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 Non-Hospitalized Adults with COVID-19
NCT number:	NCT04575597
Document Date:	15-AUG-2021

Title Page

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

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

Protocol Number: 002-04

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:

One Merck Drive

P.O. Box 100

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

Regulatory Agency Identifying Number(s):

EudraCT	2020-003368-24
IND	147734
NCT	NCT04575597

Approval Date: 15 August 2021

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	15-AUG-2021	To remove the enrollment target of ~50% of Part 2 participants who are >60 years of age and to add a new exploratory objective for detection of infectious virus from NP swabs.
Amendment 03	22-JUN-2021	To clarify that participants can only enroll in this study if they have chosen not to receive a SARS-CoV-2 monoclonal antibody(ies) or SARS-CoV-2 monoclonal antibodies have not been authorized or approved in their country, update the benefit/risk assessment, add new subgroup analyses, and add a description of an unblinded team in the case of a positive efficacy finding noted by the eDMC at IA4.
Amendment 02	14-APR-2021	To provide the selected dose and the dose selection rationale for Part 2 (Phase 3) of the study, revise female and male contraception requirements, update the stratification factors, revise entry criteria, and increase the sample size for Part 2 (Phase 3).
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 key secondary efficacy objective regarding COVID-19 signs/symptoms, and add a discontinuation criterion.
Original Protocol	14-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

To remove the enrollment target of ~50% of Part 2 participants who are >60 years of age and to add a new exploratory objective for detection of infectious virus from NP swabs.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design 6.3.2 Stratification	Removed the enrollment target of approximately 50% of Part 2 participants who are >60 years of age.	While the Part 2 study population will continue to be enriched for participants at increased risk for severe illness from COVID-19, including those >60 years of age (Appendix 10), the enrollment target of ~50% of participants >60 years of age was removed. Based on observed data, events are occurring across risk factors and enrichment for older participants alone is not needed. This change was also made to support increased feasibility of enrollment given increasing global vaccination rates in the older population.

Section # and Name	Description of Change	Brief Rationale
3 Hypotheses, Objectives and Endpoints 4.2.1.4 Virology Endpoints 4.2.5 Rationale for Other Exploratory Research 8.2.1 Nasopharyngeal and Oropharyngeal Swabs 9.4.1.1 Efficacy Endpoints	Added an exploratory objective to evaluate the percentage of participants with undetectable infectious SARS-CoV-2 in NP swabs at various timepoints. Added associated changes relevant to the new exploratory objective.	To evaluate the antiviral activity of MK-4482 versus placebo via detection of infectious SARS-CoV-2.
1.3 Schedule of Activities 8.1.2 Inclusion/Exclusion Criteria	Added statement that laboratory testing to confirm SARS-CoV-2 infection may be performed at screening if prior results are not available.	To clarify that sites may perform this testing at screening to confirm eligibility.
7.3 Lost to Follow-up	Removed: “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 pre-specified statistical data handling and analysis guidelines.”	A participant can be declared as lost to follow-up after the site has attempted multiple methods of contact rather than waiting until the last scheduled visit (ie, LFU Month 7). Given the length of study, it is considered reasonable to attempt contact to a point where the data that would be collected may still be considered meaningful instead of throughout the full duration of the study.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Revised footnote "a" to state that eligible participants will have laboratory-confirmed infection and signs/symptoms of COVID-19 for ≤7 days in Part 1 and ≤5 days in Part 2 prior to randomization.	To clarify the difference in eligibility requirements for each Part of the study.
Appendix 5, Section 10.5.2 Contraception Requirements	Added "user dependent" before hormonal contraceptives in the text describing those barrier methods to be used with user dependent hormonal contraceptives.	To clarify that hormonal contraceptives that require additional barrier methods to be used are "user dependent" hormonal contraceptives as described in the preceding text.
Throughout the document	Corrected minor typographical and grammatical errors.	To improve clarity and consistency throughout the document.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

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 Non-Hospitalized Adults with COVID-19.

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

Acronym: N/A
MOVe-OUT

Hypotheses, Objectives, and Endpoints:

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

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

Primary Objectives	Primary Endpoints
- To evaluate efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29. Hypothesis: MK-4482 is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29.	- Hospitalization or death
- 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 time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29.	- COVID-19 signs/symptoms

- 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 with COVID-19 not requiring hospitalization
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 ~1850 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~1550)					
MK-4482	MK-4482	800 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.

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 at 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.	

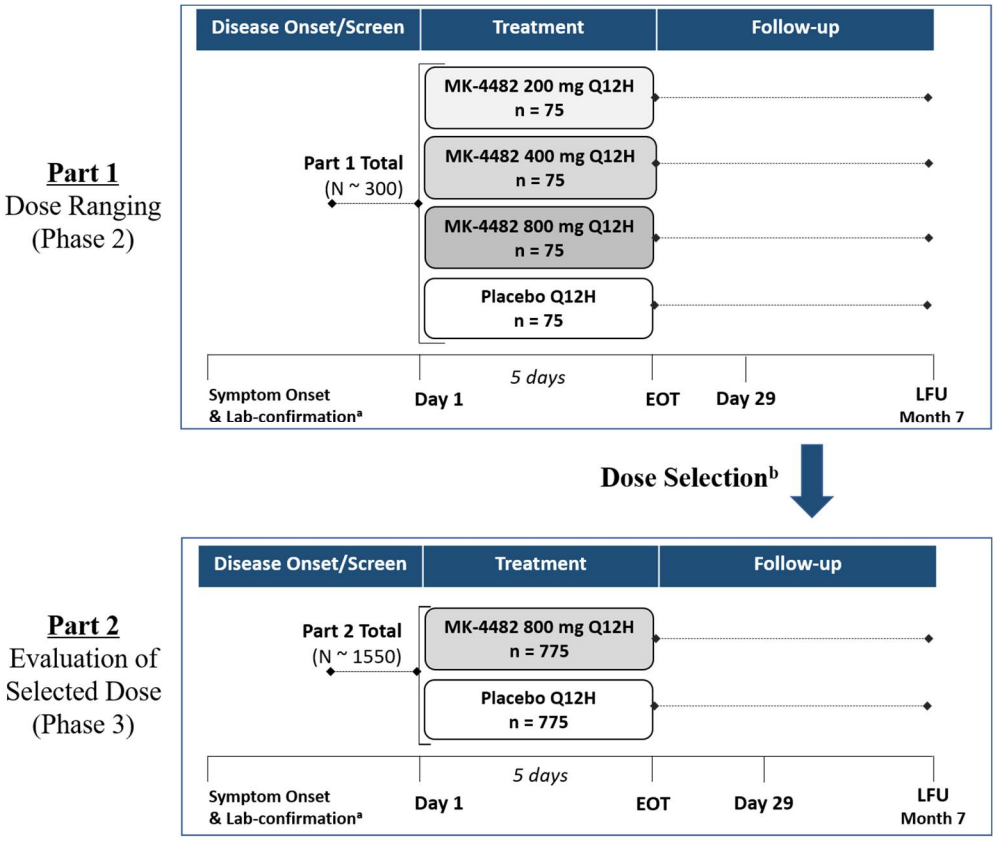
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 12.

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.

[a] Eligible participants will have laboratory-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤7 days in Part 1 and ≤5 days in Part 2 prior to randomization (Section 5.1). Calculation of the 7-/5-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 (Section 4.3.3 and Section 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 (Window)	Screening (≤48 hours before rand.)[a]	Day 1[b]	Day 2	Day 3[c]	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 month)[d]	
Type of Visit	C	C	V/C	C	V/C	C	C	C	C	V	C = Clinic or At-home visit V= Virtual visit (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 FBR (Optional)	X										Informed consent for FBR should be presented at screening, however, if delayed, present at next possible visit as outlined in Appendix 6.
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[e]	X[f]									Including review of SARS-CoV-2 (+) local test results[g]
Participant Identification Card	X	X									Randomization number must be added to card at randomization
Medical History	X	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
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

Study Period	**Screening**	**Intervention**					**Follow-up**				**Notes**
Visit Number/Title	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (Window)	Screening (≤48 hours before rand.)[a]	Day 1[b]	Day 2	Day 3[c]	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 month)[d]	
Collect/Update Secondary Contacts for Participant	X			X		X		X	X		
MK-4482 or Placebo Administration		X	X	X	X	X					All efforts should be made to administer the first dose on Day 1 (randomization), but administration of the first dose 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.
Dispense Study Intervention and Participant Study Supplies		X									Including participant diaries
Completion of Study Medication Diary		X	X	X	X	X					
Completion of MK-4482 Symptom Diary		<========== X ==========>									Completed daily from Day 1 through Day 29. The first day of diary completion should occur prior to the first dose of study intervention (Section 8.2.5).
Reminders for MK-4482 Symptom Diary Completion			X	X	X	X	X	X	X		Following EOT, reminders should be provided every other day through Day 29.
Study Staff Review and Collection of Participant's Study Diaries				X		X	X	X	X		Study Medication Diary will be collected after the last dose of study intervention. Completed pages of MK-4482 Symptom Diary will be collected at all clinic or at-home visits.

Study Period	**Screening**	**Intervention**					**Follow-up**				**Notes**
Visit Number/Title	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (Window)	Screening (≤48 hours before rand.)[a]	Day 1[b]	Day 2	Day 3[c]	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 month)[d]	
Functional Status Assessment		X		X		X	X	X	X		Participant's ability to independently perform daily activities will be assessed.
Efficacy Procedures											
NP (Parts 1 and 2) and OP (Part 1 only) Swabs		X		X		X	X	X	X		Both NP and OP swabs will be collected in Part 1. Only NP swabs will be collected in Part 2.
Serum and Plasma for Exploratory Research		X				X	X		X		Research samples will be stored for testing as described in Section 4.2.5 and Section 8.8.
Serum for Antibody Exploratory Research		X				X	X		X		
Respiratory/ Oxygenation Status	X	X		X		X	X	X	X	X[h]	SpO_2 and investigator assessment of shortness of breath, and if applicable FiO_2, PaO_2 and supplemental oxygen use.
Hospitalization, Emergency Room, and Other Acute Care Visit Status				X		X	X	X	X	X	Only hospitalization status will be collected at LFU (Month 7) visit.
Survival Status									X	X	
Safety Procedures											
Full Physical Examination	X										Including height and weight
Directed Physical Examination		X		X		X	X	X	X		
Vital Signs	X	X		X		X	X	X	X		Heart rate, blood pressure, respiratory rate, temperature
Blood Collection for Local Laboratory Evaluation	X[e]										Local laboratory collection required unless chemistry/hematology results within 72 h prior to randomization are available

Study Period	**Screening**	**Intervention**					**Follow-up**				**Notes**
Visit Number/Title	1	2	3	4	5	6	7	8	9	10	
Scheduled Day (Window)	Screening (≤48 hours before rand.)[a]	Day 1[b]	Day 2	Day 3[c]	Day 4	EOT	Day 10 (±1 day)	Day 15 (+3 days)	Day 29 (+3 days)	LFU Month 7 (±1 month)[d]	
Blood Collection for Central Laboratory Evaluation		X		X		X	X	X	X		Including hematology and chemistry
Pregnancy Test (WOCBP only)	X[e]								X		
Confirm Contraception Requirements (WOCBP and male participants)		X		X		X	X				Confirm participant compliance with contraception requirements as outlined in inclusion criteria and Appendix 5
AE/SAE review[i]	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics											
PK Plasma Sampling						X					Part 1: pre-dose;1.5 h post-dose Part 2: pre-dose;1.5 h post-dose
PK PBMC Sampling[j]						X					Part 1 (PBMC Cohort Only): Pre-dose, 1.5 h post-dose

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19=coronavirus disease 2019; EOT=End of Treatment (day of last study intervention dose); FBR = future biomedical research; hCG=human chorionic gonadotropin; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LFU= Late Follow-Up, NP=nasopharyngeal; OP=oropharyngeal; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; PSV=pregnancy status visit; rand.= randomization; RNA=ribonucleic acid; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation; WOCBP=women of childbearing potential.

[a] Screening and Day 1 (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] Day 3 assessments should be performed on Day 3, but if circumstances do not support performance of any procedures by study staff on Day 3, a ±24-hour window is allowed.

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

[e] The following local laboratory results must be available for all participants from within 72 h prior to randomization to support determination of eligibility: serum creatinine, platelets, and absolute neutrophil count. 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 pregnancy test is required within 24 hours of the first dose of study intervention per inclusion criteria. All other inclusion/exclusion criteria determination (eg, HIV status) can be based on participant-reported medical history, available medical records, and the most recently available laboratory results for the participant (eg, HIV RNA VL).

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

[g] If prior results are not available, laboratory confirmation of SARS-CoV-2 infection may be performed at screening to confirm eligibility (Sections 5.1 and 8.1.2). Results must be available prior to randomization.

[h] 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.

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

[j] A subset of ~50 participants in Part 1 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 for COVID-19.

2.1 Study Rationale

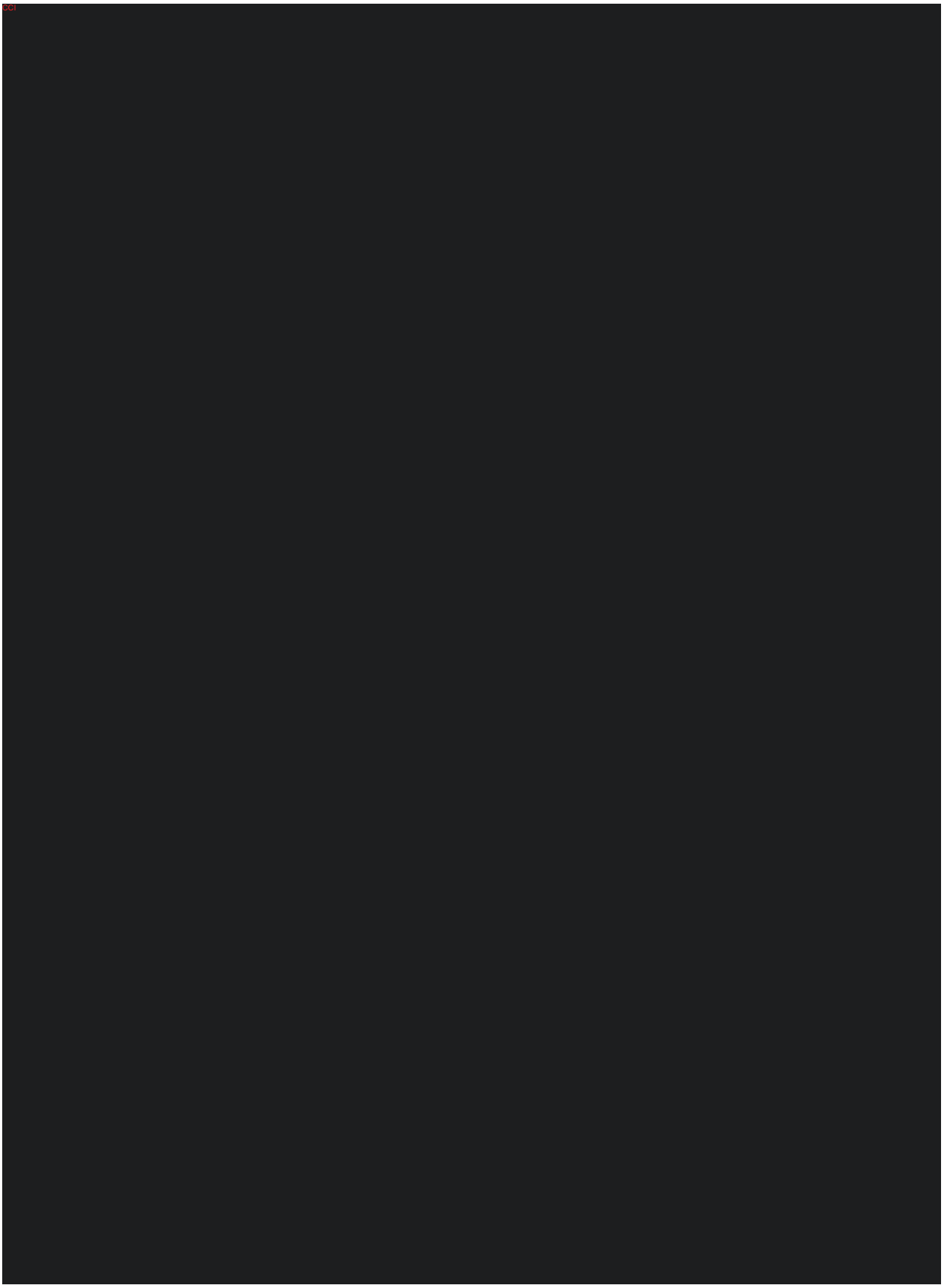
COVID-19, a disease resulting from SARS-CoV-2 infection, was declared a global pandemic by the WHO on 11-MAR-2020. Within 4 months of that declaration, there were over 11 million cases of COVID-19 reported globally and over 500 thousand associated deaths [World health Organization 2020]. With increasing numbers of cases and deaths worldwide, and very limited treatment options, there is an immediate unmet medical need for new effective therapies.

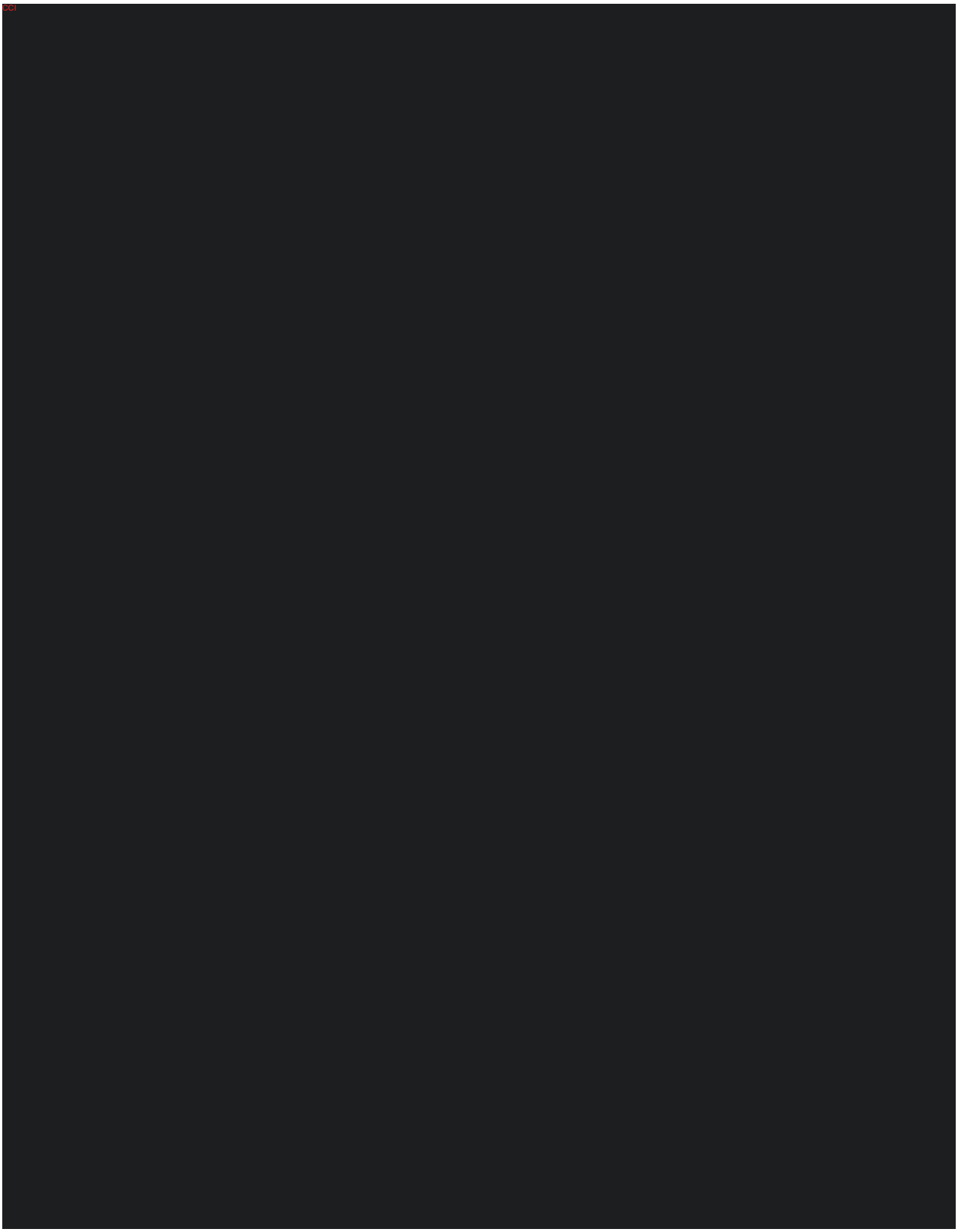
The true burden of COVID-19 is yet to be fully understood. Although most (>80%) infected individuals exhibit a mild illness (eg, fever, dry cough, fatigue), approximately 14% experience severe disease (eg, dyspnea, hypoxemia), and 5% have critical illness, which can include respiratory failure, septic 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].

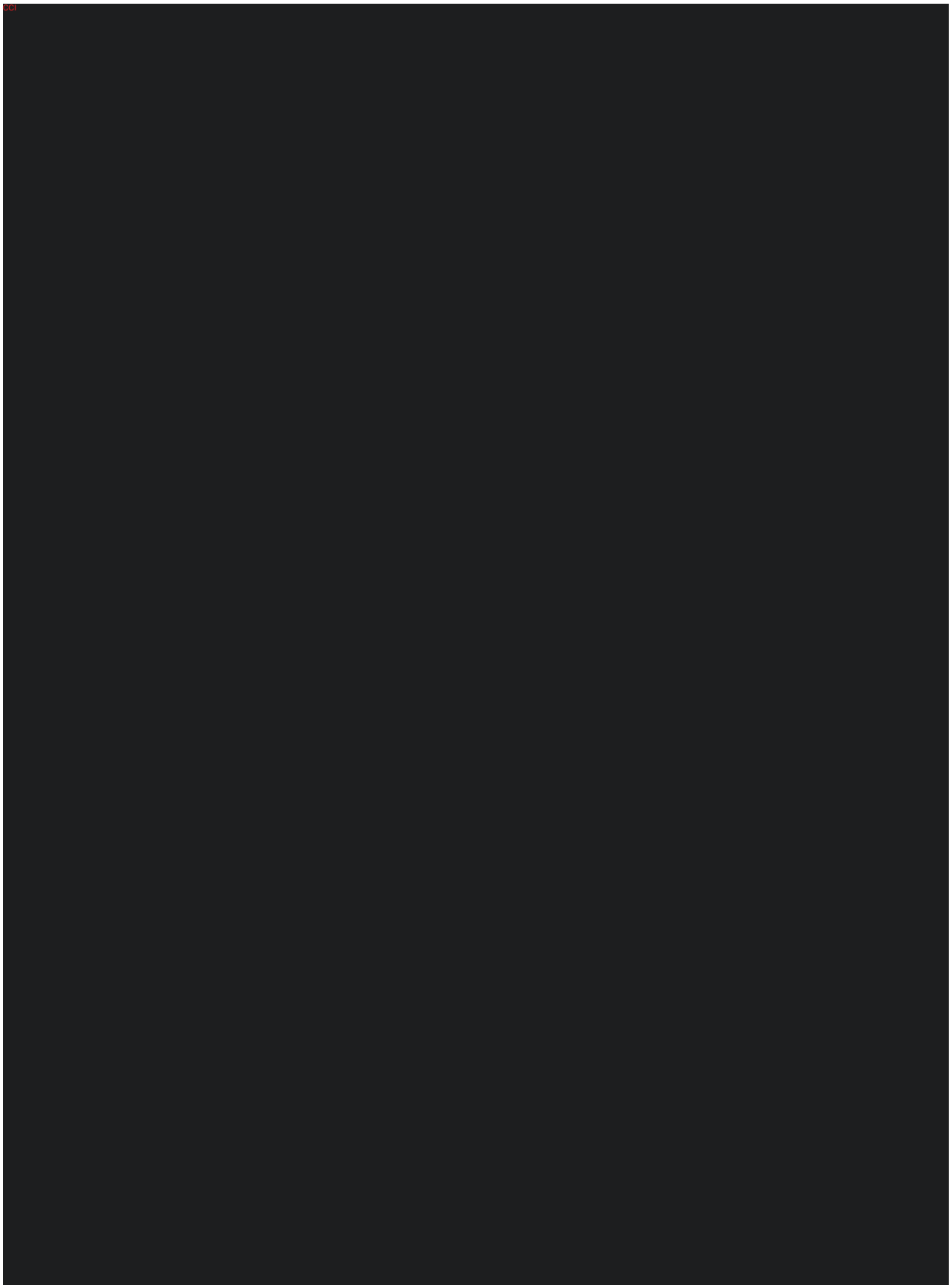
Standard of care treatment of COVID-19 is rapidly evolving and local treatment guidelines continue to be updated with emerging data [COVID-19 Treatment Guidelines Panel 2020] [Bhimraj, A., et al 2020] [World health Organization 2020]. Remdesivir is an antiviral agent approved by the US FDA for intravenous treatment of COVID-19 in patients requiring hospitalization [U.S. Prescribing Information 2021]. Use of remdesivir for the treatment of patients with pneumonia requiring supplemental oxygen has also received conditional marketing authorization by the European Commission [Beigel, J. H., et al 2020]. However, there remains a need for an orally bioavailable antiviral agent for treatment of COVID-19.

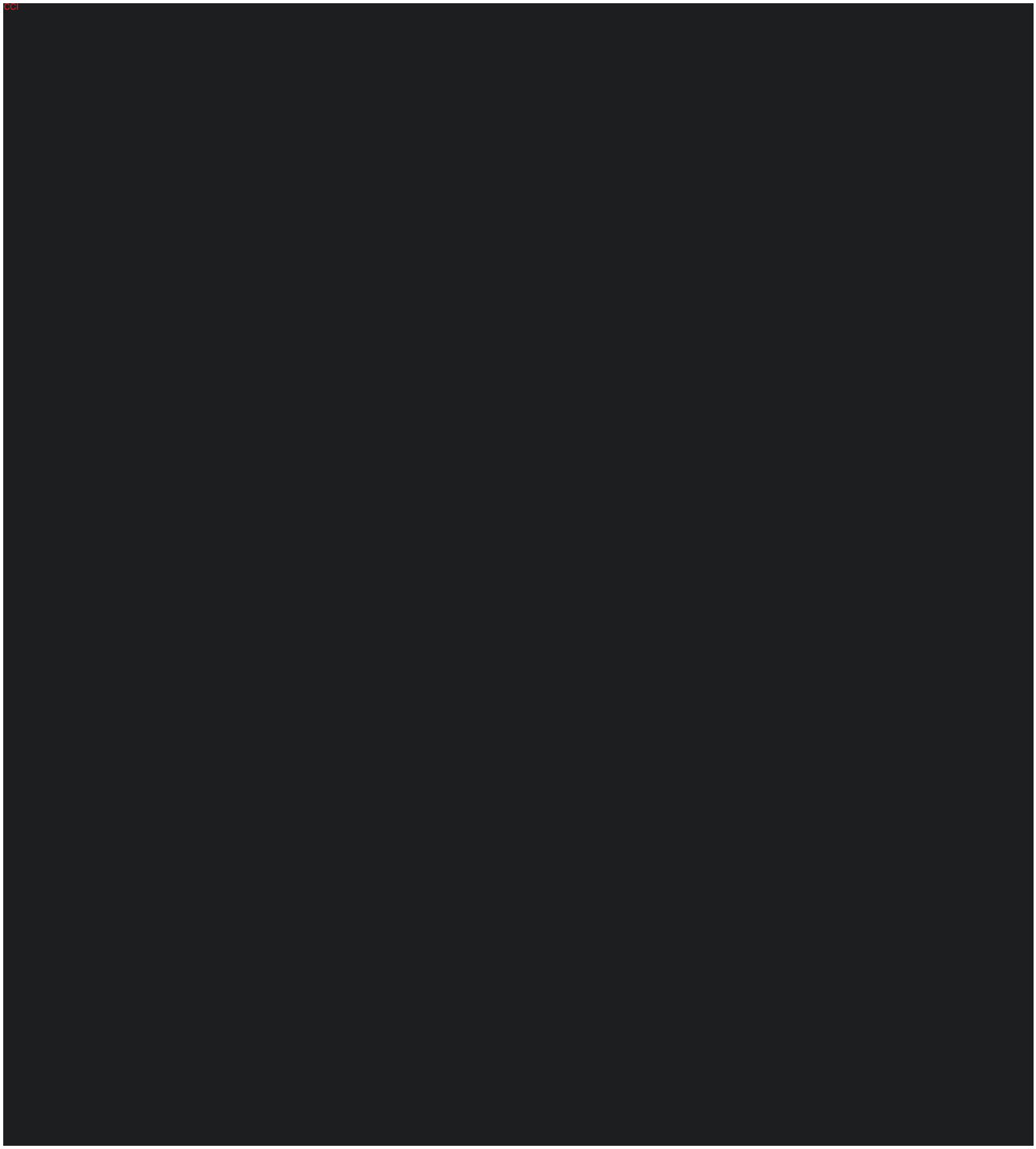
MK-4482 is a novel drug candidate with demonstrated activity against SARS-CoV-2 in vitro, efficacy against coronaviruses in animal models, and a high barrier to viral resistance. MK-4482 has been generally safe and well-tolerated to date in ongoing clinical studies.

2.2 Background









3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in non-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 percentage of participants who are hospitalized and/or die from randomization through Day 29. **Hypothesis**: MK-4482 is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29.	• Hospitalization or death
• To evaluate the safety and tolerability of MK-4482 compared to placebo.	• Adverse events • Adverse events leading to discontinuation of study intervention
Secondary	
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomization through Day 29.	• COVID-19 signs/symptoms
• 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 evaluate the efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who have any acute care visit from randomization through Day 29.	• Acute care visit

Objectives	Endpoints
• To evaluate the efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who have any COVID-19-related acute care visit from randomization through Day 29.	• COVID-19-related acute care visit
• To measure the pharmacokinetics of NHC (the parent nucleoside), and NHC-TP (the pharmacologically-active triphosphate form) in plasma and PBMC collected at various timepoints.	• Plasma (Part 1 and Part 2) and PBMC (Part 1) Pharmacokinetic concentration (eg, Ctrough)
• 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 and detection of treatment-emergent sequence variants as assessed by comparison of gene sequencing in virus isolated at baseline and post-baseline in samples with evaluable SARS-CoV-2 RNA.	• Viral RNA sequences
• To evaluate the antiviral activity of MK-4482 compared to placebo as assessed by the percentage of participants with undetectable infectious SARS-CoV-2 in nasopharyngeal swabs at various timepoints.	• Infectious SARS-CoV-2

4 STUDY DESIGN

4.1 Overall Design

This study (MOVe-OUT) 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 non-hospitalized participants ≥18 years of age with laboratory-confirmed COVID-19 and symptom onset within 5 days prior to randomization.

In Part 1, participants with mild COVID-19 and at least 75% of participants overall must have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19 (Appendix 10). In addition, enrollment of participants with moderate COVID-19 will be limited to approximately 50% of total planned sample size.

In Part 2, all participants must have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19 (Appendix 10). Age is a risk factor independent of other health conditions, so while there is no minimal enrollment for participants >60 years of age, every effort should be made to maximize enrollment of this age group.

Participants will receive assigned study intervention by oral administration Q12H for 5 days, for a total of 10 doses 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 (Section 4.3.3 and Section 9.7).

Part 2 (Phase 3 - Evaluation of Selected Dose)

In Part 2, ~1550 participants will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either of MK-4482 800 mg 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 ~50 participants in an optional PBMC Cohort (Part 1) at select sites with capability to isolate PBMCs.

Participants will be provided with a Study Medication Diary (dose administration will be recorded daily for 5 days) and a Symptom Diary (presence/absence and severity of a solicited list of signs/symptoms attributable to COVID-19 will be recorded daily for 29 days). In the event of hospitalization, all evaluations outlined in the SoA (Section 1.3) should be performed as feasible (details in Section 8.2.3).

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).

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 non-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, hospitalization, death). 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 is hospitalization or death. All-cause hospitalization (≥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) or death is intended to demonstrate the efficacy of MK-4482 relative to placebo using a clinically meaningful aspect of the disease that is relevant to non-hospitalized patients with COVID-19. This endpoint combines key clinical outcomes of interest, aiming to demonstrate the efficacy of study intervention in reducing serious complications of COVID-19.

4.2.1.1.2 Secondary Endpoints

To further evaluate efficacy of MK-4482 administered to non-hospitalized participants, additional relevant endpoints were selected, which are based on signs/symptoms associated with COVID-19 infection and other aspects of clinical progression of disease that are expected to improve with effective antiviral therapy:

- Time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom attributable to COVID-19 (Section 9.6.1) as reported by the participant through Day 29.

- WHO 11-point ordinal outcome scale 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 0.4-fold the NHC exposure at the 800 mg Q12H human dose of MK-4482. These changes were fully reversible (Section 2.3). Based on available unblinded data from the clinical development program for MK-4482, no clinically significant abnormalities in hematological laboratory tests as a function of either dose or treatment have been observed. However, based on preclinical findings, participants in this study will be monitored for any signs of bone marrow toxicity, including monitoring of CBC and platelets after initiating study intervention.

In preclinical studies, elevated liver enzymes were noted in rats at 62-fold the NHC exposure at 800 mg Q12H and noted in dogs at 19-fold the NHC exposure at 800 mg Q12H. Based on available unblinded data from the clinical development program for MK-4482, no clinically significant abnormalities in liver parameters as a function of either dose or treatment were noted . 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 incidence of these elevations was comparable between recipients of MK-4482 and placebo. 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 or lipase were considered an ECI and closely monitored in Part 1 of this

study and MK-4482-001. Based on available unblinded data from the clinical development program for MK-4482, no clinically significant abnormalities in amylase or lipase as a function of either dose or treatment were noted. Thus due to the lack of preclinical findings and no trend noted in MK-4482 studies to date, elevated amylase, or lipase >3X the upper limit of normal is not considered an ECI for Part 2.

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. In Part 1, PBMC PK parameters (eg, C_{trough}) will be estimated. In Part 2, plasma PK parameters (eg, C_{trough}) will be summarized and in Parts 1 and 2, PK plasma parameters will be measured. 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.

4.2.1.4 Virology Endpoints

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

Reducing SARS-CoV-2 VL and eradicating the virus are 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 elimination. These endpoints are aimed at assessing the antiviral activity of MK-4482 as well as evaluating the rate of viral mutagenesis with respect to MK-4482 treatment.

4.2.1.5 Future Biomedical Research

The Sponsor may provide samples, as described in Section 8.9, for which consent was provided during this study, to researchers including additional third parties (eg, a university investigator).

Such research is to address emergent questions not described in the protocol and will only be conducted on specimens as described in Section 8.9. Specimens will only be provided from appropriately consented participants. The objective of providing the specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

This study will be placebo-controlled 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 to serve as an active comparator, therefore placebo will be used.

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 and moderate COVID-19**: Participants with mild and moderate COVID-19 (Appendix 9) are typically managed outside of the hospital and may benefit from administration of MK-4482 [Food and Drug Administration 2020]. Participants with severe and critical COVID-19 at randomization are excluded because they are expected to require hospitalization and would be out of scope for this study.

- **Participants at increased risk for severe illness from COVID-19:** Certain characteristics or underlying medical conditions (Appendix 10) have been identified that place patients at increased risk for severe illness from COVID-19, which may result in hospitalization, ICU-level care, ventilatory support, or death. This study focuses on higher risk non-hospitalized participants who may benefit from MK-4482, aiming to reduce the number of participants who develop severe illness from COVID-19 and need to be hospitalized or die. Thus, all participants must have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19 to ensure the drug is being evaluated in the non-hospitalized population at higher risk.

- **Participants with signs/symptoms attributable to COVID-19 for ≤5 days**: Eligible participants must have COVID-19 signs/symptoms onset no more than 5 days prior to randomization. SARS-CoV-2 VLs 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 ≤5 days prior to randomization; all efforts should be made to administer the first dose on Day 1 (randomization), but administration of the first dose must occur 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 >5 days after signs/symptoms onset, especially in the non-

hospitalized setting wherein patients are often earlier in the course of their disease and intervention can occur sooner than in the hospital setting.

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 (Parts 1 and 2) and OP (Part 1 only) 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, coinfections, 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 coinfected with other respiratory pathogens
- Viral genome sequencing for determination of viral genotype (Clade) and detection of novel treatment-emergent variants.

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 VLs 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 cell-based infection assays. One such assay is the plaque assay, which quantifies viral titer (plaque forming unit) by counting the number of plaques formed in cell culture upon infection with serial dilutions of a virus specimen [Mendoza, E. J., et al 2020]. Plaque assays performed in Vero cells will be used to assess the impact of MK-4482 on the presence and/or titer of replication-competent virus in NP swab samples.

Coinfection 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 coinfection with SARS-CoV-2 [Lai, C. C., et al 2020]. Based on the potential for coinfection 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 coinfections.

Since initial identification of the original SARS-CoV-2 genotype, multiple viral variants of concern have been identified and continue to circulate worldwide. Viral genome sequencing will be used to determine the SARS-CoV-2 genotype detected in study participants. Genotype data may be used to assess the impact of viral genotype on MK-4482 efficacy. In addition, viral sequence data may be used to identify treatment-emergent variants that could potentially impact vaccine or antiviral drug efficacy.

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 (0.4-fold relative to the clinical NHC exposure at 800 mg Q12H) 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; 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 were no clinically significant abnormalities observed in the hematological laboratory tests. Furthermore, unblinded data obtained from participants treated in the Phase 2 program indicate that MK-4482 has been generally well-tolerated across all doses studied.

Overall, preclinical and Phase 1 and 2 clinical observations to date support a ~5-day dosing duration for 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 AUC_{0-12} exposure of ~32 µM*hr, which is 2.4-fold below the mean plasma AUC_{0-12} exposure at the highest single dose evaluated in adults of 1600 mg.

4.3.3 Dose Selection for Part 2 (Phase 3)

The MK-4482 dose of 800 mg Q12H for 5 days was selected for Part 2 of this study. The dose selection was based on data from IA2 as well as the totality of available safety, virology, PK, and clinical data from the MK-4482 program.

Enrollment of hospitalized participants in Part 1 (Phase 2) of MK-4482-001 has been completed. A total of 304 participants were randomized into 4 intervention groups: 75 participants in the MK-4482 200 mg group, 75 participants in the MK-4482 400 mg group, 76 participants in the MK-4482 800 mg group, and 78 participants in the placebo group. MK-4482 was generally well tolerated; the proportion of participants with AEs, drug-related AEs, SAEs, and AEs leading to study intervention discontinuation during the protocol-specified AE safety follow-up period were comparable across the intervention groups, with no apparent dose effect observed. There were no clinically significant differences in laboratory findings that met predetermined criteria, worsening Grade 3 or 4, in recipients of MK-4482 (any dose) compared with placebo. There was a numerically higher number of AEs resulting in death in participants treated with MK-4482 (14/218, 6.4%) compared with placebo (2/75, 2.7%) in P001. There was no apparent dose effect based on the incidence of death in each of the MK-4482 groups. None of the deaths was considered

related to study intervention by the investigator. The eDMC noted that there was no clustering of specific AEs resulting in death and concluded that no safety signals were seen at any MK-4482 dose. The most common AE resulting in death was COVID-19 and most deaths were associated with complications of COVID-19 (including pneumonia, sepsis, or thrombosis) or secondary bacterial infections. Most deaths occurred in participants who had severe COVID-19 at baseline, were >60 years of age, had underlying comorbidities, and/or had duration of symptoms >5 days prior to randomization.

Enrollment of Part 1 (Phase 2) of this study (MK-4482-002) has been completed. A total of 302 participants were randomized into 4 intervention groups: 75 participants in the MK-4482 200 mg group, 77 participants in the MK-4482 400 mg group, 76 participants in the MK-4482 800 mg group, and 74 participants in the placebo group. MK-4482 was well tolerated in non-hospitalized participants in MK-4482-002. The proportion of participants with AEs, drug-related AEs, SAEs, AEs leading to death, and AEs leading to study intervention discontinuation during the protocol-specified AE safety follow-up period were comparable across the intervention groups, with no apparent dose effect observed. No ECIs were reported and there were no clinically meaningful abnormalities in hematological, pancreatic, or hepatic parameters as a function of either dose or treatment.

The eDMC review of unblinded IA2 data from MK-4482-001 and MK-4482-002 concluded that there were no safety signals seen at any dose, and no dose-limiting toxicity was observed at the highest dose (800 mg). Furthermore, MK-4482 has been generally well-tolerated in other studies in the MK-4482 program at all doses studied with no dose-limiting toxicity observed at the highest dose (800 mg).

Virology data from IA2 in the MK-4482 program (MK-4482-001, MK-4482-002, and MK-4482-006) show that treatment with MK-4482 reduces the SARS-CoV-2 VL compared with placebo (based on change from baseline, slope of decline, and greater proportion of participants with a VL below the limit of quantitation within 15 or 29 days) in non-hospitalized participants enrolled in MK-4482-002 and participants with symptom onset ≤5 days in both MK-4482-001 and MK-4482-002. The exposure-response analyses for various virologic endpoints based on MK-4482-001 and MK-4482-002 suggest that the 800 mg Q12H dose provides a larger magnitude of virologic effect compared to 200 and 400 mg Q12H and is near the plateau of the dose-response curve. In addition, consistent with the proposed mechanism of action of MK-4482 of viral error catastrophe, the highest percentage of mutations in viral RNA post-treatment at Day 5 were observed in the 800 mg Q12H intervention group from MK-4482-001 and MK-4482-002.

Evaluation of the primary clinical efficacy endpoint for MK-4482-002 showed that 11 of 299 participants were hospitalized through Day 29 (including 1 participant treated with placebo who died); ~3% of participants in the MK-4482 intervention groups were hospitalized or died through Day 29 (compared to ~5% in the placebo group). All hospitalized participants had at least 1 risk factor for severe illness from COVID-19 including but not limited to obesity (n=8), >60 years of age (n=5), and diabetes (n=5). Protocol-specified subgroup analyses for the primary endpoint indicated potential clinical benefit from treatment with MK-4482 early in the course of disease (ie, symptom onset ≤5 days prior to the day of

randomization) as well as in individuals with risk factors for severe illness from COVID-19, including age >60 years. This trend is further supported by exposure-response analyses for the endpoint of hospitalization which suggest a trend of an increased clinical effect at MK-4482 800 mg Q12H dose over placebo or lower MK-4482 doses.

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

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 non-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 laboratory-confirmed SARS-CoV-2 infection with sample collection ≤5 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 ≤5 days prior to the day of randomization and at least 1 of the following signs/symptoms attributable to COVID-19 on the day of randomization (Appendix 9):

    - Cough
    - Sore throat
    - Nasal congestion
    - Runny nose
    - Shortness of breath or difficulty breathing with exertion
    - Muscle or body aches
    - Fatigue
    - Fever >38.0˚C
    - Chills
    - Headache
    - Nausea
    - Vomiting
    - Diarrhea
    - Loss of smell
    - Loss of taste

3. Has mild or moderate COVID-19 (refer to Appendix 9 to determine disease severity at randomization).

4. Has at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19 (refer to Appendix 10 to determine if the participant has a characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19).

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 4 days after the last dose of study intervention:

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

OR

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

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

- 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 at least 4 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

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

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.4.

- 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.

- 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/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

   Note: As outlined in the informed consent, patients can only participate in this study if 1) they have chosen not to receive treatment with a SARS-CoV-2 monoclonal antibody(ies) and reside in the US or in other countries where SARS-CoV-2 monoclonal antibodies are authorized or approved, or 2) reside outside of the US in countries where SARS-CoV-2 monoclonal antibodies are not authorized or approved.

5.2 Exclusion Criteria

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

Medical Conditions

1. Is currently hospitalized or is expected to need hospitalization for COVID-19 within 48 hours of randomization.

2. Is on dialysis or has reduced eGFR <30 mL/min/1.73 m^2 (by the MDRD equation [Appendix 11]).

3. Has any of the following conditions:

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

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

   - A neutrophilic granulocyte absolute count <500/mm^3

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

7. 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 with a recent history of mechanical ventilation, or
   - Participants with conditions that could limit gastrointestinal absorption of capsule contents.

Prior/Concomitant Therapy

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

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

Not applicable.

Other Exclusions

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

5.3 Lifestyle Considerations

There are no lifestyle restrictions for the study.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (study intervention[s] provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	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 2 800 mg	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.

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.

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 800 mg or placebo.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

Part 1

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

2. At increased risk of severe illness from COVID-19 (Appendix 10) (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 earlier treatment (≤5 days) rather than later treatment (>5 days). In addition, certain characteristics or underlying medical conditions (Appendix 10) have been identified that place patients at increased risk for severe illness from COVID-19, which may result in hospitalization, ICU-level care, ventilatory support, or death. 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, at least 75% of participants overall must have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19 as defined in Appendix 10. In addition, enrollment of participants with moderate COVID-19 (Appendix 9) will be limited to 50% of total planned sample size.

Part 2

1. Time from symptom onset prior to the day of randomization (≤3 days, >3 days)

Based on updates to inclusion criterion #2 wherein the initial onset of signs/symptoms attributable to COVID-19 was amended to ≤5 days prior to the day of randomization to target participants earlier in their COVID-19 disease course, the time from symptom onset prior to the day of randomization stratification factor was amended to ≤3 days or >3 days. 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 earlier treatment (≤3 days) rather than later treatment (>3 days).

Of note, all participants must have at least 1 characteristic or underlying medical condition associated with being at increased risk for severe illness from COVID-19 as defined in

Appendix 10. Age is a risk factor independent of other health conditions, so while there is no minimal enrollment for participants >60 years of age, every effort should be made to maximize enrollment of this age group.

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.

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.

In addition, a separate, small, cross-functional unblinded team of Sponsor personnel will also be convened for Part 2 of the study with the purpose of supporting preparation and submission of applications for emergency use and/or marketing authorizations in the case of a positive efficacy finding noted by the eDMC at IA4. The members of this team will not have access to unblinded data until an eDMC decision is reached. Additional details of the unblinding plan will be documented in an official memo prior to eDMC review. Sponsor personnel responsible for ongoing blinded data review will remain blinded to data obtained from 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 self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by review of a study medication diary during the site visits and documented in the source documents and CRF.

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

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for those medications or vaccinations. If there

is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

Prior and concomitant therapies listed as prohibited in Table 2 are not permitted for the specific time frames listed. Table 2 is not comprehensive, and the investigator should use 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. Of note, if a participant is hospitalized during the study, other medications intended as treatment for COVID-19 are permitted.

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 Monoclonal Antibodies	• Monoclonal antibodies are prohibited for treatment of the current SARS-CoV-2 infection, including prior to randomization and through Day 29.

Other COVID-19 Therapeutics	• Sponsor-designated standard of care for treatment for COVID-19[a] is permitted (eg, corticosteroids) but may require additional safety monitoring as determined by the treating clinician.
	  ○ If guidelines for local standard of care conflict with Sponsor-designated standard of care, site should consult with Sponsor.
	  ○ 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. If a participant is hospitalized during the study, other therapies intended as treatment for COVID-19 are permitted.
	• Supportive therapies (including but not limited to anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms are allowed.

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.
[a] For a detailed list of Sponsor-approved treatments, refer to the *MK-4482-002 Sponsor-Designated Standard of Care for Treatment of COVID-19 or Supportive Therapies for Management of COVID-19* document.	

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 platelet count of <50,000/μL, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

- The participant is no longer able to take oral medication or becomes intubated prior to completion of study intervention.

- 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).

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.

Both survival and hospitalization status at Day 29 and LFU are required for all randomized participants and should still be reported for participants who withdraw from the study where permitted by local guidelines. Site personnel should attempt to obtain information regarding vital status (including date last known to be alive, hospitalization, date of death, primary cause of death, and COVID-19 contribution to death) as outlined in Section 8.2.4.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.11.3 and Section 8.1.9.1. 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.

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 140 mL for participants in the PBMC Cohort or approximately 108 mL for all other participants (Appendix 2, Table 12).

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

For country-specific requirements see Appendix 7.

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 their 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 their legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.1.3 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, midturbinate swab, saliva, etc.), test method (eg, RT-PCR) and result (positive result is required). If prior results are not available, laboratory confirmation of SARS-CoV-2 infection may be performed at screening to confirm eligibility. Results must be available prior to randomization.

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. 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 urine or serum pregnancy test is required within 24 hours of the first dose of study intervention per inclusion criteria.

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

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 (Part 1 only), obesity, active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality), congestive cardiac failure, coronary artery disease, cardiomyopathies, sickle cell disease (Part 1 only), and diabetes mellitus (Appendix 10). 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. All efforts should be made to administer the first dose on Day 1 (randomization), but administration of the first dose must occur 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. Study intervention and the Study Medication Diary will be dispensed to the participant according to the pharmacy manual for at home administration. Study intervention will be self-administered by the participant Q12H at approximately the same times each day.

8.1.8.1 Timing of Dose Administration

Participants will take the appropriate number of capsules of study intervention (as described in the study intervention administration instructions) Q12H (±2 hours) for 10 doses. Study intervention can be administered without regard to food. Refer to Section 8.6.1 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, all efforts should be made to administer the first dose on Day 1 (randomization), but administration of the first dose must occur 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 administration 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 all doses, the timing of dose administration should be recorded in the Study Medication Diary.

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

- If ≤10 hours from the time the missed dose should have been taken, the missed dose should be taken, and the normal dosing schedule (ie, Q12H) 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 (ie, Q12H) resumed. The participant should not double the next dose to compensate for what has been missed.

- In the event of an out of window dose during the treatment period, the EOT visit may need to be rescheduled to accommodate collection of PK samples in association with the 9th or 10th dose. The site should communicate with the participant during the treatment period to discuss if any changes to the dosing schedule occurred, which might affect the timing of the 9th or 10th dose and thus warrant a change to the EOT visit.

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 to 6 hours prior to dialysis where possible.

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.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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

8.1.12 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. Contact information for secondary contacts or healthcare 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).

8.1.13 Participant Study Supplies

On Day 1 of the study, participants will receive bottles of study intervention along with study supplies, including:

- Copy of informed consent
- Information about the study
- Instructions on study procedures and how to take study intervention
- Pocket/wallet card with site staff contact information
- Instructions on what to do if participants have worsening symptoms/become hospitalized
- Study Medication Diary (see Section 8.1.14)

- Symptom Diary (see Section 8.2.5)

8.1.14 Study Medication Diary

A paper Study Medication Diary will be provided for documentation of doses of study intervention and assessment of compliance. Participants should complete the Study Medication Diary for each dose taken. In the event that the participant is (in the judgement 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 with each participant at the visits described in the SoA, Section 1.3, 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.

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

8.2 Efficacy Assessments

8.2.1 Nasopharyngeal and Oropharyngeal Swabs

NP (Parts 1 and 2) and OP (Part 1 only) 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, detection of infectious SARS-CoV-2, 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.

8.2.2 Respiratory/Oxygenation Status

SpO_2 will be measured via pulse oximetry (SoA, Section 1.3) after the participant has been at rest for at least 5 minutes. The first recording will be on Day 1 prior to the first dose of study intervention and then at each in-person visit through Study Day 29. In addition, investigator/designee assessment of shortness of breath at rest and with exertion will be

performed at randomization prior to the first dose of study intervention and then at each in-person visit through Study Day 29. FiO_2, PaO_2, and supplemental oxygen use if applicable should be reported.

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. If applicable, 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).

New or worsening shortness of breath or difficulty breathing should be reported to the site clinician and referral for medical attention considered.

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.

8.2.3 Hospitalization

Hospitalization status will be assessed as outlined in the SoA (Section 1.3). Hospitalization is defined as ≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic. The date and time of hospital admission, date and time of discharge, and primary reason for hospitalization (including if the admission is related to COVID-19) will be recorded. The Sponsor must be notified within 24 hours of site's awareness of a participant's hospitalization in accordance with the guidance outlined in Section 8.4.6.

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

Acute care visits must also be documented and recorded on the eCRF. Acute care visits are defined as any hospitalization (any amount of time in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic) or emergency room visit or any other acute care visit (including an urgent care visit or visit with any healthcare provider for acute care needs) from randomization through Day 29. The date and time of the acute care visit, and primary reason for acute care visit (including if the visit is related to COVID-19) will be recorded.

For any participants who become hospitalized during the study, all study procedures outlined in the SoA (Section 1.3), including study intervention administration (if applicable), should be continued. If the hospitalized participant has not completed study intervention and is unable to swallow the capsules or is intubated during hospitalization, then study intervention should be discontinued (Section 7.1). If access to the participant by study staff is not feasible while in hospital, use of a home healthcare professional (eg, through a home healthcare vendor) to perform inpatient participant visits according to the SoA (Section 1.3) should be

considered. Given the frequency of study intervention administration, it is recognized that use of nonstudy personnel may be necessary for this procedure. In such cases, documentation of these responsibilities and source documentation of study intervention administration must be maintained in the site's source documentation as appropriate. If in-person visits are not permitted by the institution in which the participant is hospitalized, a virtual visit (eg, telehealth, telephone) may be performed to collect data that does not require in-person collection. Every attempt should be made to obtain equivalent data from hospital records. In addition to information regarding hospitalization details, available pertinent information will be collected, including assessment of COVID-19 symptoms (eg, via MK-4482 Symptom Diary or Sponsor-provided interview script, if completed), vital signs, supplemental oxygenation use, ventilation procedures, concomitant medications, and adverse events, including death. In addition, every effort should also be made for a visit to be scheduled after discharge from the hospital, providing that the visit is within 28 days of initiation of dosing.

8.2.4 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.

8.2.5 MK-4482 Symptom Diary

COVID-19 signs/symptoms will be reported daily by the participant using a paper MK-4482 Symptom Diary on Days 1 to 29. Targeted symptoms assessed in the diary include cough, sore throat, nasal congestion (stuffy nose), runny nose, shortness of breath or difficulty breathing, muscle or body aches, fatigue (tiredness), feeling hot or feverish, chills, headache, nausea, vomiting, diarrhea, loss of taste and loss of smell. If the participant is able to comprehend the diary questions (in the judgement of the investigator) but is unable to record their responses on the diary on their own per investigator discretion, collection of COVID-19 signs/symptom data by study staff via an in-person or virtual (eg, telephone) participant interview using a Sponsor-provided interviewer script should be implemented.

On Day 1 (the same day as randomization), participants will complete the MK-4482 Symptom Diary prior to the first dose of study treatment. Completion of the Symptom Diary will be observed at the site or in-home visit and documented, including time of participant completion, by study staff/home healthcare professional. Following Day 1, participants should complete the diary daily at approximately the same time every day through Day 29, recording and rating each symptom at its worst (reported as none, mild, moderate, or severe) during the prior 24 hours.

In the event of hospitalization, the MK-4482 Symptom Diary should be completed during hospitalization if possible. If the participant is unable to record their responses on the diary on their own, the Sponsor-provided interviewer script should be implemented by study staff. Completion of the diary should be resumed by the participant after discharge per SoA, Section 1.3.

The MK-4482 Symptom Diary will be reviewed by study staff with each participant at the visits described in the SoA (Section 1.3) to ensure compliance with completion. To further support compliance with completion by the participant, the study staff should provide participants with regular telephone or other reminders (eg, email, text messages) regarding diary completion. Following the EOT visit, these reminders should be provided every other day through Day 29. The MK-4482 Symptom Diary will be collected per the SoA, Section 1.3, and the diary data will be recorded in the eCRF.

8.2.6 Functional Status Assessments

Functional status assessments will be performed at all in-clinic or at-home visits per the SoA (Section 1.3). The participant's ability to independently perform daily activities with minimal or no symptoms will be assessed and evaluated at the discretion of investigator/designee.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. 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 examination 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.

Vital sign measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.3.3 Clinical Safety Laboratory Assessments

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

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

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

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

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

8.3.4 Pregnancy Testing

- Pregnancy testing:

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

  Pregnancy testing should be conducted at screening (serum or urine) and on Day 29 (serum), 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 study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside 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.

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.

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

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - 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 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 postbaseline platelet value <50,000/µL, as 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/visiting nurse. 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 and Part 2	• 1 sample pre-dose[a] • 1 sample 1.5 hours post-dose (±30 min)
[a] Pre-dose sample should be collected within 2 hours of dosing.	

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

8.6.2 Blood Collection for Measurement of NHC-TP in PBMC

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 during Part 1 only:

- 2 tubes pre-dose
- 2 tubes post-dose at 1.5 hours (±30 min)

Pre-dose sample should be collected within 2 hours of dosing. The timing of blood collection will be aligned with the timing of dose administration as outlined in Section 8.1.8.1. Sample collection, storage, and shipment instructions for PBMC samples will be provided in a separate manual.

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

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 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, coinfections, 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

If the participant provides document informed consent, the following specimens may be used for exploratory research and/or FBR as outlined in Sections 8.8 and 4.2.1.5, respectively:

- Unused isolates from NP swabs (Part 2 only)
- Unused serum and plasma from serum and plasma for exploratory research (Part 2 only)
- Unused serum from serum for antibody exploratory research (Part 2 only)

8.10 Medical Resource Utilization and Health Economics

Sites are to collect hospitalization status and discharge data, including acute care visit status, per the SoA (Section 1.3) and Section 8.2.3.

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 ≤48 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 1 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 48 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
- Local laboratory assessments for inclusion/exclusion (results within 72 hours prior to randomization may be used for eligibility)
- Urine or serum β-hCG (pregnancy testing for WOCBP)
- Review of AEs

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

8.11.2.2 Clinic or At-Home Visits

In lieu of a participant travelling to the study site, an at-home visit by a healthcare provider (eg, home healthcare company or visiting nurse, etc.) may be appropriate to perform study assessments and procedures per the SoA (Section 1.3) (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), Section 8.11.2.3, 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.

8.11.2.3 Virtual Visits

The investigator or designee may conduct the Day 2 and Day 4 visits with the participant virtually (eg, by 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 9th or 10th 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.

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

8.11.4 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).

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 research plasma samples) are beyond the scope of this document or will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-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[a]) to receive 1 of the following 4 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 1550 participants will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either MK-4482 800 mg or placebo Q12H for 5 days.
Analysis Populations	**Efficacy**: MITT (Parts 1 and 2 separately) **Safety**: APaT (Parts 1 and 2 combined)

Primary Endpoints	**Efficacy**: Proportion of participants with hospitalization or death by Day 29. **Safety**: Number of participants with AEs, and discontinuing study intervention due to AEs
Key Secondary Endpoints	• Time to sustained resolution or improvement, and time to progression of each targeted self-reported sign/symptom of COVID-19 through Day 29 • 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	For the evaluation of the primary hypothesis, superiority of MK-4482 compared to placebo with respect to the percentage of participants with hospitalization or death by Day 29 will be calculated using the stratified Miettinen and Nurminen method [Miettinen, O. 1985].
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 AEs; these analyses will be performed using the unstratified Miettinen and Nurminen method [Miettinen, O. 1985].
Interim Analyses	**IA1 – Part 1 Dose Evaluation** This IA will be used to review data to inform dose selection models and analyses. **IA2 – Part 1^{b} Dose Selection** This IA will be used to evaluate the dose/exposure-response to select the dose for Phase 3. **IA3 – Part 2 Sample Size Re-estimation** This IA will be an unblinded sample size re-assessment. The conditional power approach will be employed in which the overall sample size can be adjusted upwards if the interim result is sufficiently promising without inflation of the type I error. **IA4 – 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	There are no adjustments for multiplicity other than the type I error control for interim analyses described in Section 9.7.

Sample Size and Power	The total sample size for the primary efficacy assessment (Part 2) will be ~1550 participants (~775 for MK-4482 800 mg and ~775 for the placebo group). The study has overall power of 97% to demonstrate the superiority of MK-4482 over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MK-4482 minus placebo) in the percentage of participants who are hospitalized and/or die through Day 29 is -6 percentage points. Additional details and assumptions for sample size and power calculation are in Section 9.9.
[a] Stratification in Part 1 included: 1) Time from symptom onset prior to the day of randomization (≤5 days, >5 days); and 2) At increased risk of severe illness from COVID-19 (Appendix 10) (yes, no)	

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 2 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 (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. 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. If this occurs, 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, IA4 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:

- Proportion of participants with either hospitalization (≥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) or death by Day 29.

Secondary:

- Time to sustained resolution or improvement of each targeted self-reported sign/symptom present at randomization (ie, Day 1), defined as the number of days from randomization to the first of 3 consecutive days when resolution or improvement is demonstrated for each targeted self-reported sign/symptom. Participants who meet criteria for sustained resolution or improvement after 3 consecutive days must not relapse by Day 29 (ie, have 2 or more consecutive days of each self-reported sign/symptom returning to the baseline severity or worse than baseline severity after the criteria for sustained resolution or improvement are met). Resolution or improvement is defined as follows:
    - A symptom reported at randomization as Mild and is subsequently reported as None
    - A symptom reported at randomization as Moderate and is subsequently reported as Mild or None,
    - A symptom reported at randomization as Severe and is subsequently reported as Moderate, Mild or None
    - A symptom reported at randomization as Yes and is subsequently reported as No

      NOTE: Participants without a symptom reported at randomization will not be included in the analysis
- Time to progression of the targeted self-reported signs/symptoms present at randomization, defined as the number of days from randomization to the first of

2 consecutive days when the targeted self-reported signs/symptoms worsen. Worsening is defined as follows:

- A symptom reported at randomization as None or No and is subsequently reported as Mild/Moderate/Severe or Yes, respectively
- A symptom reported as Mild at randomization and is subsequently reported as Moderate or Severe
- A symptom reported as Moderate at randomization and is subsequently reported as Severe

  NOTE: Participants with symptoms reported at randomization as Severe will not be included in the analysis

- 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: Relevant data (ie, 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) to support determination of the WHO 11-point ordinal score will be collected in eCRFs.

Exploratory:

- Percentage of participants who have any acute care visit. Acute care visit is defined as any hospitalization (any amount of time in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic) or emergency room visit or any other acute care visit (including an urgent care visit or visit with any healthcare provider for acute care needs) from randomization through Day 29
- Percentage of participants who have any COVID-19-related acute care visit. Acute care visit is defined as any hospitalization (any amount of time in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic) or emergency room visit or any other acute care visit (including an urgent care visit or visit with any healthcare provider for acute care needs) from randomization through Day 29
- 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 and detection of treatment-emergent sequence variants as assessed by comparison of baseline and post-baseline virus sequencing

- Percentage of participants with undetectable infectious SARS-CoV-2 in nasopharyngeal swabs on Day 3, EOT, Day 10, Day 15, and Day 29.

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, C_{trough}) (Parts 1 and 2)

9.4.2 Safety Endpoints

A description of safety measures is contained in Section 8.3 and Section 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 (ie, more abnormal in the direction of interest) than at baseline. The criteria will be adapted from the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, JUL 2017, version 2.1. A listing of the participants who meet the criteria will also be provided.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The MITT 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 the primary 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 1 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 1 laboratory value or vital sign obtained subsequent to at least 1 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 Section 9.7. There are no 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

For the evaluation of the primary hypothesis, superiority of MK-4482 compared to placebo with respect to the percentage of participants with either hospitalization or death by Day 29 will be assessed using the stratified Miettinen and Nurminen method [Miettinen, O. 1985]. Superiority will be concluded based on p-value boundaries as described in Section 9.7. Stratification factors include the stratification factors specified in Section 6.3.2. Geographic region will not be used as a stratification factor in the primary analyses, but it may be considered as an additional stratification factor of the stratified Miettinen and Nurminen method 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. Every effort will be made to ascertain hospitalization and survival status for all participants. For the primary analysis of this endpoint in the MITT population, unknown Day 29 survival status will be treated as failure, and early withdrawal from the study with known Day 29 survival status as alive but unknown Day 29 hospitalization status will not be treated as failure. A sensitivity analysis treating both unknown Day 29 survival status and early withdrawal from the study with known Day 29 survival status as alive but unknown Day 29 hospitalization status as failure will also be provided.

A sensitivity analysis for the primary endpoint will be conducted that includes only COVID-19 related hospitalizations or death by Day 29 in the MITT population. This treatment comparison will be assessed using the stratified Miettinen and Nurminen method as described above. An additional sensitivity analysis excluding hospitalizations that occur early in the course of the study (ie, within a certain time from randomization) will also be performed. Details will be specified in the sSAP.

Two additional sensitivity analyses will be performed using the endpoints of time to hospitalization/death and time to COVID-related hospitalization/death. These analyses will be performed in the MITT population. The stratified log-rank test will be used for the comparison of MK-4482 with placebo for these 2 endpoints. Stratification factors will be the same as those used for the primary endpoint. Hazard ratios will be based on the stratified Cox Proportional Hazards regression model. The Efron approximation will be used for handling ties. Hazard ratios less than 1 indicate a benefit for MK-4482. Censoring rules for these analyses will be specified in the sSAP.

Time to sustained resolution or improvement and time to progression of each targeted self-reported sign/symptom of COVID-19 will be summarized using data collected from a 15-item daily paper symptom diary completed by participants (Section 8.2.5). The distribution of time to sustained resolution or improvement and time to progression of each sign/symptom will be analyzed using the same method for the time to hospitalization or death endpoint, ie, the stratified log-rank test will be used for the comparison of MK-4482 with

placebo and the Cox proportional hazard model will be used to estimate the hazard ratio. Descriptive statistics and Kaplan-Meier plots will also be provided.

The proportion of participants with each sign/symptom will be summarized by severity (or presence/absence for loss of taste and loss of smell) for each treatment group at Day 1, Day 3, EOT, Day 10, Day 15, and Day 29.

These summaries above will include comparison of each individual sign/symptom. Missing symptom diary data will be imputed using LOCF method. Additional details will be specified in the sSAP.

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 (Parts 1 and 2) and OP (Part 1 only) 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 SARS-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 (Parts 1 and 2) and OP (Part 1 only) swabs will be summarized separately by treatment group and time point. Between-treatment differences and 95% CIs will be estimated using the stratified Miettinen and Nurminen method [Miettinen, O. 1985].

WHO 11-point ordinal scale score 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 Section 6.3.2. The WHO 11-point ordinal scale will be determined based on relevant data collected in eCRFs.

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

Table 5 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time point)	Primary vs. Supportive Approach[a]	Statistical Method[b]	Analysis Population	Missing Data Approach
Primary				
Proportion of participants with either hospitalization or death by Day 29	P	Stratified Miettinen and Nurminen[c]	MITT	As described in 9.6.1
Proportion of participants with either hospitalization or death by Day 29	S	Stratified Miettinen and Nurminen[c]	PP	Observed data only
Proportion of participants with either COVID-related hospitalization or death by Day 29	S	Stratified Miettinen and Nurminen[c]	MITT	M=F[d]
Proportion of participants with either COVID-related hospitalization or death by Day 29	S	Stratified Miettinen and Nurminen[c]	PP	Observed data only
Time to hospitalization or death by Day 29	S	Stratified log-rank test[e]; Stratified Cox proportional hazard regression[f]	MITT, PP	Model-based with censoring
Time to COVID- related hospitalization or death by Day 29	S	Stratified log-rank test[e]; Stratified Cox proportional hazard regression[f]	MITT, PP	Model-based with censoring
Secondary				
Time to sustained resolution or improvement of each targeted self-reported sign/symptoms of COVID-19	P (MITT) S (PP)	Stratified log-rank test[e]; Stratified Cox proportional hazard regression[f]	MITT PP	Model-based with censoring
Time to progression of each targeted self-reported sign/symptom of COVID-19	P (MITT) S (PP)	Stratified log-rank test[e]; Stratified Cox proportional hazard regression[f]	MITT PP	Model-based with censoring
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[g]	MITT PP	Model-based

EOT= end of treatment; F= failure; M= missing; MITT= modified intent-to-treat; PP= per-protocol; WHO= World Health Organization.

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

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

[c] Miettinen and Nurminen method stratified by the factors specified in Section 6.3.2.

[d] M=F is Missing equals to Failure

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

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

[g] 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. AEs (specific terms as well as system organ class terms) and events that meet 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 1 of the treatment groups)		X	X
	PDLCs[b] (incidence ≥4 participants in at least 1 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

AE=adverse event; CI=confidence interval; ECI=event of clinical interest; 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, review of conditional power for potential increase to sample size, 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.

A separate, small, cross-functional unblinded team of Sponsor personnel will also be convened for Part 2 of the study with the purpose of supporting preparation and submission of applications for emergency use and/or marketing authorization in the case of a positive efficacy finding noted by the eDMC at IA4. The members of this team will not have access to unblinded data until an eDMC decision is reached.

Membership on these cross-functional unblinded teams will be documented in an unblinding plan and the details of the planned analyses will be outlined in the MAP 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 4 interim analyses during the study as shown in Table 7.

Table 7 Description of Interim Analyses

Interim Analysis	Timing	MK-4482-002 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[a] and MK-4482-002.	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 an 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 Sample Size Re-estimation	Targeted to occur no earlier than at 30% of the full planned Part 2 enrollment and no later than IA4. Final timing to be based on enrollment timelines.	Primary efficacy endpoint at Day 29	Sample size re-estimation to be assessed by eDMC based on review of conditional power for primary endpoint with potential to increase Part 2 sample size
IA4 – Part 2 Futility/Early Efficacy	Targeted to occur during Phase 3 after ~775 participants complete Day 29 across the MK-4482 group and the placebo group (~50% of total enrollment).	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] MK-4482-001 is a companion MK-4482 dose-ranging study in 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-4482-001 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: Sample Size Re-estimation

IA3 will include an unblinded sample size re-assessment targeted to occur no earlier than at 30% of the full planned Part 2 enrollment and no later than IA4. Final timing should be as late as possible and prior to completion of enrollment based on enrollment timelines in order to obtain maximum study information for the sample size re-estimation. The conditional power approach will be employed in which the overall Part 2 sample size (see Section 9.9.1) can be adjusted upwards by 450 participants to a total of 2000 if the interim result is sufficiently promising (conditional power >51% but <80%, assuming continuing the interim analysis trend) without inflation of the type I error [Chen, Y. H. J., et al 2004]. The potential increase in total Part 2 sample size is to maintain adequate study power in the event that the observed treatment effect at the interim analysis is smaller than the original assumption but still clinical meaningful (treatment difference, MK-4482 minus placebo, in the percentage of participants who are hospitalized and/or die through Day 29 is between -0.037 and -0.053 percentage points).

While there is no intention to stop the study early at the unblinded sample size re-assessment (for the situation when this occurs before IA4) based on a positive efficacy outcome, it is recognized that the eDMC might consider a recommendation to stop the study should overwhelming efficacy in favor of MK-4482 be observed. To provide some guidance for the eDMC in this situation, a 1-sided p-value ≤0.0001 is proposed for the test of the primary endpoint. This conservative criterion for the superiority test will have no impact on the overall multiplicity strategy described in Section 9.8.

IA4 – Part 2: Futility/Early Efficacy IA

This study will include a futility/early efficacy interim analysis when ~50% of participants in the selected treatment group and the placebo group have completed the Day 29 visit (Phase 3 Interim Analysis). 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. Given the expected rapid enrollment, there are no plans in Part 2 of the study 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 in order to control overall type I error rate of 0.025, 1-sided. Assuming the information fraction of 50%, the non-binding futility boundary expressed on the absolute difference scale is -0.011. The boundary crossing probabilities for futility are 71% under H_0 and 0.8% under H_1 (absolute difference of -0.06). The p-value boundary for efficacy is 0.009, corresponding to an absolute difference of -0.048. The boundary crossing probabilities for efficacy are 0.9% under H_0 and 72% under H_1 (absolute difference of -0.06).

9.8 Multiplicity

The success of this study is based on a single primary endpoint (a composite of hospitalization or death) and a single treatment comparison (selected dose of MK-4482 vs. placebo). There are no adjustments for multiplicity other than controlling type I error for interim analyses described in Section 9.7. The p-value boundary for efficacy at the final analysis is 0.019, corresponding to an absolute difference of -0.03.

9.9 Sample Size and Power Calculations

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

The primary analysis of the Phase 3 study endpoint will include ~1550 participants from Part 2 of the study (~775 for the MK-4482 800 mg group and ~775 for the placebo group) who meet the criteria for inclusion in the MITT population. The primary endpoint is a composite of hospitalization or death. The study has overall power of 97% to demonstrate the superiority of MK-4482 800 mg over placebo at an overall one-sided, 2.5% alpha level, if the underlying treatment difference (MK-4482 minus placebo) in the percentage of participants who are hospitalized and/or die through Day 29 is -6 percentage points.

The power and sample size are based on the following assumptions: 1) an underlying percentage hospitalized/dying of 12% for placebo and 6% for MK-4482 (50% reduction in the relative risk) and 2) a futility/efficacy interim analysis at 50% information as outlined in Section 9.7. The calculation was computed using EAST. To meet the statistical criterion for success (one-sided p ≤0.019 at the final analysis), the observed treatment difference must be approximately -3.0 percentage points or lower, assuming a percentage of 12% for placebo. The observed percentages from Part 1 of this study in the full MITT cohort were 5.4% in the placebo group and 4.1% in the 800 mg group, a difference of only 1.3 percentage points. However, higher percentages of placebo participants met this endpoint within various subgroups of the full study population: 21.4% in the subgroup of participants >60 years of age, 8.0% in the subgroup of participants with TSSO ≤5 days and 11.8% in the subgroup of participants with TSSO ≤5 days and who were at increased risk for severe illness. In these subgroups, the percentages of participants in the 800 mg group were 5.0% (difference of 16.4 percentage points), 2.1% (difference of 5.9 percentage points) and 3.2% (difference of 8.6 percentage points), respectively. In each of these subgroups, the observed reduction in the relative risk of hospitalization/death associated with 800 mg exceeded 70%. Given the modification to the study population for Part 2, the assumption of 12% for placebo and a 50% reduction in the relative risk are reasonable.

Study power for different assumptions of the underlying percentage hospitalized/dying are presented in Table 8, all scenarios are based on a total sample size of 1550 participants and an overall one-sided, 2.5% alpha level [Stokes, E. K., et al 2020].

Table 8 Study Power by Percentage Hospitalized/Dying
N=1550 participants (775 for MK-4482 800 mg and 775 for placebo), alpha=0.025, 1-sided

Placebo Rate (%)	MK-4482 Rate (%)	Absolute Difference (percentage points)	Power
18%	12%	6	88%
16%	10%	6	92%
14%	8%	6	95%
12%	7%	5	89%
10%	5%	5	95%
8%	4%	4	89%
6%	2%	4	97%

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 a baseline VL 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 9 provides power calculations for true log differences of 0.75 to 1.25 and for various assumptions about the true underlying standard deviation.

Table 9 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 850 for each of MK-4482 selected dose group and placebo group. 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 >99.9% chance of observing at least 1 AE among 850 participants in the treatment group. If no AE of that type is observed among the 850 participants in any treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with the AE is <0.44 (1 of every 231 participants). Table 10 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 850 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 10 Differences in Incidence of AE Rates Between the 2 Treatment Groups That Can be Detected With a ~90% Probability (Assuming 2-sided 5% Alpha Level with 850 Participants in Each Group)

Incidence of Adverse Event		Risk Difference
Placebo (%)	**MK-4482 (%)**	**Percentage Points**
1.0	3.3	2.3
5.0	9.1	4.1
10.0	15.3	5.3
20.0	26.7	6.7
30.0	37.5	7.5
40.0	47.8	7.8
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 category (≤60 vs >60 years)
- Sex (female, male)
- Baseline (Day 1) disease severity (mild, moderate) per Appendix 9
- 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) [Part 1 only]
- Time from symptom onset prior to the day of randomization (≤3 days, >3 days) [Part 2 only]
- At increased risk for severe illness from COVID-19 (yes, no) (Appendix 10) [Part 1 only]
- Geographic region (North America, Europe, Asia Pacific, Latin America)
- Baseline (Day 1) SARS-CoV-2 quantitative assay VL status (undetectable [<500 copies/mL], low VL [500 to ≤10^6 copies/mL], high VL [>10^6 copies/mL]) [Part 2 only]

- Baseline (Day 1) SARS-CoV-2 qualitative assay VL status (undetectable, detectable) [Part 2 only]

- Baseline (Day 1) SARS-CoV-2 antibody status (negative, positive) [Part 2 only]

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 11 will be performed by the central laboratory.
- Local laboratory test is required for initial COVID-19 SARS-CoV-2 infection confirmation 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 participant management, or for either study intervention administration and/or response evaluation. If a collection of a local sample is required, it is important that the sample for central analysis is obtained at the same time; however, if it is documented for a specific participant visit that central sample analysis will not be possible, then the parallel collection of the sample for central analysis is not required. Additionally, if the local laboratory results are used for participant management, or to make either a study intervention decision or response evaluation, the results must be entered into the 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 11 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH RDW	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Calculation of: Neutrophil/lymphocyte ratio Absolute Neutrophil Count
Chemistry	BUN	Chloride	AST/SGOT
	Albumin	Calcium	ALT/SGPT
	Creatinine	Phosphorous	Alkaline phosphatase
	Glucose (nonfasting)	Amylase	GGT
	Potassium	Lipase	LDH
	Bicarbonate	Total Protein	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Sodium	Magnesium	hs-CRP (inflammatory biomarker) will be tested at all visits with chemistry collection as the test is performed on the same blood sample
	CK		
Pregnancy Testing	• Urine or Serum hCG pregnancy test (as needed for WOCBP)		
Virology	• SARS-CoV-2 RNA (real time PCR) OP (Part 1 only) and NP (Parts 1 and 2) swabs (quantitative and qualitative) • SARS-CoV-2 Gene Sequencing		
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 • Coinfection with other respiratory pathogens • Viral genotyping and treatment-emergent variant detection		

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.

Table 12 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)	
Nasopharyngeal Swab	flocked or polyester-tipped swab (3 mL universal transport medium)		X		X		X	X	X	X	NA
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	
Sub Total for all Participants for Central Laboratory	NA	**0**	**23.5**	**0**	**4.5**	**0**	**23.5**	**23.5**	**4.5**	**24**	
Pharmacokinetics	NA										
Pharmacokinetic Plasma Sampling Part 1	Plasma (EDTA)						6				
Pharmacokinetic Plasma Sampling Part 2	Plasma (EDTA)						6				

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)	
Pharmacokinetic PBMC Sampling Part 1	Whole Blood (Sodium Heparin) processed to PBMCs						32				
Total For Participants in Part 1	**NA**	0	23	0	4.5	0	29	23	4.5	24	108
Total For Participants in Part 2		0	23	0	4.5	0	29	23	4.5	24	108
Total For PBMC Cohort Participants in Part 1		0	23	0	4.5	0	61	23	4.5	24	140

EDTA: ethylenediaminetetraacetic acid; hCG: human chorionic gonadotropin; N/A: not applicable; 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 user dependent 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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for Germany

Legally Acceptable Representative

In order for a participant to be eligible to participate in Germany, he/she must be capable of signing the informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.8 Appendix 8: Ordinal Outcome Scales

10.8.1 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 Industry (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 one or more of the following: **fever >38.0ºC, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell**

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 or moderate 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.

Vital sign measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

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** as assessed by the investigator, 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** as assessed by the investigator
- 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 ≤4 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** as assessed by the investigator, 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** as assessed by the investigator
- 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 >4 liters/min supplemental oxygen for COVID-19 (but was not previously on supplemental oxygen), regardless of SpO_2
- PaO_2/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 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: Individuals at Increased Risk for Severe Illness from COVID-19

Individuals with at least 1 of the following characteristics or underlying medical conditions are at increased risk for severe illness from COVID-19, as adapted from the US CDC [Centers for Disease Control and Prevention 2020] [Centers for Disease Control and Prevention 2021] [Centers for Disease Control and Prevention 2020] and the WHO [World Health Organization 2020]. Immunocompromised state from solid organ transplant and sickle cell disease were considered high risk conditions in Part 1; however, these conditions were removed for Part 2 to align with updated CDC guidance supported by meta-analysis/systematic review rather than mostly observational studies.

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

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

10.11 Appendix 11: 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

10.12 Appendix 12: 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 2 hours
C12hr	plasma concentration value collected at 12 hours
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CD4	cluster of differentiation 4
CI	confidence interval
C_{max}	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
C_{trough}	lowest plasma concentration
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAO	data as observed
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
EAST	software platform for the statistical design, simulation and monitoring of clinical trials
ECG	electrocardiogram
ECI	event of clinical interest
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
EEA	European Economic Area
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
ePROs	electronic patient-reported outcomes
ESD	early stage development
ESR	erythrocyte sedimentation rate
EUA	emergency use authorization
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	Expanded Term
FiO_2	fraction of inspired oxygen
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
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
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 amenorrhoea method
LAR	legally acceptable representative
LFT	liver function test
LFU	late follow-up
LOCF	last observation carries forward
LSD	late stage development
MAD	multiple ascending dose
MAP	modeling analysis plan
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
MOVe-OUT	non-hospitalized outpatient study
MSD	Merck Sharp & Dohme
N/A	not applicable
NCT	National Clinical Trial
NEJM	New England Journal of Medicine
NHC	N-hydroxycytidine
NHC-TP	N-hydroxycytidine pharmacologically-active triphosphate

Abbreviation	Expanded Term
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
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
T_{max}	time to maximum plasma concentration
TSSO	time since symptom onset
t1/2	half-life
ULN	upper limit of normal
US	United States
VL	viral load
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Beigel, J. H., et al 2020]	Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - preliminary report. N Engl J Med. In press 2020.	[05JL53]
[Bhimraj, A., et al 2020]	Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VCC, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Arlington (VA): Infectious Diseases Society of America (IDSA); 2020. 82 p.	[05JSVV]
[Centers for Disease Control and Prevention 2020]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). Coronavirus disease 2019 (COVID-19): people with certain medical conditions; [updated 2020 Jun 30; cited 2020 Jul 31]; [about 30 screens]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.	[05K6RY]
[Centers for Disease Control and Prevention 2020]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). Coronavirus disease 2019 (COVID-19): older adults; [updated 2020 Jul 30; cited 2020 Jul 31]; [about 17 screens]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html.	[05K6T3]
[Centers for Disease Control and Prevention 2021]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). Underlying medical conditions associated with high risk for severe COVID-19: information for healthcare providers; [updated 2021 Mar 29; cited 2021 Apr 2]; [about 19 screens]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.	[05RJ2F]
[Cevik, M., et al 2020]	Cevik M, Bamford CGG, Ho A. COVID-19 pandemic - a focused review for clinicians. Clin Microbiol Infect. 2020;26:842-7.	[05JLPP]

[Chen, Y. H. J., et al 2004]	Chen YHJ, DeMets DL, Lan KKG. Increasing the sample size when the unblinded interim result is promising. Statist Med 2004;23:1023-38.	[03QBFQ]
[Clark, A., et al 2020]	Clark A, Jit M, Warren-Gash C, Guthrie B, Wang HHX, Mercer SW, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health. In press 2020.	[05JF2D]
[COVID-19 Treatment Guidelines Panel 2020]	COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Bethesda (MD): National Institutes of Health (NIH); 2020. 146 p.	[05JQGC]
[D'Abramo, A., et al 2020]	D'Abramo A, Lepore L, Palazzolo C, Barreca F, Liuzzi G, Lalle E, et al. Acute respiratory distress syndrome due to SARS-CoV-2 and influenza A co-infection in an Italian patient: mini-review of the literature. Int J Infect Dis. 2020;97:236-9.	[05K876]
[European Commission 2020]	European Commission. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic: version 3. Brussels (Belgium): European Commission; 2020 Apr 28. 21 p.	[05J46H]
[Farrington, C. P. and Manning, G. 1990]	Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9:1447-54.	[03QK0P]
[Food and Drug Administration 2020]	Food and Drug Administration. COVID-19: developing drugs and biological products for treatment or prevention: guidance for industry. Silver Spring, MD. May 2020.	[05JNM2]
[Gordon, C. J., et al 2020]	Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020;295(20):6785-97.	[05JT9R]

[Kim, D., et al 2020]	Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens [letter]. JAMA. 2020 May 26;323(20):2085-6.	[05K879]
[Klok, F. A., et al 2020]	Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7.	[05JLPX]
[Lai, C. C., et al 2020]	Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? J Microbiol Immunol Infect. In press 2020.	[05K8X5]
[Marshall, J. C., et al 2020]	Marshall JC, Murthy S, Diaz J, Cheng A, Denholm J, Hodgson C, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. In press 2020.	[05JNMB]
[McCullagh, P. 1980]	McCullagh P. Regression models for ordinal data. J Royal Stat Soc B 1980;42(2):109-42.	[03NZCC]
[Mendoza, E. J., et al 2020]	Mendoza EJ, Manguiat K, Wood H, Drebot M. Two detailed plaque assay protocols for the quantification of infectious SARS-CoV-2. Curr Protoc Microbiol. 2020;57:e105.	[05K87C]
[Miettinen, O. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]
[Ovsyannikova, I. G., et al 2020]	Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA, Kennedy RB. The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. Immunol Rev. 2020;296:205-19.	[05K875]
[Painter, W. P., et al 2021]	Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NCJE, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2 [manuscript]. Antimicrob Agents Chemother. 2021. 35 p.	[05QSYX]

[Stokes, E. K., et al 2020]	Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020 Jun 19;69(24):759-65.	[05JG6C]
[Tenforde, M. W., et al 2020]	Tenforde MW, Billig Rose E, Lindsell CJ, Shapiro NI, Files DC, Gibbs KW, et al. Characteristics of adult outpatients and inpatients with COVID-19 - 11 academic medical centers, United States, March-May 2020. MMWR Morb Mortal Wkly Rep. 2020 Jul 3;69(26):841-6.	[05L39W]
[U.S. Prescribing Information 2021]	U.S. Prescribing Information: VEKLURY (remdesivir) for injection, for intravenous use; VEKLURY (remdesivir) injection, for intravenous use: Feb 2021.	[05QSYW]
[Wadman, M., et al 2020]	Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. A rampage through the body. Science. 2020 Apr 24;368(6489):356-60.	[05JM53]
[Wang, T., et al 2020]	Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19 [correspondence]. Lancet. 2020 Mar 21;395:e52.	[05JM59]
[World health Organization 2020]	World health Organization. Coronavirus disease (COVID-19): situation report - 171. Geneva (Switzerland): World Health Organization (WHO); 2020. 18 p.	[05JSVX]
[World health Organization 2020]	World health Organization. Clinical management of COVID-19: interim guidance. Geneva (Switzerland): World Health Organization (WHO); 2020 May 27. 62 p.	[05JSVW]
[World Health Organization 2020]	World Health Organization. WHO COVID-19 case definition. Geneva (Switzerland): World Health Organization (WHO); 2020 Aug 7.	[05L0V2]

[World Health Organization 2020]	World Health Organization [Internet]. Geneva (Switzerland): World Health Organization (WHO); c2020. COVID-19: vulnerable and high risk groups; [cited 2020 Jul 29]; [about 6 screens]. Available from: https://www.who.int/westernpacific/emergencies/covid-19/information/high-risk-groups.	[05K6T7]
[Wu, X., et al 2020]	Wu X, Cai Y, Huang X, Yu X, Zhao L, Wang F, et al. Co-infection with SARS-CoV-2 and influenza a virus in patient with pneumonia, China [letter]. Emerg Infect Dis. 2020 Jun;26(6):1324-6.	[05K87F]
[Wu, Z. 2020]	Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42.	[05J92M]