebo.	- Adverse events - Adverse events leading to discontinuation of study intervention
Secondary Objectives	Secondary Endpoints
- To evaluate the efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who die through Day 29. Hypothesis (H2): MK-4482 is superior to placebo as assessed by the percentage of participants who die through Day 29.	- All-cause mortality

- To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response on selected ordinal outcome scales at Day 3, EOT, Day 10, Day 15, and Day 29.	- Pulmonary score - Pulmonary+ score
- To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT.	- National Early Warning Score
- To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29.	- WHO 11-point scale score

Overall Design:

Study Phase	Phase 2/Phase 3
Primary Purpose	Treatment
Indication	COVID-19
Population	Participants ≥18 years of age hospitalized with COVID-19
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 12 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:

A total of ~1300 participants will be randomized in the study.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Treatment Period
Part 1 (N~300)					
MK-4482 (200 mg)	MK-4482	200 mg	Q12H	Oral	5 days (10 doses total)
MK-4482 (400 mg)	MK-4482	400 mg	Q12H	Oral	5 days (10 doses total)
MK-4482 (800 mg)	MK-4482	800 mg	Q12H	Oral	5 days (10 doses total)
Placebo	Placebo	0 mg	Q12H	Oral	5 days (10 doses total)
Part 2 (N~1000)					
MK-4482	MK-4482	TBD mg	Q12H	Oral	5 days (10 doses total)
Placebo	Placebo	0 mg	Q12H	Oral	5 days (10 doses total)

N=number of participants to be enrolled in each part of the study; Q12H=once every 12 hours; TBD=to be determined based on dose selected in Part 1 of the study.

Total Number of Intervention Groups/ Arms

Part 1: 4 groups

Part 2: 2 groups

Duration of Participation

Each participant will be in the study for up to approximately 7 months from the time the participant provides documented informed consent through the final contact. Participants will receive 10 doses of assigned study intervention (administered Q12H) and will be followed for 28 days after randomization. In addition, participants will be contacted approximately 7 months after the last dose of study intervention.

Study Governance Committees:

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

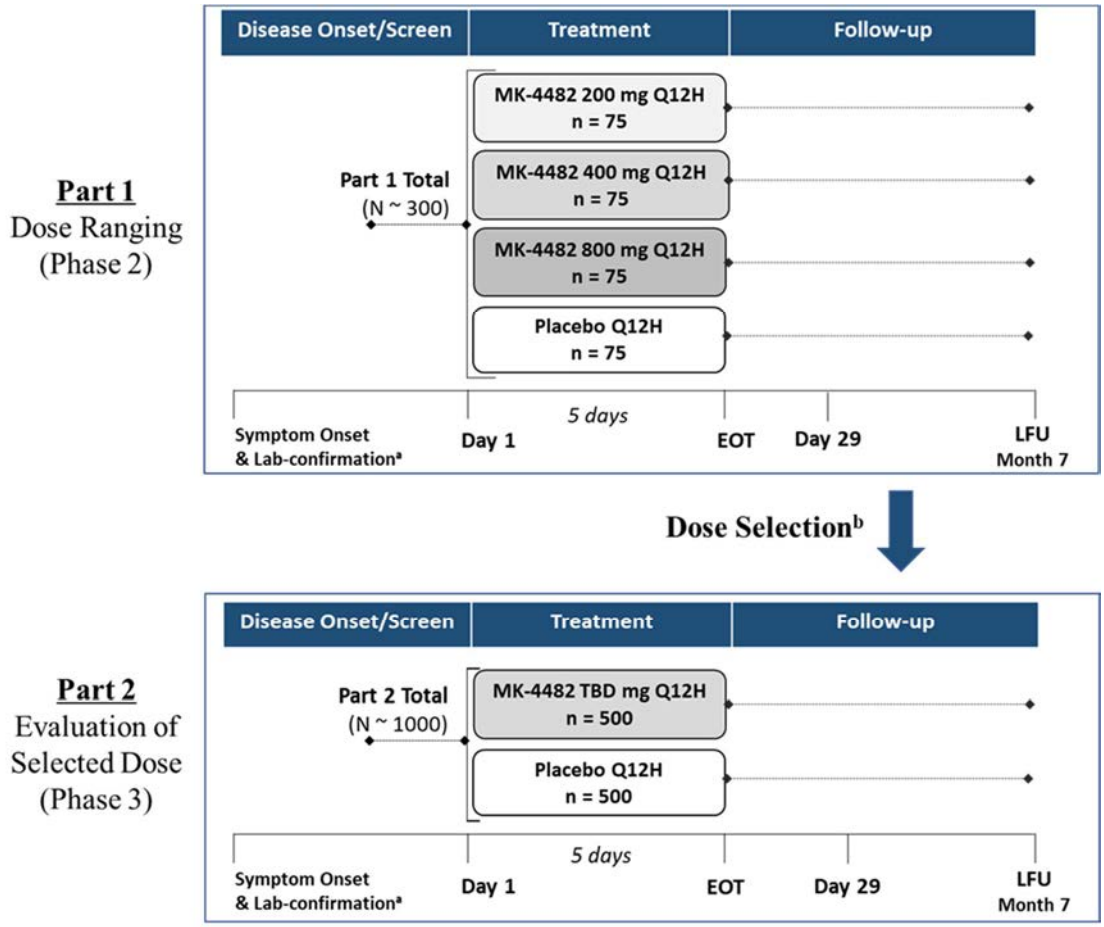
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema and Treatment Plan



EOT=End of Treatment; LFU=Late Follow-up Visit; N=total number of participants in each study part; n=number of participants per group; Q12H=administered once every 12 hours; TBD=to be determined based on dose selection in Part 1 of the study

[a] Eligible participants will have PCR-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤10 days prior to randomization (Section 5.1). Calculation of the 10-day symptom onset window does not include the date of randomization (Section 5.1).

[b] Dose selection will be based on Part 1 interim analysis(es) in combination with the totality of data available across the MK-4482 clinical program prior to initiating Part 2 (Sections 4.3.3 and 9.7).

1.3 Schedule of Activities

Study Period:	**Screening**	**Intervention**					**Follow-Up**				**Notes**
Visit Number/Title:	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (and Window):	Screening (≤24 hours before rand.)[a]	Day 1[b]	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 Month)[c]	
Type of Visit H = Hospitalized C = Clinic or At-home visit V= Virtual Visit	H	H	H/C/ V	H/C	H/C/ V	H/C	H/C	H/C	H/C	V	Virtual, Clinic, and At-home visits are only allowed after discharge. Virtual visits (Day 2 and Day 4) will consist of Concomitant Medication and AE/SAE collection only. When a virtual visit is listed, a clinic or home visit is not required. Virtual visits may be conducted at the investigator's discretion.
Administrative Procedures											
Informed Consent	X										
Informed Consent for PBMC Collection (Optional)	X										Only a subset of participants at selected sites
Register Study Visit in IRT	X	X									
Inclusion/Exclusion Criteria	X[d]	X[e]									Including review of SARS-CoV-2 (+) local test results.
Participant Identification Card	X	X									Randomization number must be added to card at randomization.
Medical History	X										Including day of onset of COVID-19 signs/symptoms
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X		Including COVID-19 standard of care therapies and supportive care

Study Period:	**Screening**	**Intervention**					**Follow-Up**				**Notes**
Visit Number/Title:	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (and Window):	Screening (≤24 hours before rand.)[a]	Day 1[b]	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 Month)[c]	
Intervention Randomization		X[b]									COVID-19 severity categorization entered in IRT at randomization must be based on values obtained on Day 1 prior to randomization
Collect/Update Secondary Contacts for Participant	X					X		X	X		Also to occur upon discharge
MK-4482 or Placebo Administration[f]		X	X	X	X	X					First dose is preferably administered on Day 1 (randomization), but must be within 24 hours of randomization.
MK-4482 or Placebo - Observed Dosing						X					The morning dose at EOT will be observed to facilitate PK blood collection.
Efficacy Procedures											
NP and OP Swabs		X		X		X	X	X	X		Based on Part 1 data, NP and OP swab collection may be adapted to remove one method or timepoints throughout the life of the study; this will be communicated via Protocol Clarification Letters.
Serum and Plasma for Exploratory Research		X				X	X		X		Research samples will be stored for testing as described in Sections 4.2.5 and 8.8.
Serum for Antibody Exploratory Research		X				X	X		X		

Study Period:	**Screening**	**Intervention**					**Follow-Up**				**Notes**
Visit Number/Title:	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (and Window):	Screening (≤24 hours before rand.)[a]	Day 1[b]	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 Month)[c]	
Assessment of COVID-19 Signs, Symptoms, Functional Status		X	X	X	X	X	X	X	X		Assess signs and symptoms daily while hospitalized and only at study visits after discharge. Functional status only assessed at Day 1, Day 3, EOT, Days 10, 15, and 29. Assessment will not be done at virtual visits.
Assessment of Level of Consciousness (AVPU)		X				X					
Respiratory/ Oxygenation Status		X	X	X	X	X	X	X	X	X[g]	SpO_2 measured daily while hospitalized via pulse oximetry. If applicable: FiO_2, PaO_2, and supplemental oxygen use. SpO_2 will not be done at virtual visits.
Hospitalization Status		X	X	X	X	X	X	X	X	X	Discharge readiness will be assessed daily while hospitalized.
Survival Status									X	X	
Safety Procedures											
Full Physical Examination	X										Including height and weight
Directed Physical Exam		X		X		X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X		Heart rate, blood pressure, respiratory rate, temperature. Assess vitals daily while hospitalized and only on study visits after discharge.

Study Period:	**Screening**	**Intervention**					**Follow-Up**				**Notes**
Visit Number/Title:	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (and Window):	Screening (≤24 hours before rand.)[a]	Day 1[b]	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 Month)[c]	
Blood Collection for Local Laboratory Evaluation	X[d]										Local laboratory collection required unless chemistry/hematology results within 72h prior to randomization are available.
Blood Collection for Central Laboratory Evaluation		X		X		X	X	X	X		Hematology and Chemistry at all indicated time points. Inflammatory biomarkers at Day 1 and EOT only.
12-lead ECG	X	X									If ECG is conducted at Screening, then do not repeat on Day 1.
Serum Pregnancy Test (hCG; WOCBP only)	X[d]								X		
Confirm Contraception Requirements (WOCBP and male participants)		X		X		X	X	X	X	X	Confirm participant compliance with contraception requirements as outlined in inclusion criteria and Appendix 5
Urinalysis		X									
AE/SAE Review[h]	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics											
PK Plasma Sampling						X					Part 1: • Pre-dose, 1, 3, 5, 8 hours post-dose Part 2: • Pre-dose, 1, 5 hours post-dose

Study Period:	**Screening**	**Intervention**					**Follow-Up**				**Notes**
Visit Number/Title:	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (and Window):	Screening (≤24 hours before rand.)[a]	Day 1[b]	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 Month)[c]	
PK PBMC Sampling[i]						X					Part 1 (PBMC Cohort only): • Pre-dose, 1, 3, 5, 8 hours post-dose

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AVPU=Alert, Voice, Pain, Unresponsive; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; EOT=End of Treatment (day of last study intervention dose); FiO_2=fraction of inspired oxygen; hCG=human chorionic gonadotropin; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LFU= Late Follow-Up; IRT=intervention randomization system; NP=nasopharyngeal; OP=oropharyngeal; PaO_2=partial pressure of oxygen; PBMC=peripheral blood mononuclear cells; PSV= Pregnancy Status Visit; PK=pharmacokinetic; rand.=randomization; RNA=ribonucleic acid; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SAE=serious adverse event; SpO2 = oxygen saturation; WOCBP=women of childbearing potential.

[a] Screening and Day1 (randomization) can be done in same session. Study assessments should not be duplicated if screening and Day 1 (randomization) are completed on the same day.

[b] Assessments required for COVID-19 severity categorization (Appendix 9) for IRT (vital signs, COVID-19 signs/symptoms assessment, respiratory measures, oxygen therapy, ongoing medical history) must be completed and documented on Day 1 prior to calling IRT in order to randomize. All other Day 1 assessments must be completed on Day 1 prior to first dose of study intervention.

[c] LFU (Month 7) visit is 7 months from the last dose of study intervention.

[d] The following local laboratory results must be available for all participants from within 72 hours prior to randomization to support determination of eligibility: serum creatinine, platelets, and absolute neutrophil count (segmented neutrophils and bands). In participants with reported history of HBV or HCV, ALT and AST must be available from within 72 hours prior to randomization to support determination of eligibility. In WOCBP, a negative local serum pregnancy test is required within 24 hours of the first dose of study drug per inclusion criteria. All other inclusion/exclusion criteria determination (eg, HIV status, pancreatitis, etc.) 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).

[e] Confirm no change in eligibility based on inclusion/exclusion criteria and/or disease severity.

[f] If participant is discharged prior to study intervention completion, study intervention and the Study Medication Diary will be dispensed to the participant according to the pharmacy manual.

[g] Respiratory/Oxygenation Status collection at the LFU visit will be limited. As LFU will be a virtual visit, SpO_2 will not be measured. Use of supplemental oxygen will be collected.

[h] AEs, SAEs, and other reportable safety events (eg, pregnancy) will be monitored according to Section 8.4.

[i] A subset of ~100 participants will take part in the PBMC Cohort at selected sites.

2 INTRODUCTION

MK-4482 (also known as molnupiravir [pINN], MOV, or EIDD-2801) is a novel ribonucleoside analog prodrug with broad-spectrum antiviral activity against a range of RNA viruses, including coronaviruses. MK-4482 is being developed as an oral treatment of COVID-19 for hospitalized and non-hospitalized adults.

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 over 500 thousand associated deaths [World health Organization 2020]. With increasing numbers of cases and deaths worldwide and very limited treatment options, there is an immediate unmet medical need for new effective therapies.

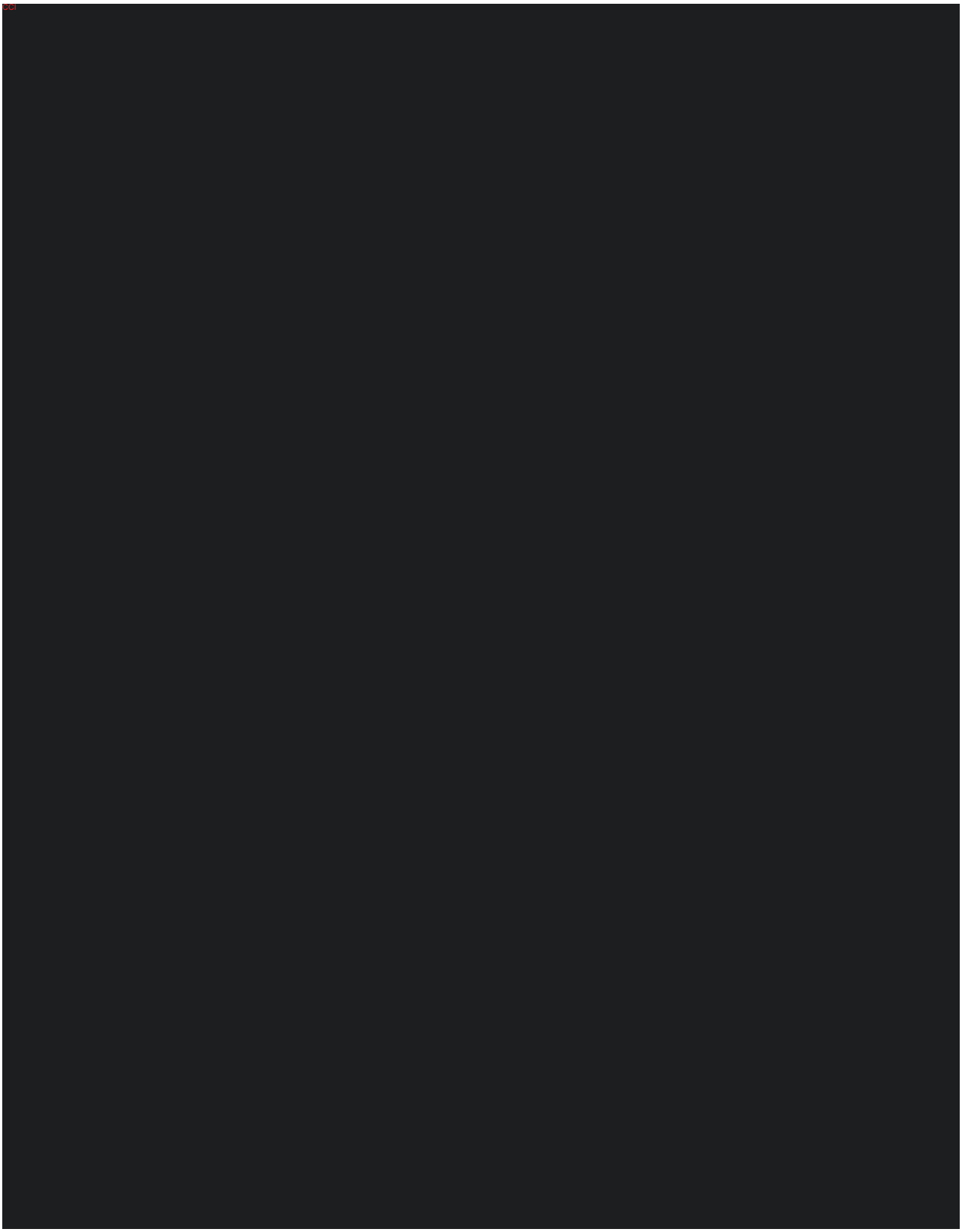
The true burden of COVID-19 is yet to be fully understood. Although most (>80%) infected individuals exhibit a mild illness (eg, fever, dry cough, fatigue), approximately 14% experience severe disease (eg, dyspnea, hypoxemia), and 5% have critical illness which can include respiratory failure, septic shock, and/or multiple organ dysfunction [Wu, Z. 2020]. There is an increased risk for progression to severe disease with increasing age and/or presence of underlying medical conditions in adults [Clark, A., et al 2020]. The burden of COVID-19 extends to extrapulmonary manifestations including neurologic complications (eg, ischemic and hemorrhagic strokes), thrombotic complications due to hypercoagulable state, gastrointestinal damage, and dermatologic and ocular manifestations [Klok, F. A., et al 2020] [Cevik, M., et al 2020] [Wang, T., et al 2020] [Wadman, M., et al 2020].

Standard of care treatment of COVID-19 is rapidly evolving and local treatment guidelines continue to be updated with emerging data [COVID-19 Treatment Guidelines Panel 2020] [Bhimraj, A., et al 2020] [World health Organization 2020]. Remdesivir is an antiviral agent administered intravenously for the treatment of hospitalized patients with COVID-19 under conditional marketing authorization by the European Commission and Emergency Use Authorization by the US FDA [Beigel, J. H., et al 2020]. However, there remains a need for an orally bioavailable antiviral agent for treatment of COVID-19.

MK-4482 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. MK-4482 has been generally safe and well tolerated to date in ongoing clinical studies.

2.2 Background

[redacted]



2.3 Benefit/Risk Assessment

[redacted]

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in hospitalized participants ≥18 years of age with COVID-19.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by the rate of sustained recovery from randomization through Day 29. **Hypothesis (H1)**: MK-4482 is superior to placebo as assessed by the rate of sustained recovery through Day 29.	• Time-to-sustained recovery
• To evaluate the safety and tolerability of MK-4482 compared to placebo.	• Adverse events • Adverse events leading to discontinuation of study intervention

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who die through Day 29. **Hypothesis (H2)**: MK-4482 is superior to placebo as assessed by the percentage of participants who die through Day 29.	• All-cause mortality
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response on selected ordinal outcome scales at Day 3, EOT, Day 10, Day 15, and Day 29.	• Pulmonary score • Pulmonary+ score
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT.	• National Early Warning Score
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29.	• WHO 11-point scale score
Tertiary/Exploratory	
• To measure the pharmacokinetics of NHC (the parent nucleoside), and NHC-TP (the pharmacologically-active triphosphate form) in plasma and PBMC at various timepoints.	• Plasma and PBMC pharmacokinetic parameters (eg, Ctrough, Cmax, tmax, t1/2, AUC0-12) (Part 1) • Plasma (Part 1 and Part 2) and PBMC (Part 1) pharmacokinetic concentrations (eg, C8hr)

Objectives	Endpoints
• To evaluate the antiviral activity of MK-4482 compared to 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 nasopharyngeal and/or oropharyngeal swabs separately at various timepoints.	• SARS-CoV-2 RNA
• To evaluate the effect of MK-4482 on viral RNA mutation rate as assessed by comparison of gene sequencing in virus isolated at baseline and post-baseline samples with evaluable SARS-CoV-2 RNA (Part 1).	• Viral RNA sequences

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-site study to evaluate the efficacy, safety, and PK of MK-4482 (also known as molnupiravir [pINN] or MOV) administered to hospitalized participants ≥18 years of age with PCR-confirmed COVID-19 and symptom onset within 10 days prior to randomization.

Enrollment of participants with severe COVID-19 (Appendix 9) will be limited to 50% of the total planned sample size in both Parts 1 and 2.

Participants will receive 10 doses of assigned study intervention by oral administration Q12H (±2 hours) and be followed for 28 days after randomization (through Day 29). In addition, participants will be contacted approximately 7 months after the last dose of study intervention.

Part 1 (Phase 2 - Dose Ranging)

Approximately 300 participants will be randomized in a 1:1:1:1 ratio (stratified per Section 6.3.2) into 1 of the following 4 blinded treatment groups (Figure 1):

- MK-4482 200 mg (n~75)
- MK-4482 400 mg (n~75)
- MK-4482 800 mg (n~75)
- Placebo (n~75)

The final dose selection will be based on analysis(es) of data from this study in combination with the totality of data available across the MK-4482 clinical program prior to initiating Part 2 (Sections 4.3.3 and 9.7).

Part 2 (Phase 3 - Evaluation of Selected Dose)

In Part 2, ~1000 participants will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either the selected dose of MK-4482 or placebo (Figure 1). An interim efficacy analysis is planned in Part 2 (Section 9.7).

Throughout the Study (Parts 1 and 2)

Participants may receive Sponsor-designated standard of care treatment of COVID-19, as appropriate, in addition to study intervention (Section 6.5). All participants will have plasma sample collection for PK assessments. The protocol will aim to enroll a subset of ~100 participants in an optional PBMC Cohort (Part 1) at select sites with capability to isolate PBMCs.

In the event of hospital discharge, study evaluations should be performed as described in Section 8. For participants who are discharged prior to end of treatment, a study intervention diary will be used to record dose administration.

All participants will have a virtual visit approximately 7 months following the last dose of study intervention (LFU visit) to assess survival status, current supplemental oxygen use, and to document any hospitalizations, according to the SoA (Section 1.3). In addition, pregnancy status for female participants of childbearing potential and female partners of male participants will be collected at this visit (Section 8.11.4).

The results of interim analyses will be reviewed by an independent eDMC (Parts 1 and 2) and Sponsor siDMC (Part 1 only) (Section 9.7 and Section 10.1.4). In addition, participant safety will be monitored by the independent eDMC through periodic review of accumulating data (received from an unblinded statistician) as detailed in the eDMC charter.

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

4.2 Scientific Rationale for Study Design

The randomized, placebo-controlled, double-blind superiority design and the selected endpoints of the study are consistent with regulatory guidance and are considered appropriate for hospitalized adult participants with COVID-19 [Food and Drug Administration 2020] [European Commission 2020].

The primary outcome is assessed through Day 29 (for 28 days of follow-up from randomization) to allow for a sufficient duration to reliably assess the safety and effectiveness of a 5-day treatment course of MK-4482. This duration is considered

appropriate to capture important clinically relevant efficacy endpoints (eg, time-to-sustained recovery, mortality). A 28-day follow-up period also aligns with the ACTT-1 Study Group's evaluation of remdesivir for treatment of COVID-19 in hospitalized adults [Beigel, J. H., et al 2020].

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Primary Clinical Endpoint

The primary endpoint selected in this study, time-to-sustained recovery, is intended to demonstrate the efficacy of MK-4482 relative to placebo using a clinically meaningful aspect of the disease relevant to hospitalized patients with COVID-19.

Sustained recovery is defined as:

1. Participant is alive and not hospitalized through Day 29 (including those re-hospitalized and discharged again before Day 29). Includes those discharged to home, home with nursing care, a rehabilitation facility, a long-term care facility, or a non-hospital intermediate care facility.

OR

2. Participant is alive and medically ready for discharge through Day 29 as determined by the investigator. Includes those hospitalized or re-hospitalized participants who no longer require ongoing medical care but remain hospitalized for infection-control reasons or due to delay in identifying living accommodation outside the hospital.

The following events do not meet the definition of sustained recovery:

- Died
- Discharged to hospice care
- Remains in facility receiving ongoing medical care
- Transferred to a general hospital unit or another hospital for ongoing medical care
- Re-hospitalized and not discharged or not medically ready for discharge again before Day 29
- Initially discharged to home, home with nursing care, a rehabilitation facility, a long-term care facility, or a non-hospital intermediate care facility, but subsequently transferred by Day 29 to hospice care or to a medical care facility due to worsening condition.
- Discharged but lost to follow-up through Day 29

4.2.1.1.2 Secondary Endpoint (Mortality)

All-cause mortality was selected as a relevant secondary endpoint to further evaluate efficacy of MK-4482 when administered to participants hospitalized with COVID-19. All-cause mortality is of particular interest in this study population, given the significant mortality caused by COVID-19 and the need for therapeutic agents to demonstrate rapid attenuation early in disease progression.

4.2.1.1.3 Secondary Endpoints (Ordinal Scales)

The Pulmonary and Pulmonary+ scales (Appendix 8) are ordinal categorical endpoints that assess intermediate measures of activity as indicators of disease progression and recovery. The Pulmonary ordinal scale focuses on the respiratory sequalae of COVID-19 and is defined based on oxygen requirements using 7 well-defined mutually exclusive categories. The Pulmonary+ ordinal scale is a 7-category assessment that captures the range of disease severity, including coagulation-related complications and respiratory dysfunction, experienced by hospitalized patients with COVID-19. The Pulmonary+ scale recognizes that non-pulmonary events are emerging as significant contributors to the overall morbidity of the disease. Of note, the Pulmonary+ scale was adapted to remove the use of the NIHSS in assessing stroke-related neurologic deficits due to challenges in implementing the NIHSS tool at all participating clinical sites. While the Pulmonary and Pulmonary+ scales are correlated, it is yet to be determined which of these 2 scales better represents clinical benefit and the impact of study intervention. Therefore, both scales will be used to assess benefit.

In addition, the National Early Warning Score will be used to assess a participant's degree of illness as assessed by clinical risk prediction categories for poor clinical outcomes including mortality within 24 hours of a set of vital sign measurements; the National Early Warning Score will be used as supportive evidence of the efficacy of MK-4482 when administered in hospitalized participants with COVID-19 (Appendix 8).

To further evaluate efficacy of MK-4482, the WHO 11-point ordinal outcome scale will also be used to assess COVID-19-associated symptom burden (severity and duration), hospitalization, and death through Day 29 (Appendix 8).

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 preclinical studies, mild hematologic toxicity was noted on Day 7 which progressed to more severe pancytopenia after 14-21 days of continuous exposure at 2.2-fold and 0.5-fold the NHC exposure at the 200 mg Q12H and 800 mg Q12H human dose of MK-4482 respectively. These changes were fully reversible (Section 2.3). There have been no clinically significant abnormalities observed in hematological laboratory tests in the Phase 1 study

(MK-4482-004). However, based on pre-clinical 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 72-fold the NHC exposure at 800 mg Q12H and not noted in dogs at 22-fold the NHC exposure at 800 mg Q12H. No clinically significant abnormalities in liver parameters were noted in the Phase 1 study at any dose. However, elevated LFTs with a DILI pattern will be considered an ECI and closely monitored.

No test-article related pathology changes in the pancreas to indicate pancreatic toxicity were noted in nonclinical studies, and lipase and amylase were not measured. Transient elevations of serum lipase were observed at least 3 days after last dose in the Phase 1 study. The occurrence and magnitude of these elevations did not appear to be dose related, and they were not associated with abdominal/gastrointestinal symptoms. However, as asymptomatic lipase elevations and clinical pancreatitis have been associated with some nucleoside analogs, changes in amylase/lipase will be considered an ECI and closely monitored.

4.2.1.3 Pharmacokinetic Endpoints

Blood samples for PK assessment and concentrations of the MK-4482 nucleoside and triphosphate will be collected from all participants as described in the SoA (Section 1.3) and Section 8.6. As appropriate, PK-efficacy and PK-AE relationships for MK-4482 will also be evaluated. PBMC PK samples will be used to evaluate the concentration of intracellular NHC-triphosphate, the active moiety resulting from dosing of MK-4482. Intracellular PBMC concentrations can help explain the relationship between MK-4482 dose and efficacy and safety.

In Part 1, plasma and PBMC PK parameters such as Ctrough, Cmax, tmax, t1/2, AUC0-12 will be estimated. In Part 2, plasma concentration values at each timepoint collected (eg, C8hr) will be summarized.

4.2.1.4 Virology Endpoints

The study will evaluate SARS-CoV-2 RNA to assess the impact of MK-4482 on various aspects of SARS-CoV-2 viral dynamics.

Reducing SARS-CoV-2 viral load or eradicating the virus is essential to recovery and has important implications for transmission and infection control strategies. The mechanism of antiviral activity of MK-4482 is viral error catastrophe predicated on increasing the viral mutation rate beyond a biologically-tolerable threshold resulting in impairment of viral fitness leading to viral extinction. These endpoints are aimed at assessing the antiviral activity of MK-4482 as well as evaluating the rate of viral mutagenesis with MK-4482 treatment.

4.2.1.5 Inflammatory Biomarkers

Inflammatory biomarkers have been shown to be correlated with the severity of COVID-19 and may provide insight on the progression of the disease [Zeng, F., et al 2020] [Velavan, T. P. 2020]. The study will explore the impact of MK-4482 on inflammatory response by evaluating select biomarkers (eg, CRP, IL-6, PCT, D-dimer, and ESR) at baseline and at EOT.

4.2.2 Rationale for the Use of Comparator/Placebo

This study will be placebo-controlled in order 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 may receive Sponsor-designated standard of care treatment (Section 6.5) as appropriate in addition to study intervention (MK-4482 or matching placebo).

There are currently no orally available direct-acting antivirals approved for the treatment of COVID-19. Remdesivir is an antiviral agent administered intravenously for treatment of patients with severe COVID-19 under conditional marketing authorization by the European Commission and Emergency Use Authorization by the US FDA. However, with blinding consideration between IV and oral administration and access limitations for sourcing in a global clinical study during the pandemic, it was not feasible to include remdesivir as the comparator for this study.

4.2.3 Rationale for the Selected Participant Population

The rationale for the participant population selected for this study is as follows:

- **Participants with mild, moderate, and severe COVID-19**: Participants with mild, moderate, and severe COVID-19 (Appendix 9) may all require hospitalization and may benefit from administration of MK-4482. Participants in this study must require medical care in the hospital for ongoing clinical manifestations of COVID-19 (not just for public health or quarantine purposes). Participants with critical COVID-19 will be excluded as antiviral therapy may have less impact on patients who have progressed to advanced critical illness due to the robust host inflammatory response that may confound antiviral treatment at this later stage in the disease. Furthermore, patients with critical COVID-19 demonstrated no difference in mortality or median time to recovery comparing placebo to remdesivir [Beigel, J. H., et al 2020].

- **Participants with signs/symptoms attributable to COVID-19 for ≤10 days**: Eligible participants must have COVID-19 signs/symptom onset no more than 10 days prior to randomization. SARS-CoV-2 viral loads are highest early in the course of disease, present 1-2 days prior to symptom onset, and persist for 7-12 days in moderate cases and up to 2 weeks in severe cases [Cevik, M., et al 2020]. Based on the viral kinetics of SARS-CoV-2 and the mechanism of action of MK-4482 (inhibition of viral replication), study participants must have signs/symptoms attributable to COVID-19 for ≤10 days prior to randomization with administration of

the first dose occurring within 24 hours of randomization. Furthermore, as the host inflammatory response predominates during later stages of disease as COVID-19 progresses, treatment with antiviral therapy is likely to have a greater benefit with early treatment rather than delayed treatment >10 days after sign/symptoms onset.

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 Other Exploratory Research Samples

Samples will be collected for other exploratory research. These samples may be utilized to perform evaluations related to SARS-CoV-2 and/or COVID-19 (including biomarkers), coinfections, or MK-4482. These samples may be tested during the course of the study or after study closure as the field of research evolves.

Blood for exploratory research, all residual material from NP and OP swabs, and all residual material from blood collections are intended for testing to address emergent questions not described elsewhere in the protocol and may be conducted on specimens from all participants. The objective of collecting/retaining specimens is to perform testing that informs the scientific understanding of SARS-CoV-2 and/or COVID-19, co-infections, or MK-4482.

Exploratory research samples will not be used for human genome testing. Samples may be used for testing such as:

- Determining if antibodies to SARS-CoV-2 are present and capable of neutralizing the virus
- Measuring the quantity of infectious, replication-competent virus present in samples
- Assessing if participants are co-infected with other respiratory pathogens

Evaluating the presence of antibodies to SARS-CoV-2 and their ability to neutralize the virus is critical to understanding the body's immune response to infection with SARS-CoV-2. COVID-19 severity may be correlated with the timing and quantity of antibody production based on participant characteristics such as gender. Antibody-dependent enhancement of disease has also been identified as a potential rationale for increased disease severity in some individuals [Ovsyannikova, I. G., et al 2020]. Antibody-related testing of participant samples

may be used to evaluate if participants receiving MK-4482 or placebo have varying production of SARS-CoV-2 antibodies.

Molecular tests detecting viral RNA are capable of quantifying viral loads in clinical samples; however, these molecular tests are incapable of quantifying infectious, replication-competent SARS-CoV-2 [Mendoza, E. J., et al 2020]. The quantity of infectious, replication-competent virus in participant samples may be measured via infectivity assays. One such assay is the plaque assay which quantifies the plaques formed in cell culture upon infection with serial dilutions of a virus specimen [Mendoza, E. J., et al 2020]. These infectivity assays may be used to evaluate the impact of MK-4482 on the quantity and/or presence of replication-competent virus.

Co-infection with other respiratory pathogens has been reported to occur to varying degrees in patients infected with SARS-CoV-2 and may be as high as 50% in non-survivors [Kim, D., et al 2020] [D'Abramo, A., et al 2020] [Wu, X., et al 2020] [Lai, C. C., et al 2020]. Participants enrolled may be coinfected with other pathogens. NHC has demonstrated broad antiviral activity against other RNA viruses including respiratory pathogens (eg, influenza, RSV, etc.) that have been observed in co-infection with SARS-CoV-2 [Lai, C. C., et al 2020]. Based on the potential for co-infection with other respiratory viruses, the potential impact of coinfection on outcomes, and the preclinical evidence of NHC antiviral activity against some of these pathogens, identifying participants coinfected with other respiratory viruses may be used to explore the impact of MK-4482 on co-infections.

4.3 Justification for Dose

4.3.1 Rationale for Dosing Duration

Three doses of MK-4482 (administered every 12 hours) were sufficient to demonstrate efficacy in a ferret model of influenza. However, the duration of dosing of MK-4482 required to achieve efficacy against SARS-CoV-2 in humans is unknown. The planned treatment regimen of 5 days in this study is consistent with other acute antiviral treatments such as oseltamivir for influenza and is supported by nonclinical and clinical safety data for MK-4482.

In a 28-day toxicity study of MK-4482 at 17 mg/kg/day (2.2-fold the predicted NHC exposure of 13.27 μM*hr at a dose of 200 mg BID) administered in dogs, reversible hematology changes consistent with bone marrow toxicity became apparent at Day 7 with increasing severity from Day 14 onward. Dosing of MK-4482 up to 800 mg Q12H for 5.5 days has been generally well tolerated by healthy participants in a Phase 1 clinical study; on review of preliminary blinded safety data, no clinically meaningful trends have been observed for changes in clinical laboratory values, vital signs, or ECGs as a function of dose or treatment. Specifically, there have been no clinically significant abnormalities observed in the hematological laboratory tests. Overall, preclinical and Phase 1 clinical observations to date support a ~5-day dosing duration for MK-4482.

4.3.2 Dose Range for Part 1 (Phase 2)

The dose range planned for Part 1 was derived based on the anticipated clinically efficacious dose range predicted from nonclinical animal models. MK-4482 demonstrated efficacy in ferrets (a relevant species for virus challenge models) against H1N1 at 7 mg/kg BID (in vitro data demonstrated similar MK-4482 potency against H1N1 and SARS-CoV-2). The efficacious 7 mg/kg BID dose in ferrets scales to ~100 mg BID in humans, based on body surface area (assuming a 70 kg adult). This is a common scaling approach used for nucleosides, with some variability in the scaling of the prodrug to active triphosphate conversion from animals to humans.

Part 1 of the study includes evaluation of the 200 mg BID dose, as it is within the efficacious dose range predicted from animals, and includes higher doses in order to characterize the dose- and exposure-response relationship for MK-4482. The highest dose of 800 mg BID has a predicted steady-state mean plasma AUC0-12 exposure of ~32 µM*hr, which is 2.4-fold below the mean plasma AUC0-12 exposure at the highest single dose evaluated in adults of 1600 mg.

4.3.3 Dose Selection for Part 2 (Phase 3)

The Phase 3 dose will be selected based on evaluation of Phase 2 data and will not exceed a dose of 800 mg Q12H. Interim analyses will be conducted as outlined in Section 9.7 to support dose selection.

4.4 Beginning and End of Study Definition

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

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. Early study termination may also be considered after review of accumulating efficacy and safety data by the eDMC (Section 9.7).

5 STUDY POPULATION

Male/female hospitalized participants ≥18 years of age with COVID-19 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:

Type of Participant and Disease Characteristics

1. Has documentation of PCR-confirmed SARS-CoV-2 infection with sample collection ≤ 10 days prior to the day of randomization.

   Note: PCR is the preferred method; however, with evolving approaches to laboratory confirmation of SARS-CoV-2 infection, other 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.

2. Had initial onset of signs/symptoms attributable to COVID-19 for ≤10 days prior to the day of randomization and ≥1 sign/symptom attributable to COVID-19 present at randomization.

3. Requires medical care in the hospital for ongoing clinical manifestations of COVID-19 (not just for public health or quarantine purposes).

4. Has mild, moderate, or severe COVID-19 (Appendix 9).

5. Is willing and able to take oral medication.

Demographics

6. Is male or female, ≥18 years of age, at the time of providing informed consent.

Male Participants

7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:

   - Refrain from donating sperm

     PLUS either:

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

     OR

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

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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

    - Is not a WOCBP

        OR

    - Is a WOCBP and using a contraceptive method that is highly effective (a low user dependency method OR a user dependent 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 for 28 days from the start 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.

    - A WOCBP must have a negative highly sensitive pregnancy test (serum test is required) within 24 hours before the first dose of study intervention.

    - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.

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

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

    - Given the elevated risk of venous thrombotic events in patients hospitalized with COVID-19 [Benson, L. S., et al 2020] [Spratt, D. I. 2020], estrogen-containing contraceptives must not be started to fulfill the contraceptive requirement of this study at any time during participant's hospitalization. If contraceptives are interrupted as standard of care management of COVID-19 patients 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

9. Participant (or legally acceptable representative) has provided documented informed consent for the study.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has critical COVID-19 (Appendix 9) with any of the following:
    - Respiratory failure defined based on resource utilization requiring at least one of the following:
        - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
    - Shock (defined by systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm Hg or requiring vasopressors)
    - Multi-organ dysfunction/failure
2. Is on dialysis or has reduced eGFR <30 mL/min/1.73m^2 by the MDRD equation (Appendix 10).
3. Has any of the following conditions:
    - HIV with a recent viral load >50 copies/mL or CD4 <200 cell/mm^3
    - Chemotherapy required within 6 weeks before randomization
    - A neutrophilic granulocyte absolute count <500/mm^3
    - Autologous or allogeneic hematopoietic stem cell transplant recipient

4. 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
5. Has a platelet count <100,000/µL or received a platelet transfusion in the 5 days prior to randomization.
6. Has a history of acute pancreatitis within 3 months prior to randomization or a history of chronic pancreatitis.
7. Has a baseline heart rate of < 50 beats per minute at rest.
8. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.
9. 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 who are not expected to survive longer than 48 hours after randomization, or
    - Participants who are expected to require mechanical ventilation within 48 hours after randomization, or
    - Participants with a recent history of mechanical ventilation, or
    - Participants with conditions that could limit gastrointestinal absorption of capsule contents.

Prior/Concomitant Therapy

10. Is taking or is anticipated to require any prohibited therapies as outlined in Section 6.5.

Prior/Concurrent Clinical Study Experience

11. Is unwilling to abstain from participating in another interventional clinical trial through Day 29 with an investigational compound or device, including those for COVID-19 therapeutics.

Diagnostic Assessments

Not applicable

Other Exclusions

12. Is anticipated to require transfer to a non-study hospital within 72 hours.

13. 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.

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	Intervention Type	Dose Formulation[a]	Unit Dose Strength(s)	Dosage Level(s)[b]	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
MK-4482	Experimental	MK-4482	Drug	Capsule	200 mg	Part 1: 200 mg, 400 mg, 800 mg Part 2: Dose to be selected	Oral	Q12H 5 days (10 doses total)	Experimental	IMP	Central
Placebo	Placebo Comparator	Placebo Matching MK-4482	Drug	Capsule	0 mg	Part 1: N/A Part 2: N/A	Oral	Q12H 5 days (10 doses total)	Placebo	IMP	Central

N/A=Not applicable; Q12H=every 12 hours

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

[a] Capsules will be administered by mouth. For participants unable to swallow study medication capsules during the treatment period, dosing of capsule contents via alternative routes (eg, nasogastric tube, orogastric tube, etc.) will be allowed.

[b] MK-4482 dose for Part 2 will be determined based on assessment of results of Part 1 and the totality of data available across the MK-4482 clinical program prior to initiating Part 2.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

For participants unable to swallow study medication capsules during the treatment period, dosing of capsule contents via alternative routes (eg, nasogastric tube, orogastric tube, etc.) will be allowed. Preparation details will be provided in the pharmacy manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. In Part 1, there are 4 study intervention arms and participants will be assigned randomly in a 1:1:1:1 ratio to MK 4482 200 mg, 400 mg, 800 mg, or placebo. In Part 2, there are 2 study intervention arms and participants will be assigned randomly in a 1:1 ratio to MK-4482 (at selected dose) or placebo.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Time from symptom onset prior to the day of randomization (≤5 days, >5 days)

2. Age (≤60 years, >60 years)

3. Remdesivir use for treatment of the index diagnosis of COVID-19 prior to or at the time of randomization (yes, no)

Based on the viral kinetics of SARS-CoV-2 and the mechanism of action of MK-4482, treatment with antiviral therapy is likely to have a greater benefit with early treatment (≤5 days) rather than late treatment (>5 days). Older age is also associated with more severe outcomes, and the WHO notes that people older than 60 years are at higher risk for severe illness due to COVID-19. Finally, remdesivir has been demonstrated to shorten the time to recovery in hospitalized patients with COVID-19 and may be used concurrently in this study. The selection of these criteria as stratification factors will help ensure that the treatment groups will be well balanced within each stratum and the study results will not be confounded by factors suspected to have a potential impact on a participant's response to study intervention.

Of note, enrollment of participants with severe COVID-19 (Appendix 9) will be limited to 50% of the total planned sample size in both Parts 1 and 2.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-4482 (all dose levels) and placebo will be packaged identically so 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.

Blinding of capsule contents for use via alternate routes (nasogastric tube, orogastric tube, etc.) will be performed by the unblinded site pharmacist or designee. Preparation details will be provided in the pharmacy manual.

To allow timely completion of dose/exposure-response analyses, select Sponsor internal or external personnel will be unblinded while Part 1 of the study is ongoing. No personnel directly associated with study conduct will be unblinded (before Part 1 database lock). Before granting select personnel access to unblinded Part 1 data, an official memo detailing the unblinding procedures and listing the personnel who will have access (before database lock) to the unblinded data will be generated per Sponsor SOP. Once all Part 1 participants have completed Day 29 (ie, achieved a final status for Day 29 endpoints), the Sponsor will initiate database lock/unblinding procedures for this part of the study. Internal blinding will be maintained for Part 2 participants until all Part 2 participants have completed Day 29 (ie, achieved a final status for Day 29 endpoints) except as documented in Section 9.7 – Interim Analyses.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. If local infection control restrictions do not allow for medical supervision, the study intervention must be administered by appropriately qualified institution (eg, hospital, clinic) staff. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. If local infection control restrictions do not allow for a confirmation at the time of dosing by a separate study site staff member, the study intervention administration source documentation must be contemporaneously reviewed by a member of the study site staff other than the person administering study intervention.

For participants who are discharged prior to receiving all 10 doses of study intervention, a Study Medication Diary will be provided for documentation of doses and assessment of compliance (Section 8.1.14).

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 his/her 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.

Table 2 Prohibited and Allowed Therapies

COVID-19 Vaccines	• SARS-CoV-2 vaccines are prohibited any time prior to randomization and through Day 29.
COVID-19 Therapeutics	• Sponsor-designated standard of care for treatment for COVID-19 is permitted (eg, remdesivir, corticosteroids, etc.) but may require additional safety monitoring as determined by the treating clinician. o If guidelines for local standard of care conflict with Sponsor-designated standard of care, site should consult with Sponsor. o Supportive therapies (including but not limited to anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms are allowed. o Unless designated by the Sponsor as acceptable standard of care for COVID-19, concomitant use of other therapies intended as specific treatment for COVID-19 are prohibited from randomization through Day 29.
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.

6.5.1 Rescue Medications and Supportive Care

Sponsor-designated standard of care for COVID-19 is permitted.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification of MK-4482 or placebo is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that 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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 8.11.3 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, places the participant at unnecessary risk from continued administration of study intervention.

- An elevated AST or ALT lab value that is ≥3X the upper limit of normal and an elevated total bilirubin lab value that is ≥2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is <2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

- The participant has any confirmed (ie, verified by repeat testing) platelet count of <50,000/μL.

- 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.

If a participant discontinues from study intervention early for any reason (ie, prior to the 9th or 10th dose), then plasma samples for PK and blood samples for PBMCs will not be collected for that participant (Section 8.6.1 and Section 8.6.2).

For country-specific requirements see Appendix 7.

7.2 Participant Withdrawal From the Study

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

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 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 utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 212 mL for participants in the PBMC Cohort or approximately 132 mL for all other participants (Appendix 2, Table 11).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent for PBMC Cohort Blood Sample Collection

The investigator or medically qualified designee will explain the PBMC Cohort blood sample collection to the participant and/or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before performing any procedure related to the PBMC Cohort blood sample collection. After applicable consent is obtained, these participants will have additional PBMC PK blood sample collection as specified in the SoA (Section 1.3) and Section 8.6.2. A copy of the signed informed consent will be given to the participant and/or participant's legally acceptable representative.

8.1.2 Inclusion/Exclusion Criteria

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

The SARS-CoV-2 test result must be reviewed for participant eligibility and data entered into the eCRF including date specimen collected, sample type (eg, NP swab, OP swab, mid-turbinate swab, saliva, etc.), test method (eg, RT-PCR) and result (positive result is required).

Assessments required for COVID-19 severity categorization (Appendix 9) for IRT (vital signs, COVID-19 signs/symptoms assessment, respiratory measures, oxygen therapy, ongoing medical history) must be completed and documented on Day 1 prior to calling IRT in order to randomize. All other Day 1 assessments must be completed on Day 1 prior to first dose of study intervention.

The following local laboratory results must be available for all participants from within 72 hours prior to randomization: serum creatinine, platelets, and absolute neutrophil count (segmented neutrophils and bands). In participants with reported history of HBV or HCV, ALT and AST must be available from within 72 hours prior to randomization to support determination of eligibility. In WOCBP, a negative local serum pregnancy test is required within 24 hours of the first dose of study drug per inclusion criteria.

All other inclusion/exclusion criteria determination (eg, HIV status, pancreatitis, etc.) 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).

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. Participants will be asked to provide any background or concomitant conditions, drug allergies and/or surgeries within the last 12 months. In addition, history of smoking (tobacco or marijuana), including use of vaping devices, will be collected. Medical history for the following

conditions will be collected separately on the Medical History Pre-Specified Conditions eCRF: chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised state from solid organ transplant, obesity, active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality), congestive cardiac failure, coronary artery disease, cardiomyopathies, sickle cell disease, and diabetes mellitus. Any oxygen therapy needs in the 7 days prior to symptom onset and through randomization will be reported in the oxygen therapy eCRF with flow rate reported in L/min. Reporting will include supplemental oxygen requirements during pre-morbid/pre-COVID-19, between the onset of COVID-19 signs/symptoms and study randomization, and any changes to oxygen therapy needs during the study treatment and follow-up periods.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medications taken by the participant within 30 days before first dose of study intervention. All prior therapeutics/vaccines for COVID-19, regardless of timing, must be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the participant during the study. All concomitant therapeutics/vaccines for COVID-19, including all supportive therapies (eg, anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms, must be reported.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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 treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Study intervention will be provided as per Table 1 and dispensed through the IRT system at the Day 1 (randomization) visit. The first dose of study intervention is preferably administered on Day 1 (randomization), but must be within 24 hours of randomization. If administered on the next calendar day following randomization, the day of administration of the first dose of study intervention in this case would be considered Day 2.

While the participant is hospitalized, study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

If a participant is discharged prior to study intervention completion, study intervention and the Study Medication Diary will be dispensed to the participant according to the pharmacy manual. Study intervention will then be self-administered by the participant Q12H at approximately the same times each day.

8.1.8.1 Timing of Dose Administration

Study staff will administer the appropriate number of capsules of study intervention per the pharmacy manual Q12H (±2 hours) each day for 10 doses. Study intervention can be administered without regard to food. Refer to Section 8.6 for details regarding PK collection.

- For participants that begin dosing in the morning on Day 1, the EOT visit will occur on Day 5. PK specimens will be collected at the EOT visit in association with the 9th dose, and the final 10th dose will occur in the evening on Day 5.
- For participants that begin dosing in the evening on Day 1, the EOT visit will occur on Day 6. PK specimens will be collected at the EOT visit in association with the 10th dose on Day 6.

As outlined in the SoA, the first dose of study intervention is preferably administered on Day 1 but may be administered within 24 hours of randomization, therefore it is possible that dosing may not begin until Day 2.

- For participants that begin dosing in the morning on Day 2, the EOT visit will occur on Day 6. PK specimens will be collected at the EOT visit in association with the 9th dose, and the final 10th dose will occur in the evening on Day 6.
- For participants that begin dosing in the evening on Day 2, the EOT visit will occur on Day 7. PK specimens will be collected at the EOT visit in association with the 10th dose on Day 7.

If the EOT visit occurs on Day 6, no additional visit is required on Day 5. And if the EOT visit occurs on Day 7, no additional visits are required on Day 5 or Day 6.

The timing of the morning dose on the EOT visit will be observed by site staff/delegate and should be aligned with the timing of blood collection for PK analyses at EOT (SoA, Section 1.3). For participants who are discharged prior to EOT, if the participant takes their

EOT dose without observation by study staff, and prior to the pre-dose PK blood draw, then the timing of the dose will be reported from the Study Medication Diary to study staff by the participant or legally acceptable representative and recorded in the appropriate source documentation.

For all doses, the timing of dose administration will be recorded by study staff. If the participant has been discharged, doses will 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 the normal dosing schedule resumed
- If >10 hours from the time the missed dose should have been taken, the missed dose should be skipped, and the normal dosing schedule resumed. The participant should not double the next dose to compensate for what has been missed

If a participant's renal function deteriorates, requiring dialysis during the study intervention, the Sponsor will not require the discontinuation of the study intervention; administration of the study intervention may continue at the discretion of the investigator. For participants who require continuous dialysis, study intervention should continue to be administered Q12H with no change to the timing of administration. For participants who require intermittent dialysis, study intervention should continue to be administered Q12H with doses administered 4-6 hours prior to dialysis where possible. For country-specific requirements see Appendix 7.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the 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.

8.1.11 Domiciling

PBMC cohort participants who have been discharged prior to the EOT visit will undergo intensive blood sampling from pre-dose to 8 hours post-dose on the EOT visit. The investigator may make arrangements (including local accommodations outside the context of a clinic visit if warranted) such that all sampling at specified timepoints can be performed as scheduled.

8.1.12 Calibration of Equipment

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

8.1.13 Collect/Update Secondary Contact Information

Sites will capture secondary contact information for 2 individuals that the site can contact if the participant cannot be reached (eg, spouse, friend, neighbor, etc.). Sites will also request healthcare provider contact information and a few hospitals that the participant is likely to go to if they get sick after discharge. Contact information for secondary contacts or health care

provider will not be recorded on any eCRF. If participants cannot be reached after 2 attempts 24 hours apart, then their listed secondary contact person(s) or healthcare provider will be contacted. At study entry only, sites will record the participant's home address in site records (it will not be reported on the eCRF).

Secondary contact information will be reviewed and updated according to the SoA (Section 1.3).

8.1.14 Study Medication Diary

For participants who are discharged prior to receiving all 10 doses of study intervention, a paper Study Medication Diary and instructions on how to take study intervention will be provided for documentation of doses and assessment of compliance. Participants should complete the Study Medication Diary for each dose taken. In the event that the participant is (in the judgment of the investigator) unable to complete the diary, information regarding study intervention administration may be recorded by an LAR or other close contact who witnesses administration of the study intervention.

The Study Medication Diary will be reviewed in conjunction with capsule counts by study staff. The participant's Study Medication Diary doses will be recorded in the eCRF for all doses after discharge. The Study Medication Diary should be reviewed in conjunction with capsule counts by study staff with the participant 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 10 visit. The study intervention data as recorded in the participant's Study Medication Diary will be entered in the eCRF.

8.2 Efficacy Assessments

8.2.1 Nasopharyngeal and Oropharyngeal Swabs

NP and OP swabs will be collected at various timepoints as outlined in the SoA (Section 1.3) for qualitative and quantitative SARS-CoV-2 RT-PCR testing and SARS-CoV-2 genome sequencing. At study entry (Day 1), the samples should be collected prior to the first dose of study intervention. Additional information, including instructions for swab collection, storage, and shipping, can be found in the laboratory manual.

NP and OP swab collection may be adapted to remove 1 method or timepoints throughout the life of the study; this will be communicated via Protocol Clarification Letters.

8.2.2 Assessment of COVID-19 Signs, Symptoms, and Functional Status

The investigator or medically qualified designee (consistent with local requirements) will assess COVID-19 signs and symptoms daily while the participant is hospitalized. After participant discharge, signs and symptoms will only be assessed on study visit days. Functional status will only be assessed at Day 1, Day 3, EOT, Day 10, Day 15, and Day 29.

The participant's ability to independently perform daily activities with minimal or no symptoms will be assessed and evaluated at the discretion of the investigator/designee.

8.2.3 Assessment of Level of Consciousness

Level of consciousness will be assessed using the Alert, Voice, Pain, Unresponsive scale [Royal College of Physicians 2012]. This assessment is conducted in sequence and only 1 outcome should be recorded as follows:

- Alert: participant is fully awake
- Voice: participant responds (in any manner) when spoken to
- Pain: participant responds to painful stimulus
- Unresponsive: participant does not respond to voice or pain

8.2.4 Respiratory/Oxygenation Status

SpO_2 will be measured once daily via pulse oximetry (SoA, Section 1.3) after the participant has been at rest for at least 5 minutes. If applicable, FiO_2 and arterial blood gas PaO2 should be reported. The oxygenation saturation level should be reported at a consistent time of day at each visit as noted in the SoA. Ensure the value is not impacted by external forces (eg, during rotating the participant's position).

Use of supplemental oxygen, including type (eg, oxygen from a conventional regulator or high flow heated and humidified device, non-invasive mechanical ventilation, invasive mechanical ventilation, ECMO) and flow rate (L/min) will be recorded on the appropriate eCRF. Supplemental oxygen requirements pre-morbid/pre-COVID-19 and between the onset of COVID-19 signs and symptoms and study randomization will be recorded (Section 8.1.4).

Note: Respiratory/Oxygenation Status collection at the LFU visit will be limited. As LFU will be a virtual visit, SpO_2 will not be measured. Use of supplemental oxygen will be collected.

8.2.5 Hospitalization Status

Hospitalization status will be assessed daily while hospitalized as outlined in the SoA (Section 1.3). The date and time that the participant is deemed medically ready for discharge will be recorded in addition to the actual date and time of discharge as applicable.

In the event of hospital discharge, the residence to which the participant was discharged and whether it was the residence occupied at the time of onset of COVID-19 symptoms will be ascertained.

In the event of re-hospitalization after initial discharge, 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. Information related to the re-hospitalization will be collected, including if the admission is related to COVID-19.

The Sponsor must be notified within 24 hours of site's awareness of a participant's hospitalization.

8.2.6 Survival Status

Survival status (ie, whether the participant is alive or dead) will be assessed per the SoA (Section 1.3).

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), per the SoA (Section 1.3).

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

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from pre-study to post-study visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Appendix 2, Table 11.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted at the screening visit by a nurse or other qualified healthcare provider. Height and weight will also be collected and recorded. A nurse or other qualified healthcare provider will also conduct directed physical examinations targeted at the participant's symptoms/complaints at all other in-person visits (in-clinic or at-home). Details of the physical examinations will be provided to an 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.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.3.3 Electrocardiograms

A local 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3). Calculation of heart rate and measurement of PR, QRS, QT, and QTc intervals may be manually calculated by a qualified physician or via an ECG machine that automatically calculates the values. Clinically significant findings must be documented in the source documents and captured in the appropriate eCRF.

If an ECG is performed for any medical reason while the participant is on study intervention or during the follow-up period, any clinically significant changes compared with the baseline ECG must be captured as AEs.

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

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

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (serum) should be conducted at screening and on Day 29, approximately 24 days after the last dose of study intervention.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

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

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

From the time of intervention randomization through 14 days following cessation of treatment, 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 of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Additionally, all pregnancies with a conception date occurring within 28 days after the first dose of study intervention for female participants or within 90 days after the last dose of study intervention for female partners of male participants must be reported by the investigator.

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

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

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 - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in). Exception: A positive pregnancy test at the time of the initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 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). From the time of randomization through 14 days following 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 following 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 lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

2. Any confirmed (ie, verified by repeat testing) platelet value <50,000 /µL, as determined by protocol-specified and/or unscheduled laboratory testing.

3. Any confirmed (ie, verified by repeat testing) amylase or lipase value >3X the upper limit of normal determined by protocol-specified and/or unscheduled laboratory testing.

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

8.6.1 Blood Collection for Measurement of NHC in Plasma

At the EOT visit, venous blood samples will be collected from all participants for the measurement of NHC concentrations in plasma (Table 4).

The timing of the morning dose on the EOT visit should be aligned with the timing of blood collection for PK analyses at EOT (Section 1.3 and Section 8.1.8.1). The EOT morning dose will be observed at the site or in-home visit and recorded by study staff/home health care personnel. If participants discontinue study intervention prior to the morning dose of the EOT visit (dose 9 or 10 depending on study intervention start), samples for PK will not be collected.

Sample collection, storage, and shipment instructions for plasma samples will be provided in a laboratory manual.

Table 4 Plasma Sample Collection Schedule for NHC Concentrations

Study Part	Plasma Sample Collection Time Points (Window)

Part 1	• 1 sample pre-dose[a]
	• 1 sample post-dose at each of the following timepoints:
	  ○ 1 hour (±30 min)
	  ○ 3 hours (±30 min)
	  ○ 5 hours (±1 hour)
	  ○ 8 hours (±1 hour)

Part 2	• 1 sample pre-dose[a]
	• 1 sample post-dose, each for the following timepoints:
	  ○ 1 hour (±30 min)
	  ○ 5 hours (±1 hour)

[a] Pre-dose sample should be collected within 2 hours prior to dosing.	

8.6.2 Blood Collection for Measurement of NHC-TP in PBMCs

At the EOT visit, venous blood samples will be collected from participants in the PBMC Cohort in Part 1 for the measurement of NHC-TP concentrations in PBMCs.

Two blood samples for PBMCs will be collected at each of the following timepoints on the EOT visit:

- 2 tubes pre-dose (within 2 hours prior to dosing)
- 2 tubes post-dose at each of the following timepoints:
    - 1 hour (±30 min)
    - 3 hours (±30 min)
    - 5 hours (± 1 hour)
    - 8 hours (±1 hour)

The timing of blood collection will be aligned with the timing of dose administration as outlined in Section 8.1.8.1. If participants discontinue study intervention prior to the morning dose of the EOT visit (dose 9 or 10 depending on study intervention start), samples for PBMCs will not be collected.

Sample collection, storage, and shipment instructions for PBMC samples will be provided in a separate manual.

In cases where PBMC cohort participants are discharged prior to the EOT visit but because of local infection control regulations are not able to return to the study site or alternate domiciling arrangements are not possible, or where home health services would not be able to obtain PBMC samples according to the laboratory manual specifications, PBMC samples are not required.

8.7 Pharmacodynamics

The virologic, clinical efficacy, and clinical safety endpoints (Section 3) will be used to evaluate any pharmacokinetic/pharmacodynamic relationships for MK-4482. For assessment of antiviral activity of MK-4482 at each study dose, baseline and post-dose virologic information (eg, viral RNA) at pre-specified timepoints (Section 1.3, SoA) will be measured. For each participant, the baseline measurement is defined as the measurement obtained pre-dose on the first day of dosing.

8.8 Biomarkers and Exploratory Research Samples

8.8.1 Biomarkers

Collection of samples for biomarker research is also part of this study, as outlined in Appendix 2. Samples for biomarker research are required and will be collected from all participants as specified in the SoA.

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the laboratory manual.

8.8.2 Exploratory Research Samples

Collection of samples for other exploratory research is also part of this study. These samples may be utilized to perform evaluations related to SARS-CoV-2 and/or COVID-19, co-infections, or MK-4482 as described in Section 4.2.5. These samples may be tested during the course of the study or after study closure as the field of research evolves.

Serum and plasma samples for exploratory research will be collected from all participants as specified in the SoA (Section 1.3) for exploratory research; in addition, residual material from NP/OP swabs and other previously collected blood samples may also be used. Sample collection, storage, and shipment instructions for the exploratory research samples will be in the laboratory manual.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

Sites will report hospitalization status and oxygenation and oxygen therapy data to support health economics assessments as per the SoA (Section 1.3) and Section 8.2.

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 LARs
- Performing at-home and/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 will occur ≤24 hours prior to study intervention randomization. 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

If the screening window has been exceeded, participants are allowed to rescreen one time if the participant still meets all the inclusion and none of the exclusion criteria at the time of rescreening. Once a participant has started the rescreening process, a new screening period (ie, an additional 24 hour window) will begin, during which time screening procedures will be repeated.

The following assessments must be repeated for participants who are rescreened:

- Vital signs and full physical examination
- Review medical history and prior/concomitant medications for new information
- 12-lead ECG
- Urinalysis (repeat if central laboratory sample from prior screening visit was not within 48 hours of first dose of study drug)
- Local laboratory assessments for inclusion/exclusion (results within 72 hours prior to randomization may be used for eligibility)
- 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 Hospitalized Visits

Screening will occur during hospitalization and ≤24 hours prior to study intervention randomization. Eligible participants must require medical care in the hospital for ongoing clinical manifestations of COVID-19 (not just for public health or quarantine purposes). Participants must be hospitalized for screening and Day 1. All other visits may occur outside of the hospital after discharge.

For participants who remain hospitalized through the study duration, study visits will be conducted as part of the hospital stay.

8.11.2.3 Clinic or At-Home Visits

For participants discharged from the hospital before completing the study, subsequent study visits may be performed at an alternative location from the hospital, such as the clinic/study site. In lieu of a participant traveling to the study site, an at-home visit by the site personnel or a healthcare provider (eg, home health care company, visiting nurse, etc.) may be appropriate to perform study assessments and procedures per the SoA (where available and when permitted by local regulations and IRB/IEC). For any visit conducted at home, the investigator/site personnel may also contact the participant virtually (on the same day) to conduct/confirm study procedures/assessments (eg, perform an investigator AE assessment).

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

8.11.2.4 Virtual Visits

For participants discharged prior to EOT, the investigator or designee may conduct the Day 2 and Day 4 visits with the participant virtually (eg, telehealth, telephone, webcast, videoconference, etc.). Identity of each participant should be confirmed according to institutional procedures and/or local guidelines prior to conduct of virtual visits. Virtual visits will consist of concomitant medication and AE/SAE collection only. When a virtual visit is listed in the SoA, a clinic or home visit is not required. Virtual visits may be conducted at the investigator's discretion.

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. Blood samples for PK will not be collected for participants who discontinue study intervention prior to their 9^{th} or 10^{th} dose. The participant should then be encouraged to complete all the remaining subsequent study visits after EOT as outlined in the SoA (Section 1.3). In the event that an active condition requires ongoing monitoring (eg, abnormal laboratory results, AEs, or progression of COVID-19 signs/symptoms), unscheduled visit(s) may be performed prior to the next study visit on Day 10.

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. Blood samples for PK will not be collected for participants who discontinue from study prior to their 9th or 10th dose of study intervention. Participants who withdraw from the study after completion of the treatment period should be encouraged to complete all applicable activities scheduled for the Day 29 visit at the time of withdrawal. This visit 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.

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

8.11.4 Late Follow-up (7 month) Visit

A virtual visit (eg, by telephone, webcast, videoconference, etc.) will be conducted at 7 months (± 1 month) after the last dose of study intervention for all participants. Information regarding survival status, current supplemental oxygen use, and any hospitalizations that occurred since last contact will be collected according to the SoA (Section 1.3).

In addition, 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 this visit. 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. Current and prior pregnancy data for any pregnancies with a conception date occurring within 28 days after the first dose of study intervention for female participants or within 90 days after the last dose of study intervention for female partners of male participants will be reported in relevant eCRFs. All reported pregnancies must be followed to the completion/termination of the pregnancy as described in Section 8.4.5.

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 a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data medical resource utilization outcomes, and plasma research 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 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19
Treatment Assignment	**Part 1:** Approximately 300 participants will be randomized in a 1:1:1:1 ratio (stratified per Section 6.3.2) to receive 1 of the following 4 blinded study interventions Q12H for 5 days. • MK-4482 200 mg (n~75) • MK-4482 400 mg (n~75) • MK-4482 800 mg (n~75) • Placebo (n~75) **Part 2:** A total of approximately 1000 participants will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either the selected dose of MK-4482 or placebo Q12H for 5 days.
Analysis Populations	**Efficacy:** MITT (Parts 1 and 2 separately) **Safety:** APaT (Parts 1 and 2 combined)
Primary Endpoint(s)	**Efficacy**: Time-to-sustained recovery from randomization through Day 29 **Safety**: Number of participants with AEs, and discontinuing study intervention due to AEs
Key Secondary Endpoints	• All-cause mortality through Day 29 • Odds of a more favorable response on Pulmonary score at Day 3, EOT, Day 10, Day 15 and Day 29 • Odds of a more favorable response on Pulmonary+ score at Day 3, EOT, Day 10, Day 15 and Day 29 • Odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT • Odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15 and Day 29

Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing MK-4482 (with selected dose) to placebo with respect to time-to-sustained recovery by Day 29 using a stratified log-rank test. The sustained recovery rate ratio will be estimated using the stratified Cox Proportional Hazards regression model.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with the adverse events; these analyses will be performed using the unstratified Miettinen and Nurminen method [Miettinen, O. 1985].
Interim Analyses	There will be 3 interim analyses during the study. **IA1 - Part 1: Dose Evaluation** This IA will be used to review data to inform dose selection models and analyses. **IA2 – Part 1: Dose Selection** This IA will be used to evaluate the dose/exposure-response to select the dose for Phase 3. **IA3 – Part 2: Futility/Early Efficacy** The purpose of this IA is to allow for early stopping in the case of futility and to allow for the initiation of marketing authorization applications in the case of a positive efficacy finding. Additional details about interim analyses are in Section 9.7.
Multiplicity	Multiplicity adjustments for interim analyses regarding type I error control are described in Section 9.7. Multiplicity adjustment strategy for sequential hypothesis testing is specified in Section 9.8.
Sample Size and Power	The total sample size for primary efficacy assessment (Part 2) will be ~1000 participants (~500 for the selected dose of MK-4482 and ~500 for the placebo group). The study has overall power of 90% to demonstrate that participants treated with MK-4482 have a higher rate of sustained recovery than participants treated with placebo at an overall one-sided, 2.5% alpha-level, if the underlying constant sustained recovery rate ratio between treatment groups is 1.3. Additional details and assumptions for sample size and power calculation are in Section 9.9.

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 has two distinct parts: Part 1 (Phase 2) and Part 2 (Phase 3). Part 2 will not be initiated until Part 1 is completed, the data have been analyzed and a dose for Part 2 is determined. Once all Part 1 participants have completed Day 29 (i.e., achieved a final status for Day 29 endpoints), the Sponsor will initiate database lock/unblinding procedures for this part of the study. Internal blinding will be maintained for Part 2 participants until all Part 2 participants have completed Day 29 (i.e., achieved a final status for Day 29 endpoints) except as documented in Section 9.7. For both parts of the study, Day 1 through Day 29 will be conducted as a double-blind study under in-house blinding procedures. The official, final database for Day 1 through Day 29 will not be unblinded within each part until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The clinical database and Sponsor personnel directly involved in the analysis and reporting of Day 1 through Day 29 will become unblinded at the time of the analyses of Part 1 and Part 2 data at Day 29, although study participants and site personnel will remain blinded until LFU. Results from after Day 29 through the LFU visit may be presented separately.

PK data may be unblinded early for the purpose of preparing a population PK model. A separate team from the protocol team will be unblinded for the purpose of preparing the PK model. Efficacy and safety data will not be unblinded for the purpose of preparing the PK model. Data or results from IA1, IA2, IA3 will not be shared with the protocol team before unblinding of the Sponsor for the relevant part of the study.

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

Blinding issues related to the planned interim analyses 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/Pharmacokinetics Endpoints

9.4.1.1 Efficacy Endpoints

Primary:

- Time-to-sustained recovery from randomization through Day 29

  Sustained recovery is defined as:

  1. Participant is alive and not hospitalized through Day 29 (including those re-hospitalized and discharged again before Day 29). Includes those discharged to home, home with nursing care, a rehabilitation facility, a long-term care facility, or a non-hospital intermediate care facility.

     OR

  2. Participant is alive and medically ready for discharge through Day 29 as determined by the investigator. Includes those hospitalized or re-hospitalized participants who no longer require ongoing medical care but remain hospitalized for infection-control reasons or due to delay in identifying living accommodation outside the hospital.

  The time to sustained recovery is the time from randomization to the day of discharge or the day that the participant is medically ready for discharge for participants who are not re-hospitalized. For participants who are re-hospitalized but discharged again before Day 29, the time to sustained recovery is the time from randomization to the day of the latest discharge.

  The following events do not meet the definition of sustained recovery:

  - Died
  - Discharged to hospice care
  - Remains in facility receiving ongoing medical care
  - Transferred to a general hospital unit or another hospital for ongoing medical care
  - Re-hospitalized and not discharged or not medically ready for discharge again before Day 29.
  - Initially discharged to home, home with nursing care, a rehabilitation facility, a long-term care facility, or a non-hospital intermediate care facility, but subsequently transferred by Day 29 to hospice care or to a medical care facility due to worsening condition.
  - Discharged but lost to follow-up through Day 29.

Section 9.6.1 describes the censoring dates for these participants.

Secondary:

- All-cause mortality through Day 29
- Odds of a more favorable response on Pulmonary score at Day 3, EOT, Day 10, Day 15, and Day 29
- Odds of a more favorable response on Pulmonary+ score at Day 3, EOT, Day 10, Day 15, and Day 29
- Odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT
- Odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15 and Day 29. This scale provides a measure of illness severity across a range from 0 (not infected) to 10 (dead).

Note: All ordinal scores will be determined programmatically by the Sponsor based on relevant data collected in eCRFs. Relevant data to support determination of each ordinal score will be collected in eCRFs as follows:

- Pulmonary and Pulmonary+ scores: supplemental oxygen use and methods, oxygen saturation, dialysis and vasopressor use, vital status, adverse events, and investigator assessment of the participant's ability to independently perform daily activities with minimal or no symptoms

- NEWS: vital signs (i.e., respiratory rate, pulse rate, blood pressure, temperature, oxygen saturation) and investigator assessment of the participant's level of consciousness using the Alert, Voice, Pain, Unresponsive scale

- WHO 11-point scale: central laboratory SARS-CoV-2 RNA results, supplemental oxygen use and methods, oxygen saturation, dialysis and vasopressor use, vital status and investigator assessment of the participant's ability to independently perform daily activities with minimal or no symptoms

Exploratory:

- Change from baseline in SARS-CoV-2 RNA titer in nasopharyngeal and oropharyngeal swabs separately at various timepoints

- Percentage of participants with undetectable SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swabs separately at various timepoints

- Viral RNA mutation rate as assessed by comparison of baseline and post-baseline virus sequencing (Part 1)

- Mean change from baseline in inflammatory biomarkers (eg, IL-6, hs-CRP, ESR, D-dimer, PCT)

In addition to the endpoints listed above, survival, supplemental oxygen use, and hospitalization status at the LFU visit (Month 7) will also be summarized.

9.4.1.2 Pharmacokinetics Endpoints

Pharmacokinetics endpoints are exploratory endpoints in this study:

- Pharmacokinetic parameters (eg, Ctrough, Cmax, tmax, t1/2, AUC0-12) (Part 1)
- Pharmacokinetic concentrations (eg, C8hr) (Part 2)

9.4.2 Safety Endpoints

A description of safety measures is contained in Sections 8.3 and 8.4. The analysis of safety results is described in Section 9.6.2.

The safety analysis endpoints include:

- The proportion of: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 serious and drug-related AE; 5) participants who discontinued study intervention due to AE; 6) participants who discontinued study intervention due to a drug-related AE; and 7) participants with AE(s) leading to death. The AE reporting period is from the time of randomization through 14 days following cessation of treatment. Additional reporting periods will be used as appropriate (eg, throughout the study for SAE).
- Events of Clinical Interest specified in Section 8.4.7.

Predefined Limits of Change (PDLC) in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a baseline and post-randomization 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 of the PDLC and are worse in grade (i.e., 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, July 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 population will serve as the primary population for the analysis of efficacy data for both parts of this study. The MITT population consists of all randomized participants who received at least 1 dose of study intervention. Part 1 (Phase 2) and Part 2 (Phase 3) of the study will be analyzed separately for efficacy endpoints. Therefore, the MITT population for Part 2 will not include Part 1 participants, and vice versa.

A supportive analysis using the Per-Protocol population will be performed for primary and secondary efficacy endpoint(s) for Part 2. The Per-Protocol population excludes participants due to deviations from the protocol that may substantially affect the results of the primary efficacy endpoint.

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.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the MITT and Per-Protocol populations.

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 one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received. Part 1 (Phase 2) and Part 2 (Phase 3) of the study will be combined for the final analysis of safety endpoints. The data presentations will focus on the selected dose group for MK-4482 and placebo.

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

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives as well as a key exploratory objective for viral RNA endpoints. Methods related to other exploratory objectives will be described in the sSAP. Methods related to PK analysis and PK/PD modeling will be described in a separate modeling and simulation plan authored by QP2. Methods related to dose response analysis using MCP-MOD will be described in a separate dose response analyses plan. Methods related to analyses of biomarkers and other exploratory samples will be described separately.

Efficacy results that will be deemed to be statistically significant after consideration of the type I error control for interim analyses are discussed in Sections 9.7 and 9.8. There are no additional adjustments for multiplicity. Statistical testing and inference for safety analyses are described in Section 9.6.2.

9.6.1 Statistical Methods for Efficacy Analyses

The stratified log-rank test will be used for the comparison of MK-4482 with placebo for the primary endpoint of the time-to-sustained recovery. Stratification factors are specified in Section 6.3.2. The relevant treatment efficacy parameter is the "sustained recovery rate ratio" (for MK-4482 relative to placebo), which is akin to the hazard ratio in survival analysis but for the beneficial outcome of sustained recovery. Sustained recovery rate ratios will be based on the stratified Cox Proportional Hazards regression model with stratification by factors specified in Section 6.3.2. Geographic region will not be used as a covariate in the primary analyses, but it may be considered as an additional stratification factor for the stratified log rank test and as a covariate for the Cox Proportional Hazards regression model for sensitivity analysis if it does not cause sparse data issues. The number of regions along with the specific countries contained within each region will be described in the sSAP. The Efron approximation will be used for handling ties. Failure to recover will be censored at Day 29. Death before Day 29, including death following a prior recovery, will be censored at Day 29 to eliminate any bias that would be introduced by censoring at time of death. Lost to follow-up before Day 29, regardless of prior recovery, will not be considered a sustained recovery and will be censored at the day of last contact. Withdrawal (ie, discontinuation from the study for reasons other than death or lost to follow up) before Day 29, regardless of prior recovery, will not be considered a sustained recovery and will be censored at the day of discontinuation.

Participants who initiate Sponsor-designated standard of care for treatment for COVID-19 48 hours or more following start of randomized study therapy will be treated as a failure to recover. Sustained recovery rate ratios greater than 1 indicate a benefit for MK-4482. Superiority will be concluded based on p-value boundaries as described in Sections 9.7 and 9.8.

A sensitivity analyses for the primary efficacy endpoint will be performed in the MITT population that does not impute "failure to recover" for participants who initiate Sponsor-designated standard of care for treatment for COVID-19 following start of randomized study therapy. In the case where the number of participants who require re-hospitalization but are then discharged again (or medically ready for discharge) before Day 29 exceeds 5% of the total MITT population, an additional sensitivity analysis will be performed in which all participants with re-hospitalizations by Day 29 are considered as not meeting the primary endpoint.

If superiority of MK-4482 over placebo is demonstrated as assessed by time-to-sustained recovery at the end of Part 2, the superiority of MK-4482 over placebo as assessed for the key secondary endpoint of all-cause mortality at Day 29 will be tested. Due to the relatively low number of deaths expected and the large number of strata levels, the unstratified Miettinen and Nurminen method [Miettinen, O. 1985] will be used to estimate and test the treatment difference for all-cause mortality. Every effort will be made to ascertain survival status for all participants. Missing data for this endpoint will be treated as failure (M=F approach) in the MITT population.

Ordinal outcome scales such as Pulmonary and Pulmonary+ will be analyzed using the cumulative logits function and the proportional odds model as described by McCullagh [McCullagh, P. 1980]. This methodology provides an estimate of the common odds ratio for assessing differences between treatment groups. In addition to a term for treatment group, the model will include terms for the stratification factors specified in Section 6.3.2. In addition, the proportion of participants in each ordinal scale category by treatment groups will also be presented.

The National Early Warning Score and the WHO 11-point ordinal scale score will be categorized to ordinal outcomes and will be further analyzed using the same approach as for Pulmonary and Pulmonary+ outcomes.

The viral RNA endpoints at earlier time points (Day 3 and EOT) will be important for the dose selection decision from Part 1 of the study. Change from baseline in SARS-CoV-2 RNA titer, calculated as $\log_{10}$ (post) minus $\log_{10}$ (baseline), as measured by quantitative RT-PCR of samples from NP and OP swabs will be summarized separately by treatment group and time point. The DAO approach will be used to handle missing data for these summary statistics. In addition to summary statistics, treatment differences in change in SAS-CoV-2 RNA titer from baseline over time will be estimated using longitudinal models. Graphical presentations of the change from baseline will be presented and the impact of baseline viral RNA level will be explored using subgroup analyses (defined by level of baseline viral RNA) and analyses/summaries that exclude participants with low baseline levels (eg, viral RNA $<10^6$ copies/mL).

Percentage of participants with undetectable viral RNA (below limit of detection) as measured by qualitative RT-PCR of samples from NP and OP swabs will be summarized separately by treatment group and time point. Between-treatment differences and 95% confidence intervals will be estimated using the stratified Miettinen and Nurminen method [Miettinen, O. 1985].

A detailed analysis strategy for key efficacy endpoints is listed in Table 5. The strategy to address multiplicity issues with regard to multiple efficacy endpoints and interim analyses is described in Section 9.7, Interim Analyses and in Section 9.8, Multiplicity.

Table 5 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method[b]	Analysis Population	Missing Data and Data Imputation Approach
Primary Endpoint				
Time-to-sustained recovery from randomization through Day 29	P (MITT) S (PP)	Stratified log-rank test[c] Stratified Cox Proportional Hazards regression[d]	MITT PP	Missing data will not be imputed. Participants who initiate Sponsor-designated standard of care for treatment for COVID-19 48 hours or more following start of randomized study therapy will be treated as a failure to recover. A sensitivity analysis for the primary efficacy endpoint will be performed in the MITT population that does not impute "failure to recover" for participants who initiate Sponsor-designated standard of care for treatment for COVID-19. Depending upon the number of participants who required re-hospitalization but were discharged or medically ready for discharge again before Day 29, an additional sensitivity analyses will be performed in which all participants with re-hospitalizations by Day 29 are considered as not meeting the primary endpoint. Failure to recover will be censored at Day 29. Death will also be censored at Day 29. Recovery followed by subsequent lost to follow up before Day 29 will be censored at the day of lost to follow up. Withdrawal (ie, discontinuation from the study for reasons other than death or lost to follow up) before Day 29 will be censored at the day of discontinuation.

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method[b]	Analysis Population	Missing Data and Data Imputation Approach
Secondary Endpoints				
All-cause mortality through Day 29	P (MITT) S (PP)	Unstratified M & N method[e]	MITT PP	Missing = Failure (M=F) – MITT Data as Observed (DAO) - PP
Odds of a more favorable response on Pulmonary score at Day 3, EOT, Day 10, Day 15, and Day 29	P (MITT) S (PP)	Proportional odds model[f]	MITT PP	Model-based
Odds of a more favorable response on Pulmonary+ score at Day 3, EOT, Day 10, Day 15, and Day 29	P (MITT) S (PP)	Proportional odds model[f]	MITT PP	Model-based
Odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT	P (MITT) S (PP)	Proportional odds model[f]	MITT PP	Model-based
Odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15 and Day 29	P (MITT) S (PP)	Proportional odds model[f]	MITT PP	Model-based

EOT=End of Treatment; MITT= modified intent-to-treat; M & N= Miettinen and Nurminen; PP=Per-protocol; WHO=World Health Organization.

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

[b] Statistical models are described in further detail below:

[c] The stratified log-rank test includes stratification factors specified in Section 6.3.2.

[d] Stratified Cox Proportional Hazards regression includes terms for treatment, stratification factors specified in Section 6.3.2.

[e] Unstratified Miettinen and Nurminen method.

[f] Proportional odds model includes terms for treatment and stratification factors specified in Section 6.3.2.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach as shown in Table 6. The tiers differ with respect to the analyses that will be performed. For this protocol, only ECIs are considered Tier 1 events. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory values or vital signs will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen method [Miettinen, O. 1985], an unconditional, asymptotic method. Since the stratification factors are not considered to be related to safety endpoints, they will not be included as stratification factors in the safety analyses.

Tier 2 Events

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

Membership in Tier 2 requires that at least 4 participants in at least one treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs 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 AEs and predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion 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.

Tier 3 Events

Safety endpoints that are not Tier 1 or 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 and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	ECIs	X	X	X
Tier 2	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
	Discontinuation due to Drug-Related AE		X	X
	Specific AEs by SOCs and PT (incidence ≥4 participants in at least one of the treatment groups)		X	X
	PDLCs[b] (incidence ≥4 participants in at least one of the treatment groups)		X	X
Tier 3	Specific AEs by SOC and PT (incidence <4 participants in each of the treatment groups)			X
	PDLCs[b] (incidence <4 participants in each of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

Note: AE=adverse event; CI=confidence interval; PT=preferred term; SOC=system organ class; PDLC=pre-defined limit of change; X=results will be provided

[a] Adverse Event references refer to both Clinical and Laboratory AEs.

[b] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints..

9.6.3 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

An eDMC and Sponsor siDMC will review results of interim analyses of this study and will make recommendations for any actions to the Sponsor Executive Oversight Committee (Table 7). Recommendations by the eDMC include possible discontinuation of the study or modifications to the protocol to protect the safety of participants and actions resulting from the crossing of an efficacy or futility boundary in Phase 3. In addition to the eDMC, the Sponsor siDMC will review unblinded data from Phase 2 for purposes of approving the proposed MK-4482 dose to advance into Phase 3.

The eDMC will be supported by an unblinded statistician who will provide treatment-level results from the interim analyses. 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. In addition, there will be a small, cross-functional unblinded team of Sponsor personnel or delegates who will perform the exposure-response and dose-response modeling and other analyses that will be used to inform the dose selection decision process and the siDMC review. Membership on this cross-functional unblinded team will be documented in an unblinding plan and the details of the planned analyses will be outlined in the Modeling Analysis Plan document prior to initiation of the analyses. Sponsor personnel responsible for ongoing blinded data review and preparation of the final study report will not be included on the cross-functional unblinded team.

Following any decision to terminate or modify the protocol, the executive committee of the sponsor (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented in a separate unblinding memo. Additional logistical details will be provided in the siDMC and eDMC Charters.

Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an internal (or external, as appropriate) unblinded cross-functional team performing the interim analyses and dose recommendation, who will have no other responsibilities associated with the study

There will be 3 interim analyses during the study as shown in Table 7.

Table 7 Description of Interim Analyses

Interim Analysis	Timing	P001 Primary Data for Analysis	Committee Action
IA1 – Part 1 Dose Evaluation	Targeted to occur during Phase 2 after ~300 participants complete EOT combined in MK-4482-001 and MK-4482-002[a].	PK, available virologic, safety & efficacy data through EOT	eDMC recommendation for discontinuation of the study or protocol modifications Sponsor siDMC review of interim safety data and review of preliminary virology data Review by the unblinded team to inform dose selection models and analyses
IA2 - Part 1[b] Dose Selection	Targeted to occur at the completion of Phase 2 after ~300 participants complete Day 29 (includes participants from IA1).	PK, safety & efficacy data through Day 29 and available virologic data	eDMC recommendation for discontinuation of the study or protocol modifications Sponsor siDMC approval of proposed MK-4482 dose for Part 2.
IA3 – Part 2 Futility/Early Efficacy	Targeted to occur during Phase 3 after ~343 of an expected 685 sustained recovery events, expected to be at approximately 50% of the full planned enrollment in the selected MK-4482 group and the placebo group in Part 2.	Safety & efficacy data through Day 29	Futility and early efficacy to be assessed by eDMC per eDMC Charter and guided by statistical criteria

eDMC=external Data Monitoring Committee; EOT=End of Treatment; IA=Interim Analysis; PK=pharmacokinetics; siDMC=standing internal Data Monitoring Committee.

[a] P002 is a companion MK-4482 dose-ranging study in non-hospitalized adults with COVID-19

[b] IA2 represents the analysis of the full Part 1 cohort of participants through Day 29.

Interim Analyses

IA1 - Part 1: Dose Evaluation

IA1 is targeted to occur during Phase 2 after data is available from ~300 participants completing EOT combined in MK-4482-001 and MK-4482-002. This IA will be used for eDMC interim data review, Sponsor siDMC review of interim safety data and review of preliminary virology data, and for unblinded team review of data to inform dose selection models and analyses.

During this interim analysis, enrollment in each study will continue in the 4 intervention groups in Phase 2 to the targeted enrollment of 300 participants.

IA2 - Part 1: Dose Selection

This analysis is targeted to occur at the completion of Phase 2 after ~300 participants (~75 per group) have completed the Day 29 visit. This IA will be used to evaluate the dose/exposure-response to select the dose for Phase 3. The relationship between dose and PK (plasma NHC and PBMC NHC-triphosphate), virologic endpoints (eg, rate of virologic RNA clearance, viral RNA mutation rate), safety, and key efficacy results will be evaluated. PK and virology data from other ongoing studies of MK-4482 including MK-4482-002 will also be examined at the time of this IA to inform the Phase 3 dose selection.

Additional details regarding dose selection criteria will be described in the siDMC Charter. The dose selected for Phase 3 will be communicated directly to sites in accordance with local regulatory requirements.

Part 2 (Phase 3) enrollment will be initiated after all participants for Part 1 of this study have completed the Day 29 visit, and after the completion of the IA2 analysis.

IA3 – Part 2: Futility/Early Efficacy

This study will include one planned interim analysis when ~50% of the expected sustained recovery events have occurred (~343 of an expected 685 events). The purpose of this interim analysis is to allow for early stopping in the case of futility and to allow for the initiation of marketing authorization applications in the case of a positive efficacy finding. The statistical criteria to inform this decision was developed as part of a group sequential design strategy that applies only to Part 2 (Phase 3) of the study. Given the expected rapid enrollment, there are no plans to discontinue enrollment prior to the planned final sample size in the case of a positive efficacy outcome.

The Gamma family spending function with $\gamma = -1$ will be used to set both efficacy and futility boundaries for the primary endpoint as a guide for the eDMC. Assuming the information fraction of 50%, the non-binding futility boundary expressed on the sustained recovery rate ratio scale is 1.071 (ie, an observed point estimate for the sustained recovery rate ration of 1.071 or lower will meet the criterion for futility). The boundary crossing probabilities for futility are 74% under H_0 and 3.6% under H_1 (sustained recovery rate

ratio=1.3). The p-value boundary for efficacy is 0.009, corresponding to a sustained recovery rate ratio of 1.289 (ie, an observed point estimate for the sustained recovery rate ratio of 1.289 or higher will meet the criterion for early efficacy). The boundary crossing probabilities for efficacy are 0.9% under H_0 and 53% under H_1 (sustained recovery rate ratio=1.3).

9.8 Multiplicity

Multiplicity adjustment with regard to controlling type I error for the Futility/Early Efficacy (Phase 3) Interim Analysis is described in Section 9.7.

There are two hierarchical superiority hypotheses in the Phase 3 part of this study (Section 3). A sequential testing approach will be employed to control overall type I error at 0.025, 1-sided across the primary efficacy endpoint (time-to-sustained recovery) and the key secondary efficacy endpoint (all-cause mortality). The all-cause mortality endpoint will not be tested at the interim analysis. At the end of Part 2, testing will be performed for the time-to-sustained recovery endpoint at an alpha level of 0.019. If superiority is demonstrated, the all-cause mortality endpoint will be tested at alpha level of 0.025. This strategy provides strong control of type I error at the study level. All tests are 1-sided unless otherwise noted.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power Calculations for Efficacy Analyses (Part 2)

The primary analysis of Phase 3 study endpoints will include ~1000 participants from Part 2 of the study (~500 for the selected MK-4482 group and ~500 for the placebo group) who meet the criteria for inclusion in the MITT population. The primary endpoint is time-to-sustained recovery. The study has overall power of 90% to demonstrate that participants treated with MK-4482 have a higher rate of sustained recovery than participants treated with placebo at an overall one-sided, 2.5% alpha-level, if the underlying constant sustained recovery rate ratio between treatment groups is 1.3.

The power and sample size are based on the following assumptions: 1) the time-to-sustained recovery follows an exponential distribution with sustained recovery rates of 0.351 and 0.270 for the MK-4482 and placebo groups, respectively, 2) a futility/efficacy interim analysis at 50% information as outlined in Section 9.7, 3) an enrollment period of 10 weeks, and 4) dropout hazard rates of 0.02 for both the MK-4482 and placebo groups, respectively. The above sustained recovery rates correspond to approximately 366 (73%) and 319 (64%) sustained recovery events for the MK-4482 and placebo groups, respectively. These are nearly identical to the recovery rates presented for remdesivir and placebo in the NEJM [Beigel, J. H., et al 2020]. The calculation was computed using both EAST and gsDesign. To meet the statistical criterion for success (one-sided p value≤0.019 at the final analysis), the observed sustained recovery rate ratio must be approximately 1.17 or larger.

9.9.2 Sample Size and Power Calculations for Virology Analyses (Part 1)

The sample size for Part 1 was not determined based on a specific hypothesis for a specific endpoint. The selection of the dose to advance to Part 2 will be based on analyses of the totality of data available across the MK-4482 clinical program. Three hundred participants (75 per group) will be sufficient to provide reasonable precision to discriminate between treatment groups with regard to the virology endpoints. An important endpoint for assessing the dose-response relationship is viral RNA change from baseline in SARS-CoV-2 RNA titer, calculated as $\log_{10}$ (post) minus $\log_{10}$ (baseline). Approximately 80% of this cohort (60/group) is expected to have baseline viral load of at least 10^6 copies/mL. A 1 log-unit difference between treatment groups in the population mean is considered to be clinically relevant. Table 8 provides power calculations for true log differences of 0.75 to 1.25 and for various assumptions about the true underlying standard deviation.

Table 8 Power by Detectable Difference and Standard Deviation Viral RNA Change from Baseline (log10 copies/mL) N=60/group, α=0.025, 1-sided

	Between Group Difference ($\log_{10}$ copies/mL)		
Standard Deviation	-0.75	-1.00	-1.25
1.25	90%	99%	>99%
1.5	78%	95%	>99%
1.75	64%	87%	97%

9.9.3 Sample Size and Power Calculations for Safety Analyses (Part 2)

Part 1 (Phase 2) and Part 2 (Phase 3) of the study will be combined for the final analysis of safety endpoints. The planned sample size for safety analysis will be 575 for MK-4482 selected dose group and placebo. 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 an AE in the study population. If the underlying incidence of an AE is 1%, there is a 99.7% chance of observing at least one AE among 575 participants in the treatment group. If no AE of that type is observed among the 575 participants in any treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with the AE is < 0.64% (1 out of every 156 participants).

Table 9 summarizes the percentage point differences between the 2 treatment groups that could be detected with 90% probability for a variety of hypothetical underlying incidences of an AE. These calculations assume 575 participants in each group and are based on a 2-sided 5% alpha level. The calculations are based on Farrington and Manning [Farrington, C. P. and Manning, G. 1990]. No multiplicity adjustments were made.

Table 9 Differences in Incidence of AE Rates Between the 2 Treatment Groups That Can be Detected With an ~90% Probability (Assuming 2-sided 5% Alpha Level with 575 Participants in Each Group)

Incidence of Adverse Event		Risk Difference
Placebo (%)	MK-4482 (%)	Percentage Points
1.0	4.0	3.0
5.0	10.0	5.0
10.0	16.5	6.5
20.0	28.2	8.2
30.0	39.1	9.1
40.0	49.5	9.5
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Calculations are based on Farrington and Manning [Farrington, C. P. and Manning, G. 1990].		

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:

- Age (≤60 years, >60 years)
- Sex (female, male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)
- Time from symptom onset prior to the day of randomization (≤5 days, >5 days)
- Baseline (Day 1) disease severity (mild, moderate, severe) per Appendix 9
- Remdesivir use prior to or at the time of randomization (yes, no)
- Corticosteroid use prior to or at the time of randomization (yes, no)
- Geographic region (North America, Europe, Asia Pacific, Latin America)

- Participants at increased risk for severe illness from COVID-19 (yes, no)
    - age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised state from solid organ transplant, obesity (BMI ≥30), serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies, sickle cell disease, diabetes mellitus

Additional subgroups may be defined in the sSAP. Categories of the above subgroups with small sample sizes (<25 per treatment group) may be combined – further detail will be provided in the sSAP.

9.11 Compliance (Medication Adherence)

Compliance will be calculated based on capsule counts. For a participant who is followed for the entire study period, the "Number of Capsules Should be Taken" is the total number of capsules should be taken from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinues from the study permanently, 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 population.

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection 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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if 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, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 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 Internal Data Monitoring Committee

A separate siDMC will review results of interim analysis(es) from Part 1 of this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will review unblinded study data at the determined frequency (Section 9.7 Interim Analyses) for dose selection as described in detailed monitoring guidelines. The siDMC will make recommendations for any actions (eg, approval of proposed dose) to the Sponsor Executive Oversight Committee.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.4.3 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 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 International Committee of Medical Journal Editors 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 trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 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, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting

from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

10.1.8 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 10 will be performed by the central laboratory.
- Local laboratory test is required for initial COVID-19 RT-PCR and determination of participant eligibility
- All other local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in 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 10 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count	RBC Indices: MCV MCH RDW	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Calculation of: Neutrophil/lymphocyte ratio Absolute Neutrophil Count
	RBC Count		
	Hemoglobin		
	Hematocrit		
Chemistry	BUN	Chloride	AST/SGOT
	Albumin	Calcium	ALT/SGPT
	Creatinine	Phosphorus	Alkaline phosphatase
	Glucose (nonfasting)	Magnesium	GGT
	Potassium	Amylase	LDH
	Bicarbonate	Lipase	Total bilirubin (and direct bilirubin if total bilirubin is elevated above upper limit of normal
	Sodium	Total protein	CK

Laboratory Assessments	Parameters
Urinalysis	• Specific gravity • Color and clarity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy Testing	• Serum hCG pregnancy test (as needed for WOCBP)
Virology	• SARS-CoV-2 RNA real time PCR OP and NP swabs (quantitative and qualitative) • SARS-CoV-2 Gene Sequencing
Inflammatory Biomarkers	• Pro-inflammatory cytokine (IL-6) • hs-CRP • Note: hs-CRP will be tested at all visits with chemistry collection as the test is performed on the same blood sample • D-dimer • Erythrocyte Sedimentation Rate • Procalcitonin
Pharmacokinetics	• Plasma for NHC • PBMC for NHC-triphosphate
Exploratory Research Samples	Samples may be used for testing such as: • SARS-CoV-2 Antibodies • Infectious SARS-CoV-2 presence/quantitation • Co-infection with other respiratory pathogens

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatine kinase; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; hs-CRP=high-sensitivity C-reactive protein; IL-6=Interleukin 6; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; NHC=N-hydroxycytidine; NP=nasopharyngeal; OP=oropharyngeal; PBMC= peripheral blood mononuclear cells; PCR=polymerase chain reaction; RBC=red blood cell; RDW=red cell distribution width; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

Table 11 Approximate Whole Blood Volumes (mL)

Study Period:	Specimen or Matrix Type (Tube Type/Additive)	Screening	Intervention					Follow-Up			Total Blood Volumes
Visit Number/Title:		1	2	3	4	5	6	7	8	9	
Scheduled Day (and Window):		Screening	Day 1	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	
Urine (~10 mL)	Urine (preservative)		X								NA
Nasopharyngeal Swab	flocked or polyester-tipped swab (3 mL universal transport medium)		X		X		X	X	X	X	
Oropharyngeal Swab	flocked or polyester-tipped swab (3 mL universal transport medium)		X		X		X	X	X	X	
Chemistry (Day 29 includes serum pregnancy)	Serum (no additive)		2.5		2.5		2.5	2.5	2.5	3.5	
Hematology	Whole Blood (EDTA)		2		2		2	2	2	2	
Plasma/Serum Research Samples	Whole Blood (clot activator and EDTA) processed to both plasma and serum		16				16	16		16	
Serum for Antibody Exploratory Research	Serum (no additive)		2.5				2.5	2.5		2.5	
Procalcitonin	Plasma (EDTA)		2				2				
Erythrocyte Sedimentation Rate (ESR)	Whole Blood (NA Citrate)		1.2				1.2				
Interleukin-6 (IL-6)	Serum (no additive)		2.5				2.5				
D-Dimer	Plasma (Na Citrate)		1.8				1.8				
Sub Total for all Participants for Central Laboratory	NA	0	30.5	0	4.5	0	30.5	23	4.5	24	
Pharmacokinetics	NA										
Pharmacokinetic Plasma Sampling Part 1	Plasma (EDTA)						15				
Pharmacokinetic Plasma Sampling Part 2	Plasma (EDTA)						9				
Pharmacokinetic PBMC Sampling Part 1	Whole Blood (Sodium Heparin) processed to PBMCs						80				

Study Period:	Specimen or Matrix Type (Tube Type/Additive)	Screening	Intervention					Follow-Up			Total Blood Volumes
Visit Number/Title:		1	2	3	4	5	6	7	8	9	
Scheduled Day (and Window):		Screening	Day 1	Day 2	Day 3	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	
Total For Participants in Part 1	**NA**	0	30.5	0	4.5	0	45.5	23	4.5	24	132
Total For Participants in Part 2		0	30.5	0	4.5	0	39.5	23	4.5	24	126
Total For PBMC Cohort Participants in Part 1		0	30.5	0	4.5	0	125.5	23	4.5	24	212

hCG=human chorionic gonadotropin; PBMC= peripheral blood mononuclear cells; WOCBP=women of childbearing potential

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

10.3.1 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

Assessment of intensity /toxicity

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

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) 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 case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

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

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

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

Not Applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia 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 hormonal contraceptives 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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for South Korea

Section 7.1 Discontinuation of Study Intervention

The following discontinuation criterion applies to participants in South Korea:

The participant’s renal function deteriorates leading to dialysis while on study intervention.

Section 8.1.8.1 Timing of Dose Administration

The following information is not applicable in South Korea:

If a participant's renal function deteriorates, requiring dialysis during the study intervention, the Sponsor will not require the discontinuation of the study intervention; administration of the study intervention may continue at the discretion of the investigator. For participants who require continuous dialysis, study intervention should continue to be administered Q12H with no change to the timing of administration. For participants who require intermittent dialysis, study intervention should continue to be administered Q12H with doses administered 4-6 hours prior to dialysis where possible.

10.8 Appendix 8: Ordinal Outcome Scales

10.8.1 Pulmonary and Pulmonary+

The Pulmonary ordinal outcome focuses on the respiratory sequalae of COVID-19 and is defined based on oxygen requirements using the following 7 well-defined mutually exclusive categories:

1. Can independently undertake personal usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual personal activities
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements but not high-flow oxygen
5. Non-invasive assisted ventilation or high-flow oxygen
6. Invasive assisted ventilation, ECMO or mechanical circulatory support
7. Death

The Pulmonary+ ordinal outcome is also a 7-category assessment that captures the range of severity, including coagulation-related complications and respiratory dysfunction, experienced by hospitalized patients with COVID 19 as follows:

1. Can independently undertake personal usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual personal activities
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements but not high-flow oxygen) or any of the following: stroke, meningitis, encephalitis, myelitis, myocardial ischemia, myocarditis, pericarditis, symptomatic congestive heart failure, or arterial or deep venous thrombosis
5. Non-invasive assisted ventilation or high-flow oxygen
6. Invasive assisted ventilation, ECMO or mechanical circulatory support or vasopressor therapy or renal replacement therapy
7. Death

The Pulmonary and Pulmonary+ scales are reproduced based on the NAIDS and NIH Therapeutics for Inpatients with COVID-19 (TICO) protocol. Of note, the Pulmonary+ scale was adapted to remove the use of the NIHSS in assessing stroke-related neurologic deficits due to challenges in implementing the NIHSS tool at all participating clinical sites.

10.8.2 National Early Warning Score

The National Early Warning Score is as follows [Royal College of Physicians 2012]:

Physiological Parameter	Point Value
Respiration Rate (breaths per minute)	
≤8	3
9-11	1
12-20	0
21-24	2
≥25	3
Oxygen Saturation (%)	
≤91	3
92-93	2
94-95	1
≥96	0
Any Supplemental Oxygen	
Yes	2
No	0
Temperature (ºC)	
≤35.0	3
35.1-36.0	1
36.1-38.0	0
38.1-39.0	1
≥39.1	2
Systolic BP (mmHg)	
≤90	3
91-100	2
101-110	1
111-219	0
≥220	3
Heart Rate (beats per minute)	
≤40	3
41-50	1
51-90	0
91-110	1
111-130	2
≥131	3
Level of Consciousness	
A	0
V,P,U	3

A, V, P, U= Alert, Voice, Pain, Unresponsive

10.8.3 World Health Organization 11-Point Scale

The WHO 11-point ordinal scale for clinical progression is as follows, with 0 assigned to "Uninfected; no viral RNA detected" and 10 assigned to "Dead" [Marshall, J. C., et al 2020]:

- **Patient State: "Uninfected"**
  - Uninfected; no viral RNA detected
- **Patient State: "Ambulatory Mild Disease"**
  - Asymptomatic; viral RNA detected
  - Symptomatic; independent
  - Symptomatic; assistance needed
- **Patient State: "Hospitalized; Moderate Disease"**
  - Hospitalized; no oxygen therapy*
  - Hospitalized; oxygen by mask or nasal prongs
- **Patient State "Hospitalized; Severe Disease"**
  - Hospitalized; oxygen by non-invasive ventilation or high-flow
  - Intubation and mechanical ventilation; $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
  - Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
  - Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or extracorporeal membrane oxygenation
- **Patient State "Dead"**
  - Dead

Abbreviations: FiO_2=fraction of inspired oxygen; pO_2=partial pressure of oxygen; SpO_2=Oxygen saturation.

* If hospitalized for isolation only, record status as for ambulatory patient.

10.9 Appendix 9: COVID-19 Severity Categorization

Adapted from "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry" US Food and Drug Administration (May 2020), WHO COVID-19 case definition, and COVID-19 symptoms recognized by CDC [Food and Drug Administration 2020] [World Health Organization 2020] [Tenforde, M. W., et al 2020].

For inclusion in the study, the following are required of all participants:

- A **positive SARS-CoV-2 test** result (Inclusion Criterion #1)
- Signs/symptoms attributable to COVID-19 present at randomization (Inclusion Criterion #2), including but not limited to one or more of the following: **fever >38.0ºC, chills, cough, sore throat, shortness of breath or difficulty breathing, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell**
    - Of note, symptoms attributable to COVID-19 not listed above can be considered per the investigator as supportive for COVID-19 baseline severity categorization

In addition to the above criteria, the participant must be categorized into one of the following COVID-19 severity categories at the time of randomization: **mild, moderate, or severe COVID-19** (Inclusion Criterion #3). The COVID-19 severity category that is entered in IRT at randomization must be based on assessments (vital signs, COVID-19 signs/symptoms, respiratory measures, oxygen therapy, ongoing medical history) completed and documented on Day 1 prior to calling IRT in order to randomize.

Mild COVID-19:

Must have **ALL** of the following:

- Respiratory rate <20 breaths per minute
- Heart rate <90 beats per minute
- SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms

AND

Must **NOT** have shortness of breath **at rest or with exertion**, respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Moderate COVID-19:

Must have **ONE or MORE** of the following:

- Shortness of breath **with exertion**
- Respiratory rate ≥20 to <30 breaths per minute
- Heart rate ≥90 to <125 beats per minute

AND

Must have SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms [or only on ≤ 2 liters/min supplemental oxygen for COVID-19 (but was not previously on supplemental oxygen), regardless of SpO_2]

AND

Must **NOT** have shortness of breath **at rest**, respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Severe COVID-19:

Must have **ONE or MORE** of the following:

- Shortness of breath **at rest**
- Respiratory rate ≥30 breaths per minute
- Heart rate ≥125 beats per minute
- SpO_2 ≤93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms
- On supplemental oxygen for a reason other than COVID-19 which HAS increased since onset of COVID-19 signs/symptoms, regardless of SpO_2
- On > 2 liters/min supplemental oxygen for COVID-19 (but was not previously on supplemental oxygen), regardless of SpO_2
- PaO2/FiO_2 <300

AND

Must **NOT** have respiratory failure, shock, or multi-organ dysfunction/failure (see definitions in Critical COVID-19 below)

Critical COVID-19:

Must have **ONE or MORE** of the following:

- **Respiratory failure** defined based on resource utilization requiring at least 1 of the following:
  - Endotracheal intubation and mechanical ventilation
  - Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5)
  - Noninvasive positive pressure ventilation
  - ECMO
  - Clinical diagnosis of respiratory failure (ie, clinical need for 1 of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- **Shock** defined as systolic blood pressure <90 mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressors
- **Multi-organ dysfunction/failure** defined as participants that are acutely ill with evidence of either dysfunction or failure, at the discretion of the investigator, of more than 1 of the following organ systems: respiratory, cardiovascular, renal, hematologic, hepatic, and/or central nervous systems

10.10 Appendix 10: Calculation of eGFR

Modification of Diet in Renal Disease Study (MDRD) equation

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

- Notes:
  - eGFR = estimated glomerular filtration rate
  - SCr = standardized serum creatinine
  - age = years

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ACTT 1	Adaptive COVID-19 Treatment Trial
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
APaT	all-participants-as-Treated
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BUN	blood urea nitrogen
C2hr	plasma concentration value collected at 2hours
C12hr	plasma concentration value collected at 12hours
CBC	complete blood count
CD4	cluster of differentiation 4
CI	confidence interval
Cmax	maximum plasma concentration
CMH	Cochran–Mantel–Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus infectious disease 2019
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CTFG	clinical trial facilitation group
Ctrough	lowest plasma concentration
DAO	data as observed
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
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
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
ePROs	electronic patient-reported outcomes
ESD	early stage development

Abbreviation	Expanded Term
ESR	erythrocyte sedimentation rate
EUA	Emergency Use Authorization
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FiO_2	fraction of inspired oxygen
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
H1	Hypothesis 1
H1N1	Hemagglutinin Type 1 and Neuraminidase Type 1 (influenza strain)
H2	Hypothesis 2
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
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
IEC	Independent Ethics Committee
IA	interim analysis
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-6	interleukin 6
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	intervention randomization system
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LAR	legally acceptable representative
LAM	lactational amenorrhea method
LAM	lactational amenorrhea method
LFU	late follow-up
LSD	late stage development
mAb	monoclonal antibody

Abbreviation	Expanded Term
MAD	multiple ascending doses
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MERS	Middle East respiratory syndrome
MHP	medical history pre-specified
MITT	modified intent-to-treat
MOV	molnupiravir
MSD	Merck Sharp & Dohme
NAIDS	National Institute of Allergy and Infectious Diseases
NEJM	New England Journal of Medicine
NEWS	National Early Warning score
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine pharmacologically-active triphosphate
NIH	National Institutes of Health
NIHSS	NIH Stroke Scale
NIMP	non-investigational medicinal product
NP	nasopharyngeal
NSAE	nonserious adverse event
OP	oropharyngeal
PaO_2	partial pressure of oxygen
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PCT	procalcitonin
PDLC	pre-defined limit of change
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic
PPE	personal protective equipment
PQC	product quality complaint
PRO	patient-reported outcome
PT	preferred term
Q12H	administered once every 12 hours
QP2	department of quantitative pharmacology and pharmacometrics
RBC	red blood cell
RdRp	RNA-dependent RNA polymerase
RDW	red cell distribution width
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	real time polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event

Abbreviation	Expanded Term
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
siDMC	standing internal data monitoring committee
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
TBD	to be determined
Tmax	time to maximum plasma concentration
t1/2	half life
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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