

Study Protocols and Statistical Analysis Plans

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This supplement contains the following items:

1. Original protocol, final protocol, and summary of changes
2. Original statistical analysis plan, final statistical analysis plan, and summary of changes.

Please note that the statistical analysis plan is embedded in the protocol as section 8.

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Title Page

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

Protocol Number: 002-00

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 |

Approval Date: 14 September 2020

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|-------------------|----------------------|--------------------------|
| Original Protocol | 14-SEP-2020 | Not applicable |

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1 PROTOCOL SUMMARY

1.1 Synopsis

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

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

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

| Primary Objectives | Primary Endpoints |
|--|---|
| <p>- 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.</p> <p>Hypothesis: MK-4482 is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29</p> | <p>- Hospitalization or death</p> |
| <p>- To evaluate the safety and tolerability of MK-4482 compared to placebo.</p> | <p>- Adverse events - Adverse events leading to discontinuation of study intervention</p> |
| Secondary Objectives | Secondary Endpoints |
| <p>- To evaluate the efficacy of MK-4482 compared to placebo as assessed by time to improvement/ resolution, and time to progression of targeted self-reported signs/symptoms of COVID-19 from randomization through Day 29.</p> | <p>- COVID-19 signs/symptoms</p> |
| <p>- 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.</p> | <p>- WHO 11-point scale score</p> |

Overall Design:

| | |
|-----------------------------|--|
| Study Phase | Phase 2/Phase 3 |
| Primary Purpose | Treatment |
| Indication | COVID-19 |
| Population | Participants \geq 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 ~1450 participants will be randomized in the study.

Intervention Groups and Duration:

| Intervention Groups | <table border="1"> <thead> <tr> <th>Intervention Group Name</th> <th>Drug</th> <th>Dose Strength</th> <th>Dose Frequency</th> <th>Route of Administration</th> <th>Treatment Period</th> </tr> </thead> <tbody> <tr> <td colspan="6">Part 1 (N~300)</td> </tr> <tr> <td>MK-4482 (200 mg)</td> <td>MK-4482</td> <td>200 mg</td> <td>Q12H</td> <td>Oral</td> <td>5 days (10 doses total)</td> </tr> <tr> <td>MK-4482 (400 mg)</td> <td>MK-4482</td> <td>400 mg</td> <td>Q12H</td> <td>Oral</td> <td>5 days (10 doses total)</td> </tr> <tr> <td>MK-4482 (800 mg)</td> <td>MK-4482</td> <td>800 mg</td> <td>Q12H</td> <td>Oral</td> <td>5 days (10 doses total)</td> </tr> <tr> <td>Placebo</td> <td>Placebo</td> <td>0 mg</td> <td>Q12H</td> <td>Oral</td> <td>5 days (10 doses total)</td> </tr> <tr> <td colspan="6">Part 2 (N~1150)</td> </tr> <tr> <td>MK-4482</td> <td>MK-4482</td> <td>TBD mg</td> <td>Q12H</td> <td>Oral</td> <td>5 days (10 doses total)</td> </tr> <tr> <td>Placebo</td> <td>Placebo</td> <td>0 mg</td> <td>Q12H</td> <td>Oral</td> <td>5 days (10 doses total)</td> </tr> </tbody> </table> | 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~1150) | | | | | | MK-4482 | MK-4482 | TBD mg | Q12H | Oral | 5 days (10 doses total) | Placebo | Placebo | 0 mg | Q12H | Oral | 5 days (10 doses total) |
|--|---|-------------------------|---------------|----------------|-------------------------|-------------------------|------------------|-----------------------|--|--|--|--|--|------------------|---------|--------|------|------|-------------------------|------------------|---------|--------|------|------|-------------------------|------------------|---------|--------|------|------|-------------------------|---------|---------|------|------|------|-------------------------|------------------------|--|--|--|--|--|---------|---------|--------|------|------|-------------------------|---------|---------|------|------|------|-------------------------|
| | 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~1150) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | MK-4482 | MK-4482 | TBD mg | Q12H | Oral | 5 days (10 doses total) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Placebo | Placebo | 0 mg | Q12H | Oral | 5 days (10 doses total) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N=number of participants to be enrolled in each part of the study; Q12H= once every 12 hours; TBD=to be determined based on dose selection in Part 1 of the study. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total Number of Intervention Groups/ Arms | Part 1: 4 groups Part 2: 2 groups | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Duration of Participation | Each participant will be in the study for up to approximately 7 months from the time the participant provides documented informed consent through the final contact. Participants will receive 10 doses of assigned study intervention (administered Q12H) and will be followed for 28 days after the first dose. 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. | |

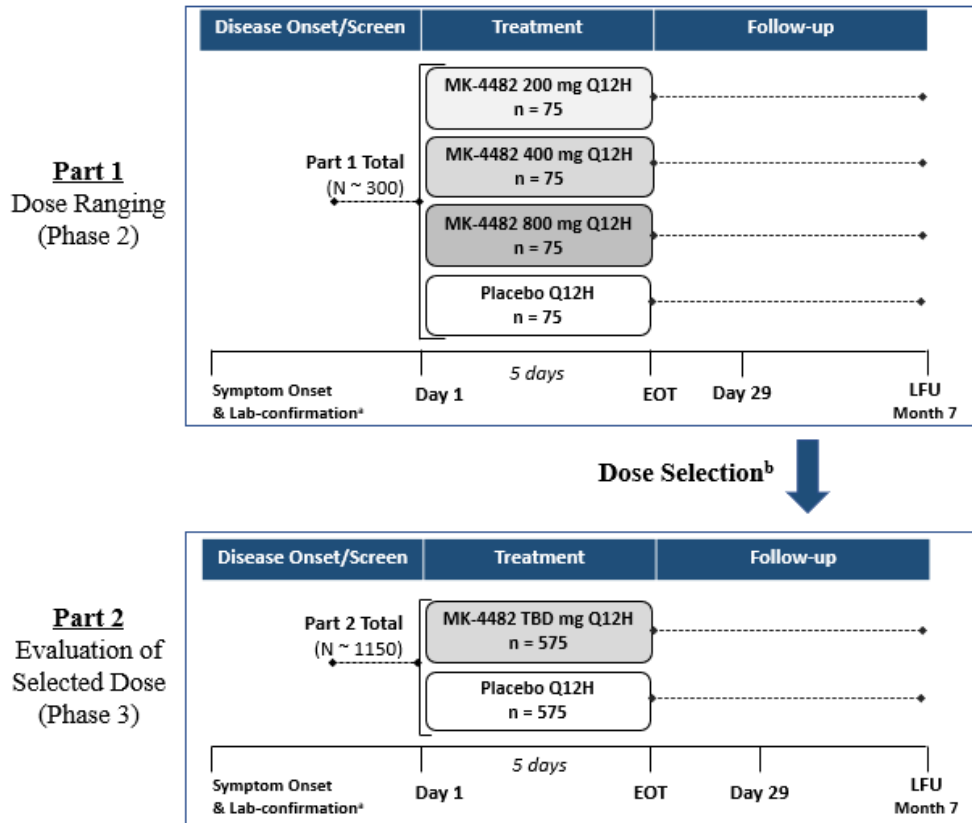
Study Accepts Healthy Volunteers: No

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; TBD=to be determined based on dose selection in Part 1 of the study.

^a Eligible participants will have PCR-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤ 7 days prior to 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 (+20 days) | |
| Type of Visit | C | C | V | C | V | C | C | C | C | V | C = Clinic or At home visit V= Virtual visit |
| Administrative Procedures | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | |
| Informed Consent for PBMC Collection (Optional) | X | | | | | | | | | | Only a subset of participants at selected sites |
| Register Study Visit in IRT | X | X | | | | | | | | | |
| Inclusion/Exclusion Criteria ^d | X | | | | | | | | | | Including review of SARS-CoV-2 (+) local test results. Local chemistry/hematology results within 72 h prior to randomization may be used for eligibility. |
| Participant Identification Card | X | X | | | | | | | | | Randomization number must be added to card at randomization |
| Medical History | X | | | | | | | | | | Including day of onset of COVID-19 signs/symptoms |
| Prior/Concomitant Medication Review | X | X | X | X | X | X | X | X | X | | Including COVID-19 standard of care therapies and supportive care |
| Intervention Randomization | | X | | | | | | | | | |
| Collect/Update Secondary Contacts for Participant | X | | | X | | X | | X | X | | |
| MK-4482 or Placebo Administration | | X | X | X | X | X | | | | | 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 |

| 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 (+20 days) | |
| 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). |
| Study Staff Review and Collection of Participant's Study Diaries | | | | X | | X | X | X | X | | Study Medication Diary will be collected at EOT. Completed pages of MK-4482 Symptom Diary will be collected at all clinic or at home visits. |
| Functional Status Assessment | | X | | X | | X | X | X | X | | Participant's ability to independently perform daily activities will be assessed. |
| Efficacy Procedures | | | | | | | | | | | |
| NP and OP Swabs | | X | | X | | X | X | X | X | | Based on Part 1 data, NP and OP swab collection may be adapted to remove 1 method or timepoints throughout the life of the study; this will be communicated via Protocol Clarification Letters. |
| Serum and Plasma for Exploratory Research | | X | | | | X | X | | X | | Research samples will be stored for testing as described in Section 4.2.5 and Section 8.8. |
| Respiratory/ Oxygenation Status | X | X | | X | | X | X | X | X | X ^e | SpO ₂ and investigator assessment of shortness of breath, and, if applicable, FiO ₂ , PaO ₂ and any details on supplemental oxygen use. |
| Hospitalization Status | | | | X | | X | X | X | X | X | |



| Study Period | Screening | Intervention | | | | | Follow-up | | | | Notes |
|--|---|--------------------|-------|--------------------|-------|-----|-----------------|------------------|------------------|------------------------|--|
| Visit Number/Title | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| Scheduled Day (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 (+20 days) | |
| 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 Central Laboratory Evaluation | | X | | X | | X | X | X | X | | Including hematology and chemistry |
| Pregnancy Test (WOCBP only) ^d | X | | | | | | | | X | | |
| AE/SAE review ^f | X | X | X | X | X | X | X | X | X | X | |
| Pharmacokinetics | | | | | | | | | | | |
| PK Plasma Sampling | | | | | | X | | | | | Part 1: predose; 1.5 h postdose Part 2: predose; 1.5 h postdose |
| PK PBMC Sampling ^g | | | | | | X | | | | | Part 1 (PBMC Cohort Only): predose, 1.5 h postdose |

AE=adverse event; COVID-19=coronavirus disease 2019; EOT=End of Therapy (day of last study intervention dose); hCG=human chorionic gonadotropin; 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; SpO₂ = oxygen saturation; WOCBP=women of child-bearing potential.

^a Screening and Day1 (randomization) can be done in same session. Laboratory collections and study assessments should not be duplicated if screening and Day 1 (randomization) are completed on the same day.

^b Day 1 assessments must be completed prior to first dose of study intervention.

^c Day 3 assessments are preferred. If circumstances do not support performance of procedures by study staff on Day 3, a 24-hour window is allowed.

^d The following local laboratory results must be available from within 72 h prior to randomization to support determination of eligibility: serum creatinine, platelets, absolute neutrophil count (neutrophils [segments and bands]). In WOCBP, a negative local pregnancy test is required within 24 hours of the first dose of study drug per inclusion criteria. All other inclusion/exclusion criteria determination (eg, HIV status, hepatitis, pancreatitis, etc.) can be based on participant-reported medical history, available medical records, and the most recently available laboratory results for the participant (eg, HIV RNA viral load or CD4 count).

^e Respiratory/Oxygenation Status collection at the LFU visit will be limited. As LFU will be a virtual visit, SpO₂ will not be measured. Use of supplemental oxygen will be collected.

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

^g A subset of ~50 participants will take part in the PBMC Cohort at selected sites.

2 INTRODUCTION

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

2.1 Study Rationale

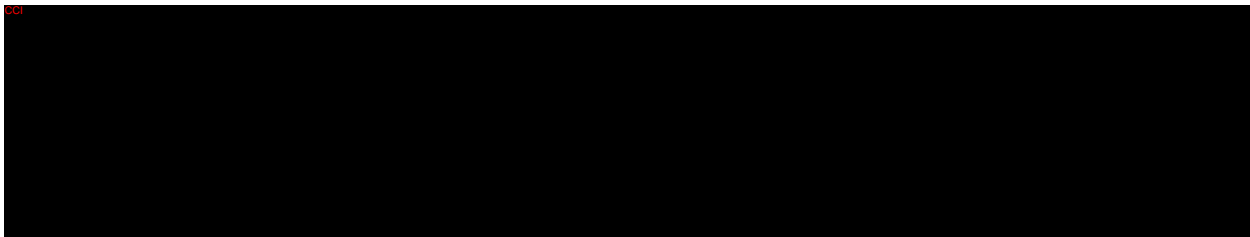
COVID-19, a disease resulting from SARS-CoV-2 infection, was declared a global pandemic by the WHO on 11-MAR-2020. Within 4 months of that declaration, there were over 11 million cases of COVID-19 reported globally and over 500 thousand associated deaths [World health Organization 2020]. With increasing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

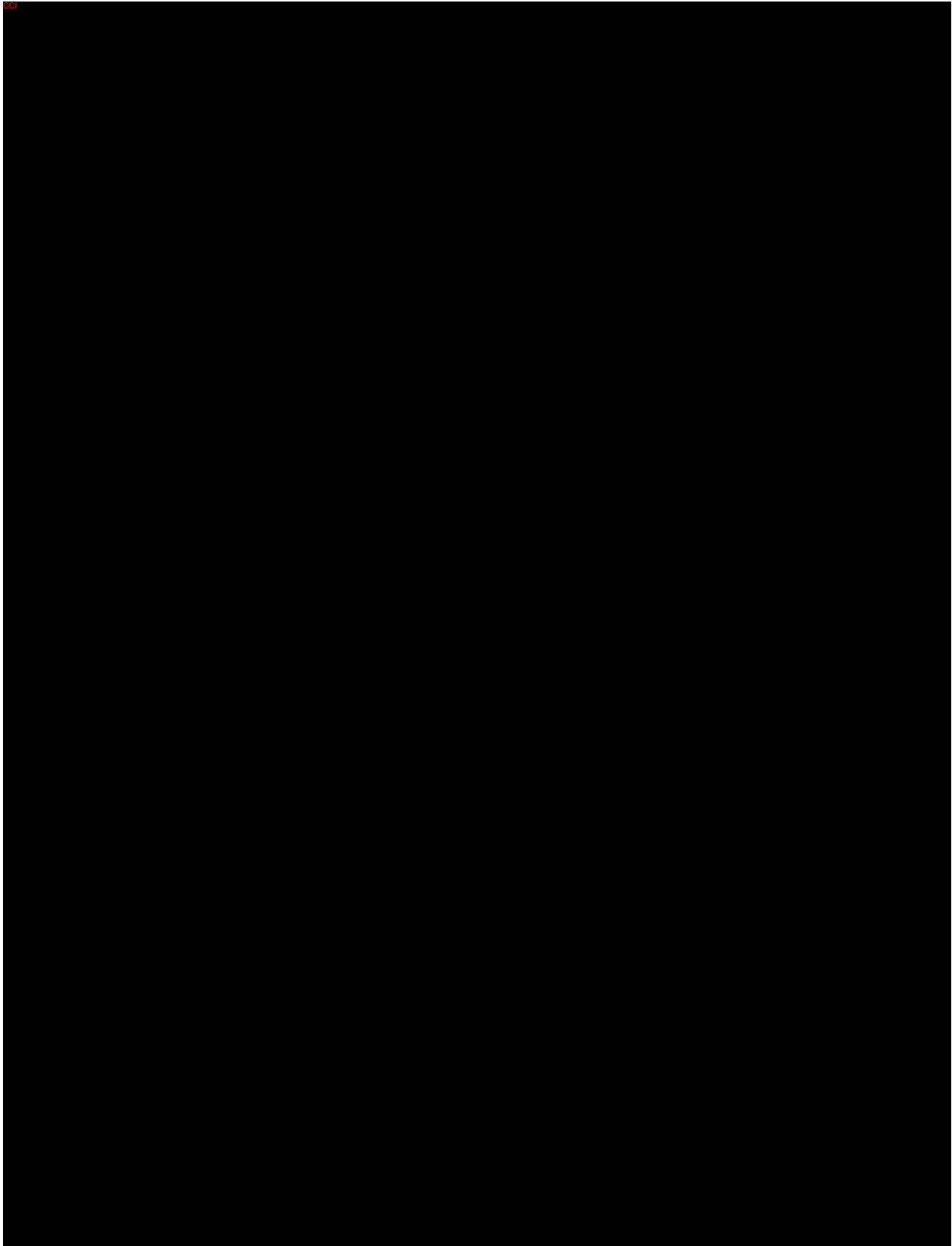
The true burden of COVID-19 is yet to be fully understood. Although most (>80%) infected individuals exhibit a mild illness (eg, fever, dry cough, fatigue), approximately 14% experience severe disease (eg, dyspnea, hypoxemia), and 5% have critical illness which can include respiratory failure, septic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

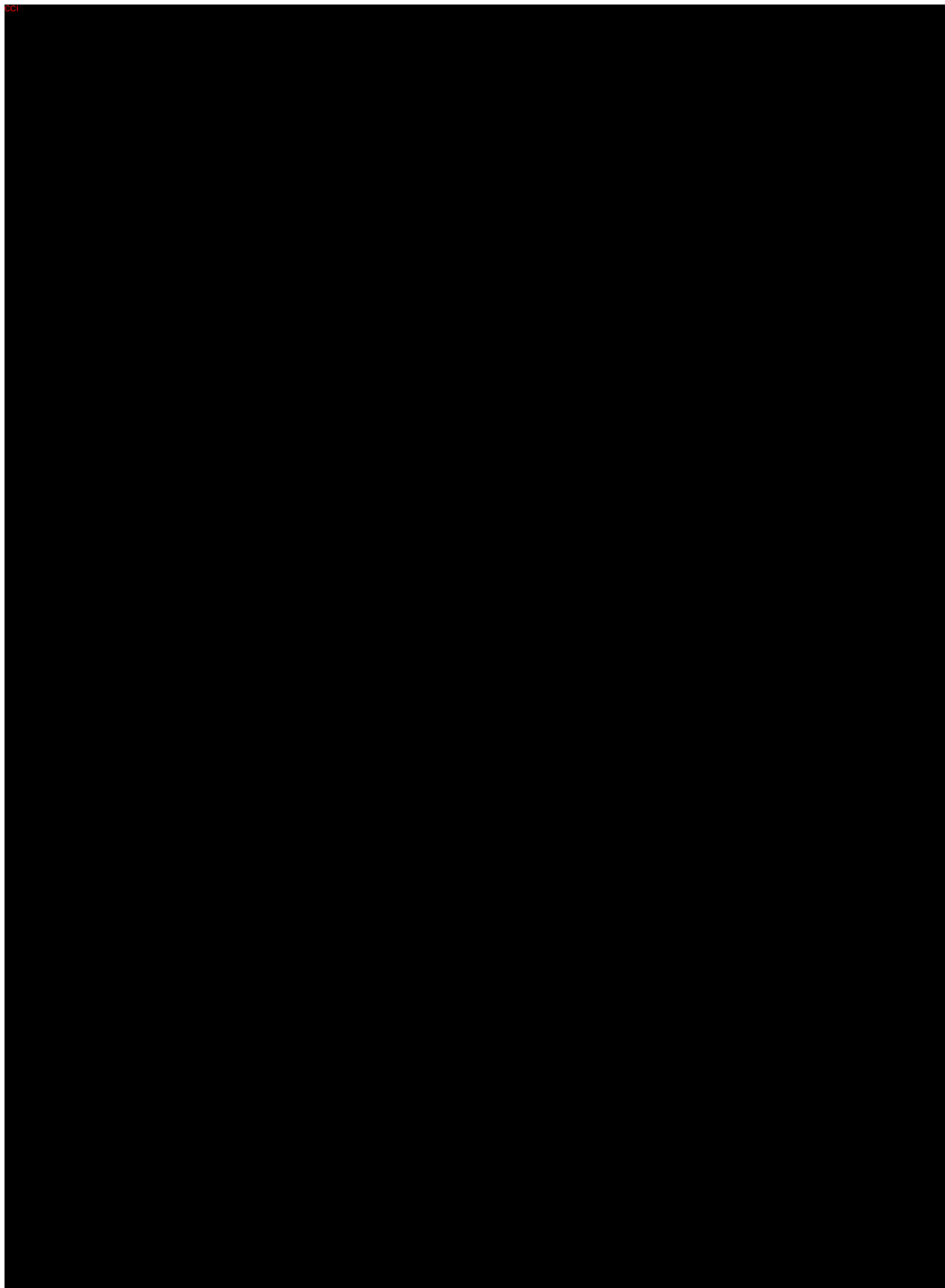
Standard of care treatment of COVID-19 is rapidly evolving and local treatment guidelines continue to be updated with emerging data [COVID-19 Treatment Guidelines Panel 2020] [Bhimraj, A., et al 2020] [World health Organization 2020]. Remdesivir is an antiviral agent administered intravenously for the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

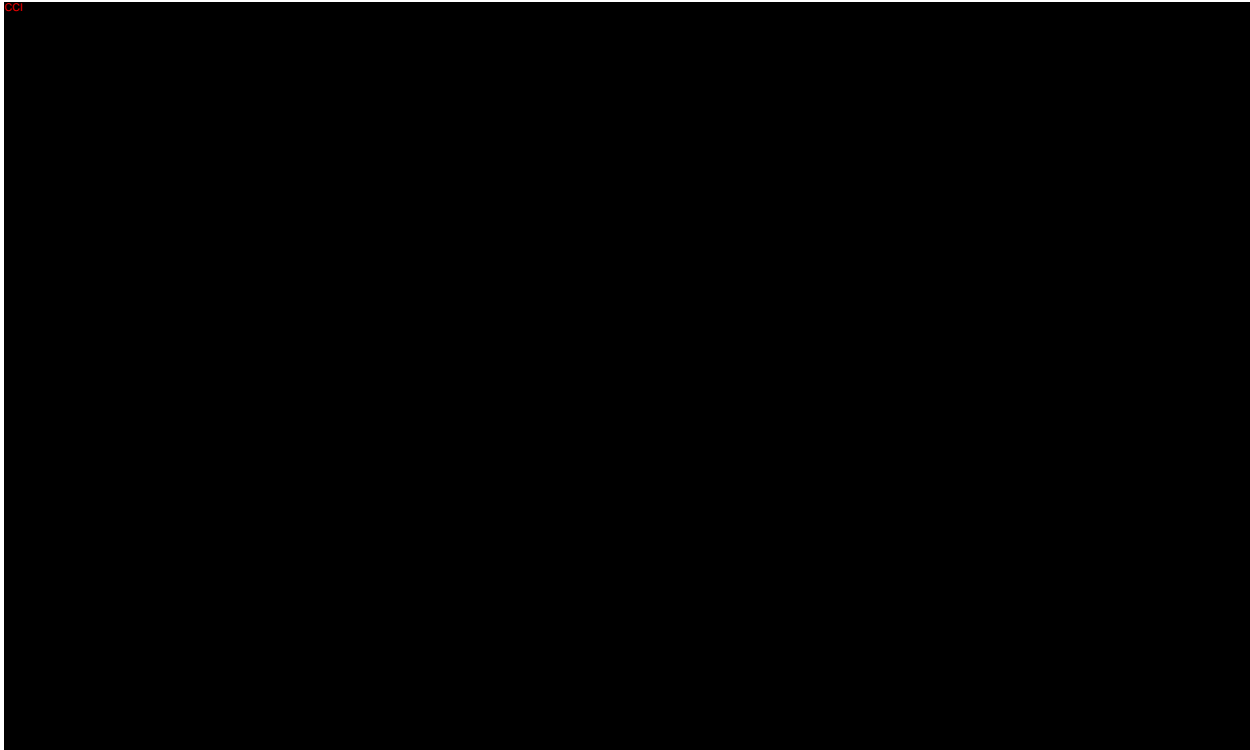
MK-4482 is a novel drug candidate with demonstrated activity against SARS-CoV-2 in vitro, efficacy against coronaviruses in animal models, and a high barrier to viral resistance. MK-4482 has been generally safe and well-tolerated to date in ongoing clinical studies.

2.2 Background









3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

| Objectives | Endpoints |
|--|--|
| Primary | |
| <ul style="list-style-type: none">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. <p>Hypothesis: MK-4482 is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29</p> | <ul style="list-style-type: none">Hospitalization or death |
| <ul style="list-style-type: none">To evaluate the safety and tolerability of MK-4482 compared to placebo. | <ul style="list-style-type: none">Adverse eventsAdverse events leading to discontinuation of study intervention |

| Objectives | Endpoints |
|--|--|
| Secondary | |
| <ul style="list-style-type: none"> To evaluate the efficacy of MK-4482 compared to placebo as assessed by time to improvement/resolution, and time to progression of targeted self-reported signs/symptoms of COVID-19 from randomization through Day 29. | <ul style="list-style-type: none"> COVID-19 signs/symptoms |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> WHO 11-point scale score |
| Tertiary/Exploratory | |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> Plasma (Part 1 and Part 2) and PBMC (Part 1) Pharmacokinetic concentration (eg, Ctrough) |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> SARS-CoV-2 RNA |
| <ul style="list-style-type: none"> To evaluate the effect of MK-4482 on viral RNA mutation rate as assessed by comparison of gene sequencing in virus isolated at baseline and post-baseline in samples with evaluable SARS-CoV-2 RNA (Part 1). | <ul style="list-style-type: none"> Viral RNA sequences |

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-site study to evaluate the efficacy, safety and PK of MK-4482 administered to non-hospitalized participants ≥ 18 years of age with PCR-confirmed COVID-19 and symptom onset within 7 days prior to randomization. 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). Enrollment of participants with moderate COVID-19 will be limited to 50% of total planned sample size in both Parts 1 and 2.

Participants will receive 10 doses of assigned study intervention by oral administration Q12H (± 2 hours) and be followed for 28 days after the first dose (through Day 29).

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, ~1150 participants will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either the selected dose of MK-4482 or placebo (Figure 1). An interim efficacy analysis is planned in Part 2 (Section 9.7).

Throughout the Study (Parts 1 and 2)

Participants may receive Sponsor-designated standard of care treatment of COVID-19, as appropriate, in addition to study intervention (Section 6.5). All participants will have plasma sample collection for PK assessments. The protocol will aim to enroll a subset of ~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). In addition, pregnancy status for female participants of childbearing potential and female partners of male participants will be collected at this visit.

The results of an 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 Day 1) 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 disease.

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 improvement/resolution, and time to progression of targeted self-reported signs/symptoms attributable to COVID-19 (Section 8.2.5) 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 2.2-fold and 0.5-fold the NHC exposure at the 200 mg Q12H and 800 mg Q12H human dose of MK-4482 respectively. These changes were fully reversible (Section 2.2). There have been no clinically significant abnormalities observed in hematological laboratory tests in the Phase 1 study (MK-4482-004). However, based on pre-clinical findings, participants in this study will be monitored for any signs of bone marrow toxicity, including monitoring of CBC and platelets after initiating study intervention.

In preclinical studies, elevated liver enzymes were noted in rats at 72-fold the NHC exposure at 800 mg Q12H and not noted in dogs at 22-fold the NHC exposure at 800 mg Q12H. No clinically significant abnormalities in liver parameters were noted in the Phase 1 study at any dose. However, elevated LFTs with a DILI pattern will be considered an ECI and closely monitored.

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

4.2.1.3 Pharmacokinetic Endpoints

Blood samples for PK assessment and concentrations of the MK-4482 nucleoside and triphosphate will be collected from all participants as described in the SoA (Section 1.3) and Section 8.6. As appropriate, PK-efficacy and PK-AE relationships for MK-4482 will also be evaluated. 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 to assess the impact of MK-4482 on various aspects of SARS-CoV-2 viral dynamics.

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

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 with mild COVID-19 at randomization, and at least 75% of participants enrolled in this study, 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 ≤ 7 days:** Eligible participants must have COVID-19 signs/symptoms onset no more than 7 days prior to randomization. SARS-CoV-2 viral loads are highest early in the course of disease, present 1-2 days prior to symptom onset, and persist for 7-12 days in moderate cases and up to 2 weeks in severe cases [Cevik, M., et al 2020]. Based on the viral kinetics of SARS-CoV-2 and the mechanism of action of MK-4482 (inhibition of viral replication), study participants must have signs/symptoms attributable to COVID-19 for ≤ 7 days prior to randomization with administration of the first dose occurring within 24 hours of randomization. Furthermore, as the host inflammatory response predominates during later stages of disease as COVID-19 progresses, treatment with antiviral therapy is likely to have a greater benefit with early treatment rather than delayed treatment >7 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 and OP swabs, and all residual material from blood collections are intended for testing to address emergent questions not described elsewhere in the protocol and may be conducted on specimens from all participants. The objective of collecting/retaining specimens is to perform testing that informs the scientific understanding of SARS-CoV-2 and/or COVID-19, co-infections, or MK-4482.

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

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

Evaluating the presence of antibodies to SARS-CoV-2 and their ability to neutralize the virus is critical to understanding the body's immune response to infection with SARS-CoV-2. COVID-19 disease severity may be correlated with the timing and quantity of antibody production based on participant characteristics such as gender. Antibody-dependent enhancement of disease has also been identified as a potential rationale for increased disease severity in some individuals [Ovsyannikova, I. G., et al 2020]. Antibody-related testing of participant samples may be used to evaluate if participants receiving MK-4482 or placebo have varying production of SARS-CoV-2 antibodies.

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

may be used to evaluate the impact of MK-4482 on the quantity and/or presence of replication-competent virus.

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 coinfecting with other pathogens. NHC has demonstrated broad antiviral activity against other RNA viruses including respiratory pathogens (eg, influenza, RSV, etc.) that have been observed in co-infection with SARS-CoV-2 [Lai, C. C., et al 2020]. Based on the potential for 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 coinfecting with other respiratory viruses may be used to explore the impact of MK-4482 on coinfections.

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 anti-viral treatments such as oseltamivir for influenza and is supported by non-clinical and clinical safety data for MK-4482.

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

4.3.2 Dose Range for Part 1 (Phase 2)

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

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

4.3.3 Dose Selection for Part 2 (Phase 3)

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

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 PCR-confirmed SARS-CoV-2 infection with sample collection ≤ 7 days prior to randomization.

Note: PCR is the preferred method; however, with evolving approaches to laboratory confirmation of SARS-CoV-2 infection, other diagnostic methods are allowed if authorized for use in the country.

2. Has initial onset of signs/symptoms attributable to COVID-19 for ≤ 7 days prior to 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
- 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 (Appendix 9); participants with mild COVID-19 must have at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19 (Appendix 10).
4. Has oxygenation saturation of $>93\%$ (on room air OR on supplemental oxygen prior to randomization which has not increased since onset of COVID-19 signs/symptoms) obtained at rest by study staff at randomization.
5. Is willing and able to take oral medication.

Demographics

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

Male Participants

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

- Refrain from donating sperm

PLUS either:

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

OR

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

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

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

Female Participants

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (a low user dependency method OR a user dependent method in combination with barrier method), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 7 months 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 for the study.

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 m² (by the MDRD equation [Appendix 11]).
3. Has any of the following conditions:
 - HIV with a recent viral load >50 copies/mL or CD4 <200 cell/mm³
 - Chemotherapy required within 6 weeks before randomization
 - A neutrophilic granulocyte absolute count <500 /mm³
 - Autologous or allogeneic hematopoietic stem cell transplant recipient
4. Has an active diagnosis of hepatitis due to any cause, including active HBV infection (defined as HBsAg-positive) or HCV infection (defined as detectable HCV RNA).
5. Has a platelet count $<100,000$ /μL or received a platelet transfusion in the 5 days prior to randomization.
6. Has a history of acute pancreatitis within 3 months prior to randomization or a history of chronic pancreatitis.

7. Has a baseline heart rate of <50 beats per minute at rest.
8. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.
9. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments including but not limited to:
 - Participants who are not expected to survive longer than 48 hours after randomization, or
 - Participants with a recent history of mechanical ventilation not associated with COVID-19, or
 - Participants with conditions that could limit gastrointestinal absorption of capsule contents.

Prior/Concomitant Therapy

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

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

Not applicable.

Other Exclusions

12. 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) ^a | Route of Administration | Regimen/ Treatment Period | Use | IMP/ NIMP | Sourcing |
|----------|--------------------|--------------------------|-------------------|------------------|-----------------------|--|-------------------------|------------------------------|--------------|-----------|----------|
| MK-4482 | Experimental | MK-4482 | Drug | Capsule | 200 mg | Part 1: 200 mg, 400 mg, 800 mg; Part 2 Dose to be selected | Oral | Q12H 5 days (10 doses total) | Experimental | IMP | Central |
| Placebo | Placebo Comparator | Placebo Matching MK-4482 | Drug | Capsule | 0 mg | Part 1: N/A Part 2: N/A | Oral | Q12H 5 days (10 doses total) | Experimental | IMP | Central |

N/A= not applicable; Q12H= every 12 hours.

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

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Time from symptom onset to 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 early treatment (≤ 5 days) rather than late 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.

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. Internal blinding will be maintained for Part 2 participants until all Part 2 participants have completed Day 29 (ie, achieved a final status for Day 29 endpoints) except as documented in Section 9.7 – Interim Analyses.

6.4 Study Intervention Compliance

When participants 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 | <ul style="list-style-type: none"> • SARS-CoV-2 vaccines are prohibited any time prior to randomization and through Day 29. |
| COVID-19 Therapeutics | <ul style="list-style-type: none"> • Sponsor-designated standard of care for treatment for COVID-19 is permitted (eg, remdesivir, dexamethasone, etc.) but may require additional safety monitoring as determined by the treating clinician. <ul style="list-style-type: none"> ○ If guidelines for local standard of care conflict with Sponsor-designated standard of care, site should consult with Sponsor. ○ Supportive therapies (including but not limited to anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms are allowed. ○ Unless designated by the Sponsor as acceptable standard of care for COVID-19, concomitant use of other medications intended as specific treatment for COVID-19 are prohibited from randomization through Day 29. If a participant is hospitalized during the study, other medications intended as treatment for COVID-19 are permitted. |
| Investigational Agents | <p>All non-study investigational agents including devices are prohibited within 30 days prior to randomization and through Day 29.</p> |

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 8.11.2, unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a platelet count of $<50,000/\mu\text{L}$.
- The participant is no longer able to take oral medication or becomes intubated prior to completion of study intervention.

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

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

7.2 Participant Withdrawal From the Study

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

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.11.3. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 145 mL for participants in the PBMC Cohort or approximately 113 mL for all other participants (Appendix 2, [Table 11](#)).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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 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).

The following local laboratory results must be available from within 72 hours prior to randomization: serum creatinine, platelets, absolute neutrophil count (neutrophils [segments and bands]). In WOCBP, a negative local urine or serum pregnancy test is required within 24 hours of the first dose of study drug per inclusion criteria.

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

most recently available laboratory results for the participant (eg, HIV RNA viral load or CD4 count).

8.1.3 Participant Identification Card

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

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Participants will be asked to provide any background or concomitant conditions, drug allergies and/or surgeries within the last 12 months. In addition, history of smoking (tobacco or marijuana), including use of vaping devices, will be collected. Medical history for the following conditions will be collected separately on the Medical History Pre-Specified Conditions eCRF: chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised state from solid organ transplant, obesity, active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality), congestive cardiac failure, coronary artery disease, cardiomyopathies, sickle cell disease, and diabetes mellitus. Any oxygen therapy needs in the 7 days prior to symptom onset and through randomization will be reported in the oxygen therapy eCRF with flow rate reported in L/min. Reporting will include supplemental oxygen requirements during pre-morbid/pre-COVID-19, between the onset of COVID-19 signs/symptoms and study randomization, and any changes to oxygen therapy needs during the study treatment and follow-up periods.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the participant during the study. All concomitant therapeutics/vaccines for COVID-19 including

all supportive therapies (eg, anti-pyretic and anti-inflammatory agents) to manage COVID-19 signs/symptoms, must be reported.

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention will be provided as per [Table 1](#) and dispensed through the IRT system at the Day 1 visit. Study intervention and the Study Medication Diary will be dispensed to the participant according to the pharmacy manual for at home administration.

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.

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). If the participant takes their EOT dose without observation by site staff/delegate, and prior to the predose PK blood draw, then the timing of the dose will be reported from the Study Medication Diary to study staff/delegate by the participant or legally acceptable representative and recorded in the appropriate source documentation.

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

Administration of study intervention in participants who require continuous hemodialysis or peritoneal dialysis is allowed. For participants who require intermittent hemodialysis or peritoneal dialysis, study intervention should continue to be administered Q12H with doses administered 4-6 hours prior to dialysis.

8.1.9 Discontinuation and Withdrawal

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

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

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

8.1.10 Participant Blinding/Unblinding

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

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

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

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

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

8.1.11 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.

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. 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, the individual administering the study intervention (eg, study or nonstudy staff) will collect information corresponding to study intervention administration (source notes should be maintained as part of participant records at site).

8.2 Efficacy Assessments

8.2.1 Nasopharyngeal and Oropharyngeal Swabs

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

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

8.2.2 Respiratory/Oxygenation Status

SpO₂ 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 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. FiO₂, PaO₂, 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, SpO₂ 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.

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.

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 in-patient participant visits according to the SoA (Section 1.3) should be considered. Given the frequency of study medication administration, it is recognized that use of non-study 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 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 using a paper MK-4482 Symptom Diary on Days 1 to 29. Targeted symptoms assessed in the diary include shortness of breath or difficulty breathing, muscle or body aches, fatigue, feeling hot or feverish, chills, headache, nausea, vomiting and diarrhea. On Day 1, 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 complete the diary on their own, collection of symptom data via an in-person or virtual participant interview using a Sponsor-provided interviewer script should be implemented. If not completed during hospitalization, completion of the diary should be restarted 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. 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. 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 10](#).

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 measured 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.

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

8.3.3 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 treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

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

Additionally, all pregnancies from the day of randomization through 7 months (for female participants) or 90 days (for female partners of male participants) after the last dose of study intervention must be reported by the investigator.

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

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

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

| Type of Event | <u>Reporting Time Period:</u> Consent to Randomization/ Allocation | <u>Reporting Time Period:</u> Randomization/ Allocation through Protocol-specified Follow-up Period | <u>Reporting Time Period:</u> 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 |

| Type of Event | <u>Reporting Time Period:</u> Consent to Randomization/ Allocation | <u>Reporting Time Period:</u> Randomization/ Allocation through Protocol-specified Follow-up Period | <u>Reporting Time Period:</u> After the Protocol-specified Follow-up Period | Time Frame to Report Event and Follow-up Information to Sponsor: |
|---|--|---|---|--|
| ECI (do not require regulatory reporting) | Report if: - due to intervention - causes exclusion | Report - non-DILI ECIs and those not requiring regulatory reporting | Not required | Within 5 calendar days of learning of event |
| Cancer | Report if: - due to intervention - causes exclusion | Report all | Not required | Within 5 calendar days of learning of event (unless serious) |
| Overdose | Report if: - receiving placebo run-in or other run-in medication | Report all | Not required | Within 5 calendar days of learning of event |

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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



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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy.

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

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

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

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

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

2. Any confirmed (ie, verified by repeat testing) platelet value $<50,000/\mu\text{L}$, as determined by protocol-specified and/or unscheduled laboratory testing.
3. Any confirmed (ie, verified by repeat testing) amylase or lipase value $>3\text{X}$ the ULN 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 | <ul style="list-style-type: none">• 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, co-infections, or MK-4482 as described in Section 4.2.5. These samples may be tested during the course of the study or after study closure as the field of research evolves.

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

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

Sites are to collect hospitalization status and discharge data 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.

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.

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

8.11.4 Late Follow-up (7 month) Visit

A virtual visit (eg, by telephone, webcast, videoconference, etc.) will be conducted at 7 months (+20 days) after the last dose of study intervention for all participants. Information regarding survival status, current supplemental oxygen use, and any hospitalizations that occurred since last contact will be collected according to the SoA (Section 1.3).

In addition, pregnancy status (eg, estimated date of conception and delivery date) for female participants of childbearing potential and female partners of male participants will be collected at this visit. Collection of pregnancy data for female partners of male participants is not required if the male participant is confirmed to be azoospermic (vasectomized or secondary to medical cause) as documented in medical history. Current and prior pregnancy data for any pregnancies with a conception date occurring within 90 days after the last dose of study intervention for female partners of male participants or within 7 months of the last dose for female participants will be reported in relevant eCRFs. All reported pregnancies must be followed to the completion/termination of the pregnancy as described in Section 8.4.5.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to the primary hypothesis, or the statistical methods related to this hypothesis, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data, medical resource utilization outcomes, and 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 | <p>Part 1: Approximately 300 participants will be randomized in a 1:1:1:1 ratio (stratified per Section 6.3.2) to receive 1 of the following 4 study interventions, Q12H for 5 days.</p> <ul style="list-style-type: none"> • MK-4482 200 mg (n~75) • MK-4482 400 mg (n~75) • MK-4482 800 mg (n~75) • Placebo (n~75) <p>Part 2: A total of approximately 1150 participants will be randomized in a 1:1 ratio (stratified per Section 6.3.2) to receive either the selected dose of MK-4482 or placebo Q12H for 5 days.</p> |
| Analysis Populations | Efficacy: MITT Safety: APaT |
| Primary Endpoints | <p>Efficacy: Proportion of participants with hospitalization or death by Day 29.</p> <p>Safety: Number of participants with AEs, and discontinuing study intervention due to AEs</p> |
| Key Secondary Endpoints | <ul style="list-style-type: none"> • Time to improvement/resolution, and time to progression of targeted self-reported signs/symptoms 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. and Nurminen, M. 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. and Nurminen, M. 1985]. |
| Interim Analyses | <p>IA1 – Part 1 Dose Evaluation This IA will be used to evaluate the dose/exposure-response for dose evaluation.</p> <p>IA2 – Part 1^b Dose Confirmation This IA will be used to evaluate the dose/exposure-response to either: 1) Confirm the selected Phase 3 dose from IA1 (if the dose/exposure response relationship can be characterized in IA1). Or, 2) Select the dose for Phase 3 (if the dose/exposure response relationship cannot be characterized in IA1).</p> <p>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.</p> <p>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.</p> <p>Additional details about interim analyses are in Section 9.7.</p> |
| 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 | <p>The total sample size for the primary efficacy assessment will be approximately 1150 (~575 for the selected dose of MK-4482 and ~575 for the placebo group). The study has overall power of 92% 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.</p> <p>Additional details and assumptions for sample size and power calculation are in Section 9.9.</p> |



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). 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 improvement or resolution of the targeted self-reported sign/symptoms present at randomization, defined as the number of days from randomization to the first day on or before study Day 29 by which the targeted self-reported signs/symptoms improve or resolve (ie, when any symptoms reported at randomization as mild are subsequently reported as absent, or when moderate are subsequently reported as mild or absent, or when severe are subsequently reported as moderate, mild or absent).
- Time to progression of the targeted self-reported signs/symptoms present at randomization, defined as the number of days from randomization to the first day on or before study Day 29 by which the targeted self-reported signs/symptoms worsen (ie, when any symptoms not reported at randomization are newly reported or when any symptoms reported as mild at randomization are subsequently reported as moderate or severe, or when moderate are subsequently reported as severe).
- Odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15 and Day 29

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:

- Change from baseline in SARS-CoV-2 RNA titer in nasopharyngeal and oropharyngeal swabs separately at various timepoints
- Percentage of participants with undetectable SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swabs separately at various timepoints
- Viral RNA mutation rate as assessed by comparison of baseline and post-baseline virus sequencing (Part 1)

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 in this study. The MITT population consists of all randomized participants who received at least 1 dose of study intervention.

A supportive analysis using the Per-Protocol population will be performed for the primary efficacy endpoint(s). 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.

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. Methods related to 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 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. and Nurminen, M. 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 and geographic region. Geographic region will not be used for any interim analysis due to concerns about sparse data associated with smaller sample size, but it may be considered as an additional stratification factor of the stratified Miettinen and Nurminen method for final 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. Missing data for this endpoint will be treated as failure (M=F approach) in the MITT population.

A sensitivity analysis for the primary endpoint will be conducted that includes only COVID-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.

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 improvement or resolution and time to progression of targeted signs/symptoms of COVID-19 will be summarized using data collected from a symptom diary completed by participants (Section 8.2.5). The distribution of time to improvement or resolution and time to progression of signs/symptoms 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 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 improvement or resolution and with progression to a worse status from randomization of each of the targeted self-reported signs/symptoms present at randomization will also be summarized by treatment group at Day 3, EOT, Day 10, Day 15, and Day 29.

These summaries above will include comparison of individual signs/symptoms as well as overall signs/symptoms. Missing symptom diary data will be imputed using LOCF method. Additional details will be specified in the sSAP.

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 | M=F ^d |
| 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 improvement or resolution of targeted signs/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 targeted signs/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 |
| 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; P= primary approach; PP= per-protocol; S= secondary approach; 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 and possibly geographic region. d M=F is Missing equals to Failure e The stratified log-rank test includes stratification factors specified in Section 6.3.2 and possibly geographic region f Stratified Cox Proportional Hazards regression includes terms for treatment, stratification factors specified in Section 6.3.2 and possibly geographic region g Proportional odds model includes terms for treatment and stratification factors specified in Section 6.3.2 and possibly geographic region. | | | | |



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 predefined limits of change (PDLC) 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 adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance 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. and Nurminen, M. 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% confidence intervals provided for differences in the proportion of participants with events (also via the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 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 at least 1 of the treatment groups) | | | X |
| | PDLCs [‡] (incidence < 4 participants in all 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 that will be used to inform the dose selection decision process and the siDMC review. Membership on this cross-functional unblinded team will be documented in an unblinding memo 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 | P002 Primary Data for Analysis | Committee Action |
|--|---|--|--|
| IA1 – Part 1 Dose Evaluation | Targeted to occur during Phase 2 after at least 200 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 approval of proposed MK-4482 dose if the dose/exposure response relationship can be characterized from IA1 |
| IA2 – Part 1 ^b Dose Confirmation | 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 If the dose/exposure response relationship can be characterized from IA1: Sponsor siDMC confirmation of dose selected at IA1 If the dose/exposure response relationship cannot be characterized from IA1: Sponsor siDMC approval of proposed MK-4482 dose. The dose selection will occur at the IA2 from either the MK-4482-001 or the MK-4482-002 study, whichever occurs first, and after all Phase 2 participants in 1 of the 2 studies have completed the Day 29 visit. Thereafter, the IA2 data for the study that subsequently completes Phase 2 will be examined and summarized. |
| 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. |

| Interim Analysis | Timing | P002 Primary Data for Analysis | Committee Action |
|--|---|---------------------------------------|--|
| IA4 – Part 2 Futility/Early Efficacy | Targeted to occur during Phase 3 after ~575 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 |
| <p>eDMC=external Data Monitoring Committee; EOT=End of Treatment; IA=Interim Analysis; PK=pharmacokinetics; siDMC=standing internal Data Monitoring Committee.</p> <p>a = P001 is a companion MK-4482 dose-ranging study in hospitalized adults with COVID-19</p> <p>b = Although identified as IA2, this represents the final analysis of the full Part 1 cohort of participants through Day 29. A subsequent analysis of the Month 7 endpoints will also be performed.</p> | | | |

Interim Analyses

IA1 – Part 1: Dose Evaluation

IA1 is targeted to occur during Phase 2 after data is available from at least 200 participants completing EOT combined in MK-4482-001 and MK-4482-002. This IA will be used to evaluate the dose/exposure-response for dose evaluation. For both IA1 and IA2, 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 available at the time of the interim analyses will be evaluated. The totality of available PK/PD relationship data from the MK-4482 program will be considered in the 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 without a protocol amendment.

During this interim analysis, enrollment in the study will continue in the 4 intervention groups in Phase 2 until N~300.

Notes:

- If the dose/exposure response relationship can be characterized at the first interim analysis (IA1) to support Phase 3 dose selection, then dose selection will occur at IA1 and enrollment will begin in the Phase 3 portion of the study at the selected dose after enrollment in Phase 2 completes. IA2 will then be utilized to confirm the dose selected by repeating the analyses from IA1 using all available data from Phase 2 through Day 29.
- If the dose/exposure response relationship cannot be characterized sufficiently to select a dose from IA1, then Phase 3 dose selection will not occur at IA1. The dose selection will instead occur at the IA2 from either the MK-4482-001 or the MK-4482-002 study, whichever occurs first, and after all Phase 2 participants in 1 of the 2 studies have completed the Day 29 visit. Thereafter, the IA2 data for the study that subsequently completes Phase 2 will be examined and summarized.

IA2 – Part 1: Dose Confirmation

Although identified as IA2, this analysis is targeted to occur at the completion of Phase 2 after ~300 participants (~75 per group) in either MK-4482-001 or MK-4482-002 have completed the Day 29 visit. This IA will be used to evaluate the dose/exposure-response to either:

1) Confirm the selected Phase 3 dose from IA1 (if the dose/exposure response relationship can be characterized in IA1). Enrollment in Phase 3 at the dose selected in IA1 will be ongoing while this IA is conducted.

Or



2) Select the dose for Phase 3 (if the dose/exposure response relationship cannot be characterized in IA1). The dose selection will occur at the IA2 from either the MK-4482-001 or the MK-4482-002 study, whichever occurs first, and after all Phase 2 participants in 1 of the 2 studies have completed the Day 29 visit. Thereafter, the IA2 data for the study that subsequently completes Phase 2 will be examined and summarized.

In the unlikely event that dose confirmation by the siDMC at IA2 results in a different Phase 3 dose than previously approved at IA1, the Phase 3 sample size will be increased to account for all participants enrolled under a randomization plan that did not include the final selected dose (ie, participants from both active and placebo groups will be replaced).

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 to be based on enrollment timelines. 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 350 participants to a total of 1500 if the interim result is sufficiently promising (conditional power >54% but <81%, 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 (conditional power will range from 72% to 94% after the sample size adjustment) in the event that the observed treatment effect at the interim analysis is smaller than the original assumption but still clinically meaningful (treatment difference, MK-4482 minus placebo, in the percentage of participants who are hospitalized and/or die through Day 29 is between -0.035 and -0.051 percentage points).

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 -0.015. The boundary crossing probabilities for futility are 73% under H0 and 2.8% under H1 (absolute difference of -0.06). The p-value boundary for efficacy is 0.009, corresponding to an absolute difference of -0.056. The boundary crossing probabilities for efficacy are 0.9% under H0 and 57% under H1 (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.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power Calculations for Efficacy Analyses

The primary analysis of the Phase 3 study endpoint will include approximately 1150 participants from Part 2 of the study (~575 for the selected dose of MK-4482 and ~575 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 92% 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.

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 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 $p \leq 0.019$ at the final analysis), the observed treatment difference must be approximately -3.5 percentage points or lower, assuming a percentage of 12% for placebo. The ACTIV-2 protocol assumes an underlying percentage hospitalized/dying of 15% for placebo and a 33% relative reduction with an active therapy. 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 1150 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=1150 participants (575/group), alpha=0.025, 1-sided

| Placebo Rate (%) | MK-4482 Rate (%) | Absolute Difference (percentage points) | Power |
|------------------|------------------|---|------------|
| 24% | 16% | 8 | 90% |
| 22% | 14% | 8 | 92% |
| 20% | 13% | 7 | 86% |
| 18% | 11% | 7 | 90% |
| 16% | 9% | 7 | 93% |
| 14% | 8% | 6 | 87% |
| 12% | 6% | 6 | 92% |
| 10% | 5% | 5 | 86% |
| 8% | 3% | 5 | 94% |

9.9.2 Sample Size and Power Calculations for Safety Analyses

The probability of observing at least 1 of a particular type of AE in this study depends on the number of participants treated and the underlying percentage of participants with an AE in the study population. If the underlying incidence of an AE is 1%, there is a 99.7% chance of observing at least 1 AE among 575 participants in the treatment group. If no AE of that type is observed among the 575 participants in any treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with the AE is <0.64 (1 out of every 157 participants). Table 9 summarizes the percentage point differences between the 2 treatment groups that could be detected with 90% probability for a variety of hypothetical underlying incidences of an AE. These calculations assume 575 participants in each group and are based on a 2-sided 5% alpha level. The calculations are based on Farrington and Manning [Farrington, C. P. and Manning, G. 1990]. No multiplicity adjustments were made.

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

| Incidence of Adverse Event | | Risk Difference |
|----------------------------|-------------|-------------------|
| Placebo (%) | MK-4482 (%) | Percentage Points |
| 1.0 | 4.0 | 3.0 |
| 5.0 | 10.1 | 5.1 |
| 10.0 | 16.5 | 6.5 |
| 20.0 | 28.2 | 8.2 |
| 30.0 | 39.1 | 9.1 |
| 40.0 | 49.5 | 9.5 |

Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Calculations are based on Farrington and Manning [Farrington, C. P. and Manning, G. 1990]

9.10 Subgroup Analyses

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

- Age 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 to randomization (> 5 days, ≤ 5 days)
- At increased risk for severe illness from COVID-19 (yes, no) (Appendix 10)
- Geographic Region (North America, Europe, Asia Pacific, Latin America)

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.

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

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

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

9.12 Extent of Exposure

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



10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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



3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.



D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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



10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names



and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 Internal Data Monitoring Committee

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

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

10.1.4.3 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 10](#) will be performed by the central laboratory.
- Local laboratory test is required for initial COVID-19 RT-PCR and determination of participant eligibility.
- All other local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- The investigator (or medically qualified designee) must document their review of each laboratory safety report (eg, hematology, chemistry, pregnancy).
- Laboratory/analyte results that could unblind the participant's intervention group will not be reported to blinded site and Sponsor personnel. These laboratory results include but may not be limited to virology results with the exception of screening results and error reports.

Table 10 Protocol-required Laboratory Assessments

| Laboratory Assessments | Parameters | | |
|--|--|-----------------------------------|--|
| Hematology | Platelet Count | RBC Indices: MCV MCH RDW | WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Calculation of: Neutrophil/lymphocyte ratio Absolute Neutrophil Count |
| | RBC Count | | |
| | Hemoglobin | | |
| | Hematocrit | | |
| Chemistry | BUN | Chloride | AST/SGOT |
| | Albumin | Calcium | ALT/SGPT |
| | Creatinine | 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 marker) will be tested at all visits with chemistry collection as the test is performed on the same blood sample |
| | CK | | |
| Pregnancy Testing | <ul style="list-style-type: none"> Urine or Serum hCG pregnancy test (as needed for WOCBP) | | |
| Virology | <ul style="list-style-type: none"> SARS-CoV-2 RNA (real time PCR) OP and NP swabs (quantitative and qualitative) SARS-CoV-2 Gene Sequencing | | |
| Pharmacokinetics | <ul style="list-style-type: none"> Plasma for NHC PBMC for NHC- triphosphate | | |
| Exploratory Research Samples | Samples may be used for testing such as: <ul style="list-style-type: none"> SARS-CoV-2 Antibodies Infectious SARS-CoV-2 presence/quantitation Co-infection with other respiratory pathogens | | |
| ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatinine kinase; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; hs-CRP= High-sensitivity C-reactive protein; IL-6=Interleukin 6; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; NHC=N-hydroxycytidine; NP=nasopharyngeal; OP=oropharyngeal; PBMC= peripheral blood mononuclear cells; PCR= polymerase chain reaction; RBC=red blood cell; RDW=red cell distribution width; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential. | | | |



Table 11 Approximate Whole Blood Volumes (mL)

| Study Period: | 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) | |
| Chemistry | | 2.5 | | 2.5 | | 2.5 | 2.5 | 2.5 | 2.5 | N/A |
| Hematology | | 2 | | 2 | | 2 | 2 | 2 | 2 | |
| Serum Pregnancy Test (hCG; WOCBP only) | 2 | | | | | | | | 2 | |
| Plasma/Serum Research Samples | | 19 | | | | 19 | 19 | | 19 | |
| Sub Total for all Participants | 2 | 23.5 | 0 | 4.5 | 0 | 23.5 | 23.5 | 4.5 | 25.5 | |
| Pharmacokinetics | | | | | | | | | | |
| Pharmacokinetic Plasma Sampling Part 1 | | | | | | 6 | | | | |
| Pharmacokinetic Plasma Sampling Part 2 | | | | | | 6 | | | | |
| Pharmacokinetic PBMC Sampling Part 1 | | | | | | 32 | | | | |
| Total For Participants in Part 1 | 2 | 23.5 | 0 | 4.5 | 0 | 29.5 | 23.5 | 4.5 | 25.5 | |
| Total For Participants in Part 2 | 2 | 23.5 | 0 | 4.5 | 0 | 29.5 | 23.5 | 4.5 | 25.5 | 113 |
| Total For PBMC Cohort Participants in Part 1 | 2 | 23.5 | 0 | 4.5 | 0 | 61.5 | 23.5 | 4.5 | 25.5 | 145 |

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 <i>Failure rate of <1% per year when used consistently and correctly.</i> |
| <ul style="list-style-type: none">• Progestogen-only subdermal contraceptive implant^b• IUS^c• Non-hormonal IUD• Bilateral tubal occlusion |
| <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• 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) <ul style="list-style-type: none">• Combined (estrogen- and progestogen- containing) hormonal contraception^b<ul style="list-style-type: none">- Oral- Intravaginal- Transdermal- Injectable• Progestogen-only hormonal contraception^b<ul style="list-style-type: none">- Oral- Injectable |
| Barrier methods to be used with hormonal contraceptives above (male condoms are preferred method) <ul style="list-style-type: none">• 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) |
| <p>^a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>^b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.</p> <p>^c IUS is a progestin releasing IUD.</p> <p>^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).</p> <p>Note: The following are not acceptable methods of contraception alone or in combination:</p> <ul style="list-style-type: none">- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.- Male and female condom should not be used together (due to risk of failure with friction). |



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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for 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 Disease Severity

COVID-19 BASELINE 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].

| Symptoms | Signs |
|--|---|
| Mild disease: SARS-CoV-2 test positive AND | |
| <p>One or more of the following:</p> <ul style="list-style-type: none"> • Fever >38.0°C • Chills • Cough • Sore throat • Fatigue • Nasal congestion • Runny nose • Headache • Muscle or body aches • Nausea • Vomiting • Diarrhea • Loss of taste • Loss of smell <p>AND</p> <p>NO shortness of breath at rest</p> <p>AND</p> <p>NO shortness of breath at exertion</p> | <p>Must fulfill ALL of the following:</p> <ul style="list-style-type: none"> • Respiratory rate <20 breaths per minute <p>AND</p> <ul style="list-style-type: none"> • Heart rate <90 beats per minute <p>AND</p> <ul style="list-style-type: none"> • Saturation of oxygen (SpO₂) >93% EITHER: <ul style="list-style-type: none"> ○ on room air OR ○ on supplemental oxygen prior to randomization which HAS NOT increased since onset of COVID-19 signs/symptoms <p>AND</p> <ul style="list-style-type: none"> • Does NOT have respiratory failure, shock, or multi-organ dysfunction/failure |



| Symptoms | Signs |
|---|--|
| Moderate disease: SARS-CoV-2 test positive AND | |
| <p>One or more of the following:</p> <ul style="list-style-type: none"> • Fever >38.0°C • Chills • Cough • Sore throat • Fatigue • Nasal congestion • Runny nose • Headache • Muscle pain • Nausea • Vomiting • Diarrhea • Loss of taste • Loss of smell <p>OR</p> <p>Shortness of breath with exertion (with no shortness of breath at rest)</p> | <p>One or both of the following:</p> <ul style="list-style-type: none"> • Respiratory rate ≥ 20 to <30 breaths per minute • Heart rate ≥ 90 to 124 beats per minute <p>AND</p> <ul style="list-style-type: none"> • Saturation of oxygen (SpO₂) >93% EITHER: <ul style="list-style-type: none"> ○ on room air OR ○ on supplemental oxygen prior to randomization which HAS NOT increased since onset of COVID-19 signs/symptoms <p>AND</p> <ul style="list-style-type: none"> • Does NOT have respiratory failure, shock, or multi-organ dysfunction/failure |
| Severe disease: SARS-CoV-2 test positive AND | |
| <p>One or more of the following:</p> <ul style="list-style-type: none"> • Fever >38.0°C • Chills • Cough • Sore throat • Fatigue • Nasal congestion • Runny nose • Headache • Muscle pain • Nausea • Vomiting • Diarrhea • Loss of taste • Loss of smell | <p>One or more of the following:</p> <ul style="list-style-type: none"> • Respiratory rate ≥ 30 breaths per minute <p>OR</p> <ul style="list-style-type: none"> • Heart rate ≥ 125 beats per minute <p>OR</p> <ul style="list-style-type: none"> • Saturation of oxygen (SpO₂) $\leq 93\%$ EITHER: <ul style="list-style-type: none"> ○ on room air OR ○ on supplemental oxygen prior to randomization which HAS NOT increased since onset of COVID-19 signs/symptoms |



| Symptoms | Signs |
|--|--|
| <p>OR</p> <p>Shortness of breath with exertion</p> <p>OR</p> <p>Shortness of breath at rest</p> | <p>OR</p> <ul style="list-style-type: none"> • On supplemental oxygen prior to randomization which HAS increased since onset of COVID-19 signs/symptoms <p>OR</p> <ul style="list-style-type: none"> • SpO₂/FiO₂<200 <p>AND</p> <ul style="list-style-type: none"> • Does NOT have respiratory failure, shock, or multi-organ dysfunction/failure |
| <p>Critical disease: SARS-CoV-2 test positive AND</p> | |
| <p>One or more of the following: respiratory failure, shock, or multi-organ dysfunction/failure.</p> <p>Respiratory failure defined based on resource utilization requiring at least 1 of the following:</p> <ul style="list-style-type: none"> • 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) <p>Shock defined as systolic blood pressure <90 mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressors</p> <p>Multi-organ dysfunction/failure defined as participants that are acutely ill with evidence of either dysfunction or failure, at the discretion of the investigators, of at least 1 of the following organ systems: respiratory, cardiovascular, renal, hematologic, hepatic, and/or central nervous systems.</p> | |



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 2020] and the WHO [World Health Organization 2020]:

- Age >60 years
- Active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality [eg, basal cell carcinomas, and participants who have received immunosuppressive therapy within the 6 weeks prior to randomization]; See Section 5.2)
- Chronic kidney disease (excluding participants on dialysis or has reduced eGFR <30 mL/min/1.73m²; See Section 5.2)
- Chronic obstructive pulmonary disease
- Immunocompromised state from solid organ transplant
- Obesity (body mass index* of 30 or higher)
- Serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease
- 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

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

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 2hours |
| C12hr | plasma concentration value collected at 12hours |
| CBC | complete blood count |
| 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 |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| ECI | event of clinical interest |
| ECMO | extracorporeal membrane oxygenation |
| eCRF | electronic Case Report Form |
| EDC | electronic data collection |
| eDMC | external data monitoring committee |
| EAST | software platform for the statistical design, simulation and monitoring of clinical trials |
| EEA | European Economic Area |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| 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 |
| FiO ₂ | fraction of inspired oxygen |
| GCP | good clinical practice |
| H1 | hypothesis 1 |
| H1N1 | Hemagglutinin Type 1 and Neuraminidase Type 1 (influenza strain) |



| Abbreviation | Expanded Term |
|---------------------|---|
| H2 | hypothesis 2 |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| hCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| 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 | legal acceptable representative |
| LFT | liver function test |
| LOCF | last observation carries forward |
| LSD | late stage development |
| mAb | monoclonal antibody |
| 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 |
| MSD | Merck Sharp & Dohme |
| N/A | not applicable |
| NEJM | New England Journal of Medicine |
| NHC | N-hydroxycytidine |
| NHC-TP | N-hydroxycytidine pharmacologically-active triphosphate |
| 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 |



| Abbreviation | Expanded Term |
|---------------------|---|
| PDLC | pre-defined limit of change |
| 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 |
| Tmax | time to maximum plasma concentration |
| t _{1/2} | half life |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | woman/women of childbearing potential |
| WONCBP | women of nonchildbearing potential |

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Title Page

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

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

Investigator Signatory

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

| | |
|-------------|------|
| Typed Name: | Date |
| Title: | |

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in 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 |
|--|--|
| <ul style="list-style-type: none">- 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. <p>Hypothesis: MK-4482 is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29.</p> | <ul style="list-style-type: none">- Hospitalization or death |
| <ul style="list-style-type: none">- To evaluate the safety and tolerability of MK-4482 compared to placebo. | <ul style="list-style-type: none">- Adverse events- Adverse events leading to discontinuation of study intervention |
| Secondary Objectives | Secondary Endpoints |
| <ul style="list-style-type: none">- 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. | <ul style="list-style-type: none">- 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 \geq 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. | |

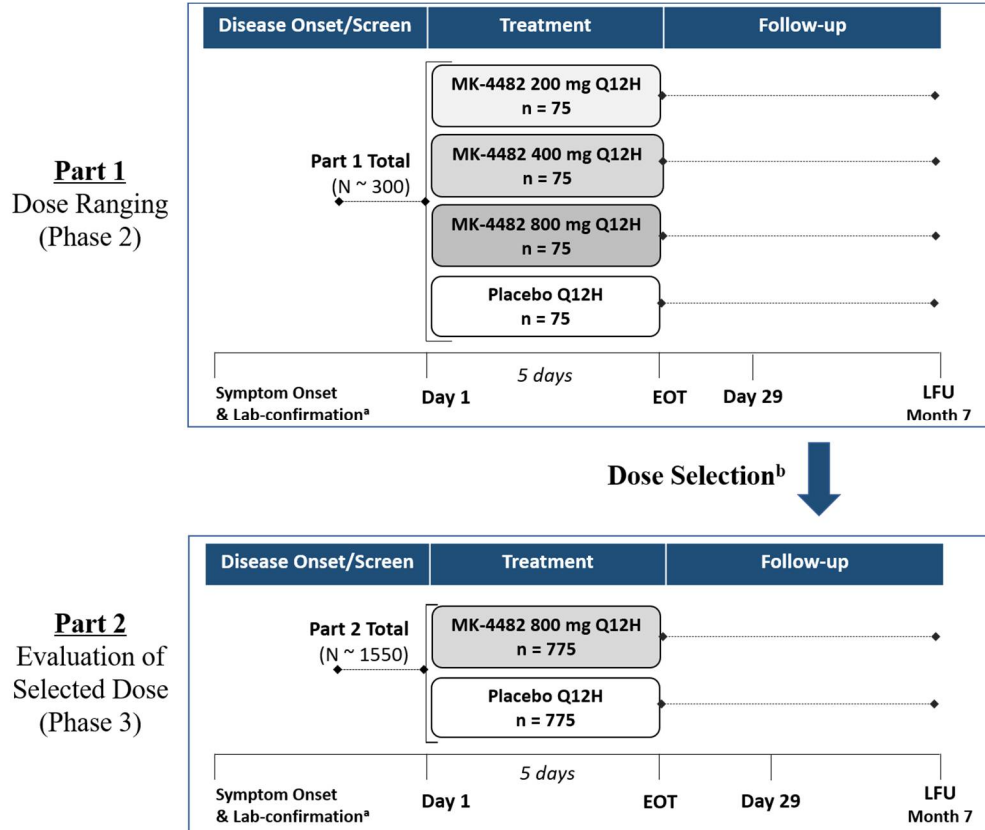
Study Accepts Healthy Volunteers: No

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 |
| <p>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; SpO₂ = oxygen saturation; WOCBP=women of childbearing potential.</p> <p>^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.</p> <p>^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.</p> <p>^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.</p> <p>^d LFU (Month 7) visit is 7 months from the last dose of study intervention.</p> <p>^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).</p> <p>^f Confirm no change in eligibility based on inclusion/exclusion criteria and/or disease severity.</p> <p>^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.</p> <p>^h Respiratory/Oxygenation Status collection at the LFU visit will be limited. As LFU will be a virtual visit, SpO₂ will not be measured. Use of supplemental oxygen will be collected.</p> <p>ⁱ AEs, SAEs, and other reportable safety events (eg, pregnancy) will be monitored according to Section 8.4.</p> <p>^j A subset of ~50 participants in Part 1 will take part in the PBMC Cohort at selected sites.</p> | | | | | | | | | | | |

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

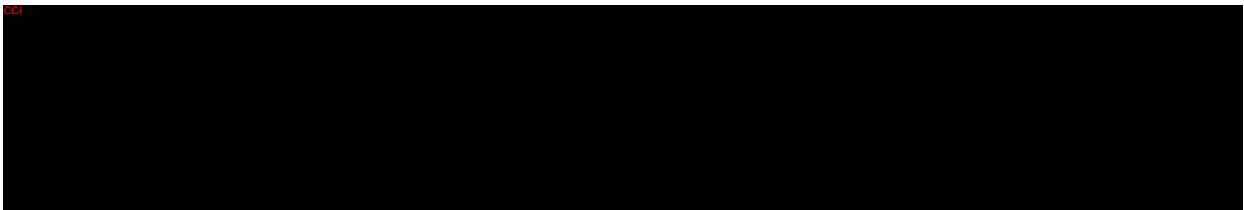
COVID-19, a disease resulting from SARS-CoV-2 infection, was declared a global pandemic by the WHO on 11-MAR-2020. Within 4 months of that declaration, there were over 11 million cases of COVID-19 reported globally and over 500 thousand associated deaths [World health Organization 2020]. With increasing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

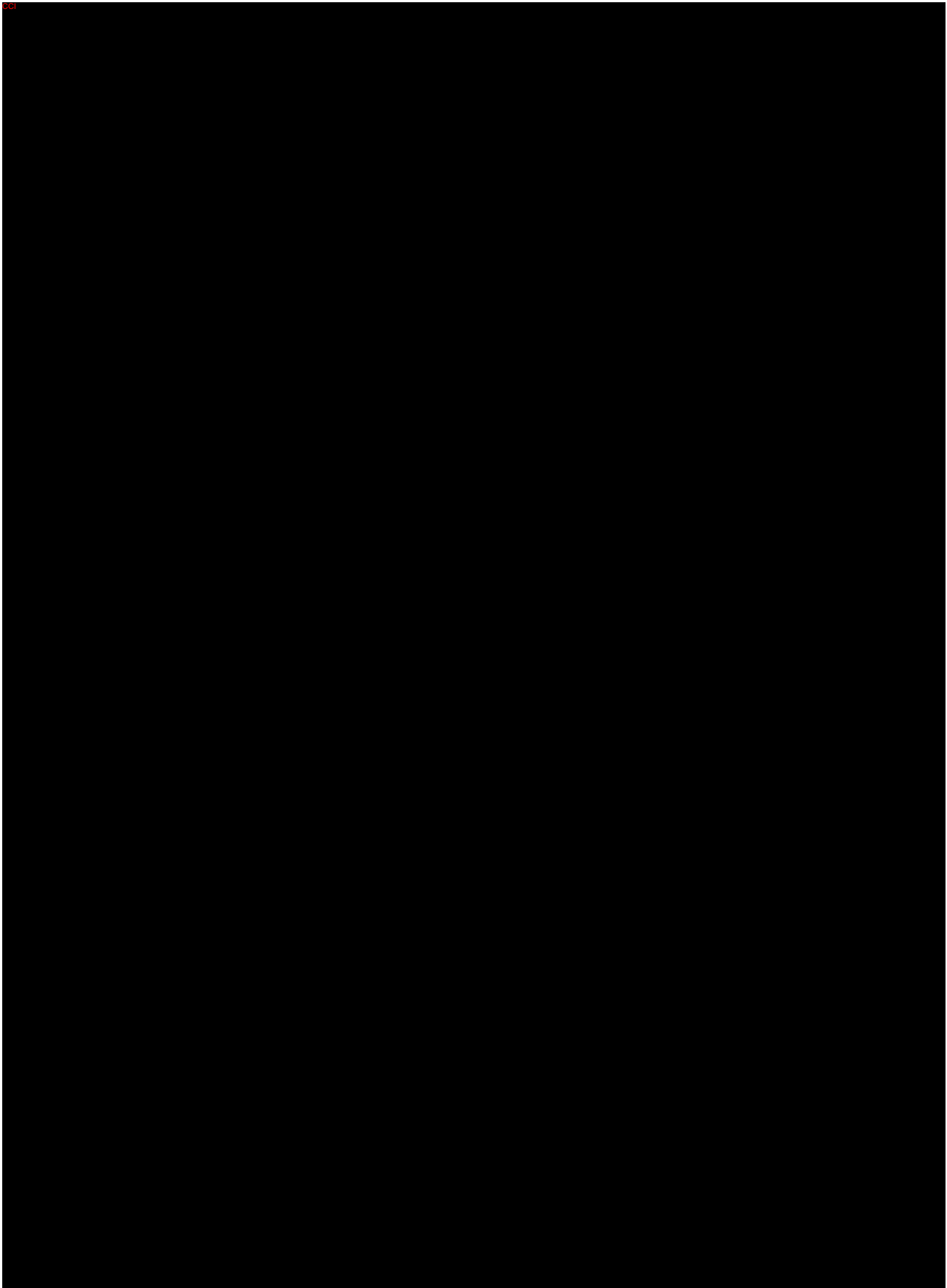
The true burden of COVID-19 is yet to be fully understood. Although most (>80%) infected individuals exhibit a mild illness (eg, fever, dry cough, fatigue), approximately 14% experience severe disease (eg, dyspnea, hypoxemia), and 5% have critical illness, which can include respiratory failure, septic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

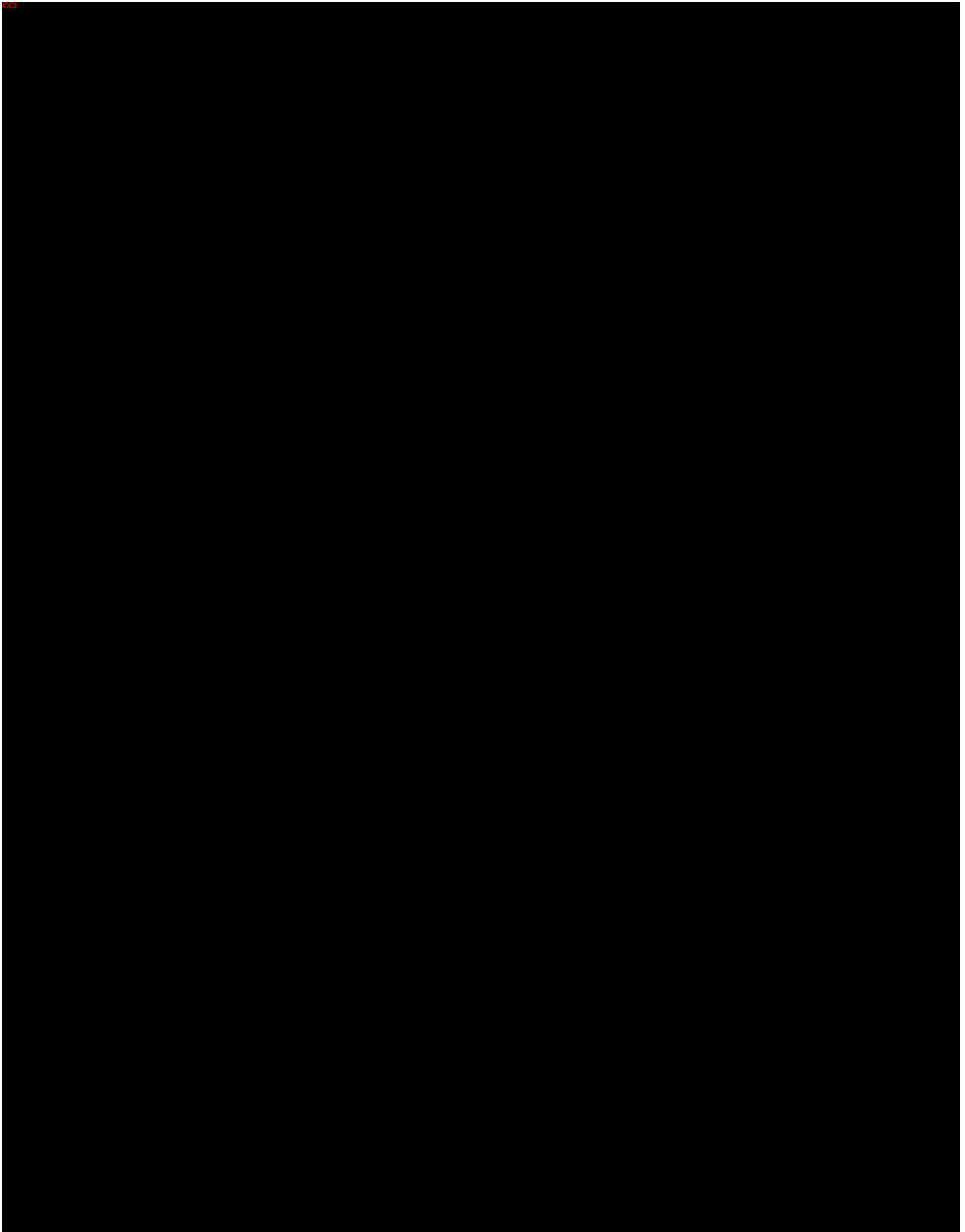
Standard of care treatment of COVID-19 is rapidly evolving and local treatment guidelines continue to be updated with emerging data [COVID-19 Treatment Guidelines Panel 2020] [Bhimraj, A., et al 2020] [World health Organization 2020]. Remdesivir is an antiviral agent approved by the US FDA for intravenous 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.

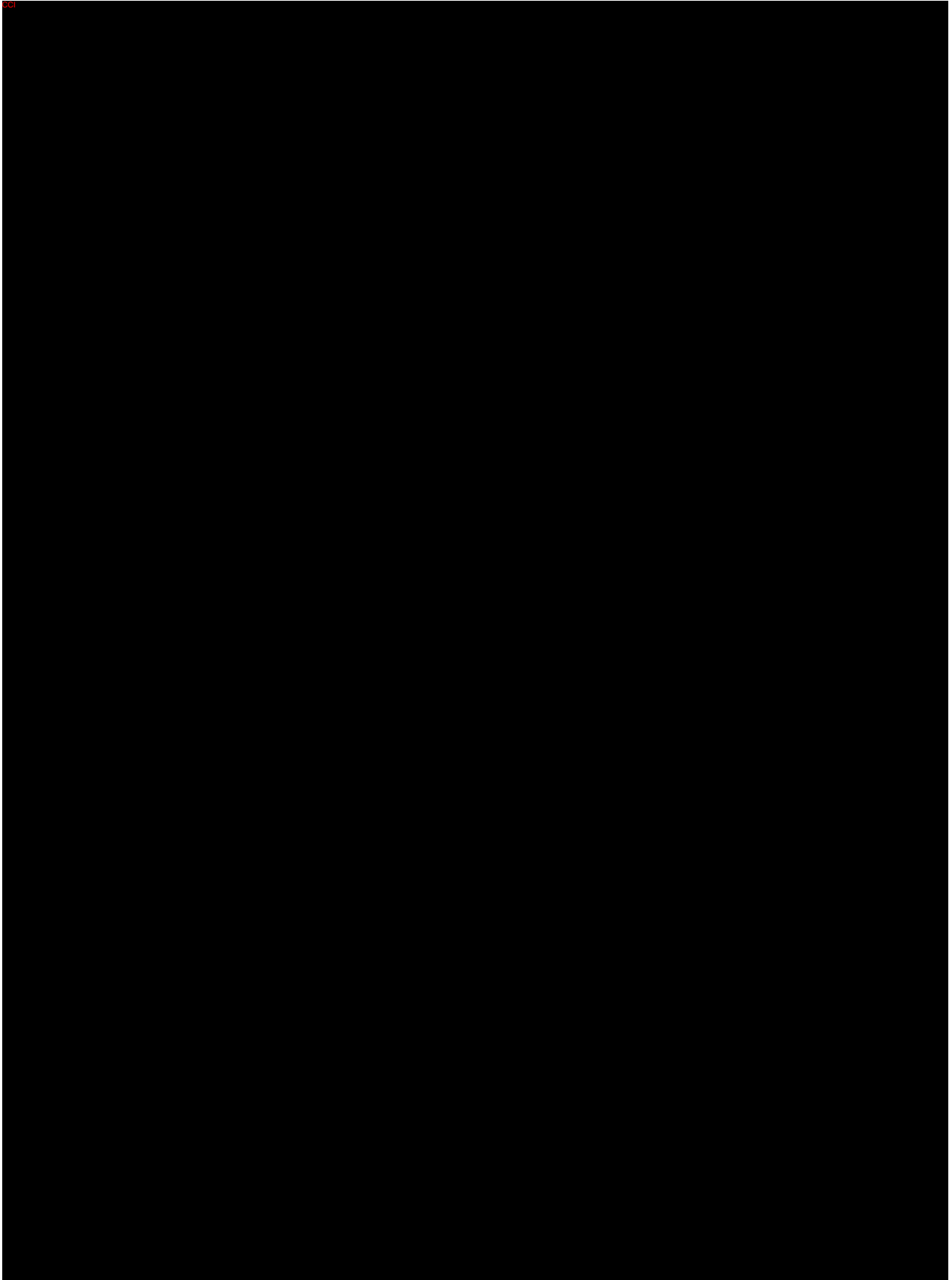
MK-4482 is a novel drug candidate with demonstrated activity against SARS-CoV-2 in vitro, efficacy against coronaviruses in animal models, and a high barrier to viral resistance. MK-4482 has been generally safe and well-tolerated to date in ongoing clinical studies.

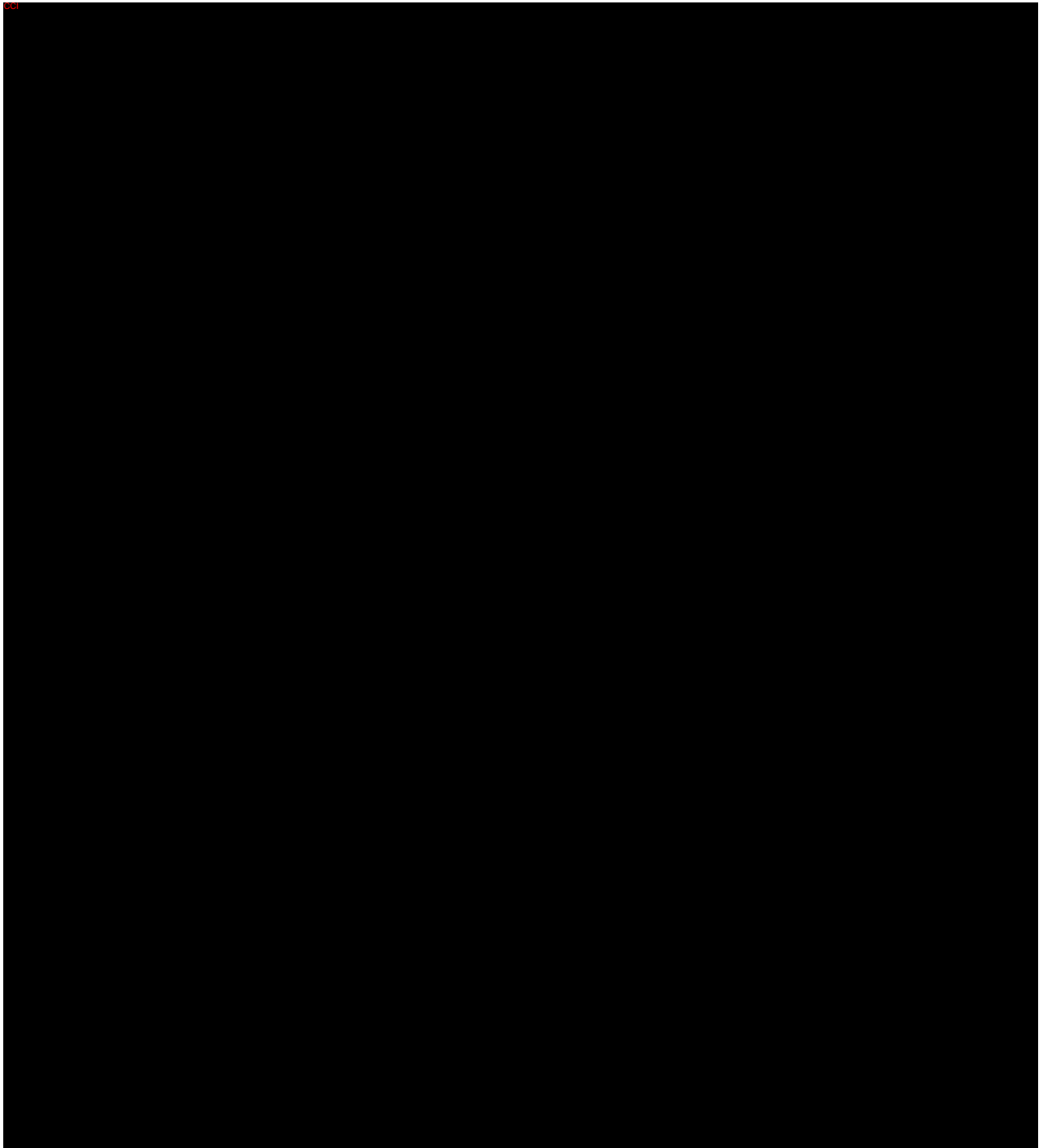
2.2 Background











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 | |
| <ul style="list-style-type: none"> 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. <p>Hypothesis: MK-4482 is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through Day 29.</p> | <ul style="list-style-type: none"> Hospitalization or death |
| <ul style="list-style-type: none"> To evaluate the safety and tolerability of MK-4482 compared to placebo. | <ul style="list-style-type: none"> Adverse events Adverse events leading to discontinuation of study intervention |
| Secondary | |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> COVID-19 signs/symptoms |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> WHO 11-point scale score |
| Tertiary/Exploratory | |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> Acute care visit |

| Objectives | Endpoints |
|--|--|
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> COVID-19-related acute care visit |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> Plasma (Part 1 and Part 2) and PBMC (Part 1) Pharmacokinetic concentration (eg, Ctrough) |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> SARS-CoV-2 RNA |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> Viral RNA sequences |
| <ul style="list-style-type: none"> 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. | <ul style="list-style-type: none"> 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 coinfecting 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 coinfecting 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 coinfecting 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 AUC₀₋₁₂ exposure of ~32 $\mu\text{M}\cdot\text{hr}$, which is 2.4-fold below the mean plasma AUC₀₋₁₂ exposure at the highest single dose evaluated in adults of 1600 mg.

4.3.3 Dose Selection for Part 2 (Phase 3)

The 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 $>38.0^{\circ}\text{C}$
 - 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 m² (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 $<500/\text{mm}^3$
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/ μ L 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 |
| <p>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.</p> | | | | | | | | | | | |

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 | <ul style="list-style-type: none">• SARS-CoV-2 vaccines are prohibited any time prior to randomization and through Day 29. |
| COVID-19 Monoclonal Antibodies | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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.<ul style="list-style-type: none">○ 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 <i>MK-4482-002 Sponsor-Designated Standard of Care for Treatment of COVID-19 or Supportive Therapies for Management of COVID-19</i> 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 $\geq 3X$ the upper limit of normal and an elevated total bilirubin lab value that is $\geq 2X$ 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 $< 50,000/\mu\text{L}$, 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.

- 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

SpO₂ 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. FiO₂, PaO₂, 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, SpO₂ 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 $<50,000/\mu\text{L}$, 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 | <ul style="list-style-type: none">• 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 re-consent 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 | <p>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.</p> <ul style="list-style-type: none">• MK-4482 200 mg (n~75)• MK-4482 400 mg (n~75)• MK-4482 800 mg (n~75)• Placebo (n~75) <p>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.</p> |
| Analysis Populations | <p>Efficacy: MITT (Parts 1 and 2 separately)</p> <p>Safety: APaT (Parts 1 and 2 combined)</p> |

| | |
|--|---|
| Primary Endpoints | <p>Efficacy: Proportion of participants with hospitalization or death by Day 29.</p> <p>Safety: Number of participants with AEs, and discontinuing study intervention due to AEs</p> |
| Key Secondary Endpoints | <ul style="list-style-type: none"> • 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 | <p>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].</p> |
| Statistical Methods for Key Safety Analyses | <p>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].</p> |
| Interim Analyses | <p>IA1 – Part 1 Dose Evaluation This IA will be used to review data to inform dose selection models and analyses.</p> <p>IA2 – Part 1^b Dose Selection This IA will be used to evaluate the dose/exposure-response to select the dose for Phase 3.</p> <p>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.</p> <p>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.</p> |
| Multiplicity | <p>There are no adjustments for multiplicity other than the type I error control for interim analyses described in Section 9.7.</p> |

| | |
|---|---|
| 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 $\log_{10}(\text{post}) - \log_{10}(\text{baseline})$, 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 $p \leq 0.019$ 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 (\log_{10} copies/mL) N=60/group, $\alpha=0.025$, 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 $\leq 10^6$ 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:

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

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.

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 Indices: MCV MCH RDW | WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Calculation of: Neutrophil/lymphocyte ratio Absolute Neutrophil Count |
| | RBC Count | | |
| | Hemoglobin | | |
| | Hematocrit | | |
| Chemistry | BUN | Chloride | AST/SGOT |
| | Albumin | Calcium | ALT/SGPT |
| | Creatinine | 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 | <ul style="list-style-type: none"> Urine or Serum hCG pregnancy test (as needed for WOCBP) | | |
| Virology | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> Plasma for NHC PBMC for NHC- triphosphate | | |
| Exploratory Research Samples | Samples may be used for testing such as: <ul style="list-style-type: none"> 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 <i>Failure rate of <1% per year when used consistently and correctly.</i> |
| <ul style="list-style-type: none">• Progestogen-only subdermal contraceptive implant^b• IUS^c• Non-hormonal IUD• Bilateral tubal occlusion |
| <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• 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) <ul style="list-style-type: none">• Combined (estrogen- and progestogen- containing) hormonal contraception^b<ul style="list-style-type: none">- Oral- Intravaginal- Transdermal- Injectable• Progestogen-only hormonal contraception^b<ul style="list-style-type: none">- Oral- Injectable |
| Barrier methods to be used with user dependent hormonal contraceptives above (male condoms are preferred method) <ul style="list-style-type: none">• 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) |
| <p>^a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>^b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.</p> <p>^c IUS is a progestin releasing IUD.</p> <p>^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).</p> <p>Note: The following are not acceptable methods of contraception alone or in combination:</p> <ul style="list-style-type: none">- 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.

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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 >38.0°C, 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
- SpO₂ >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
- $SpO_2 \leq 93\%$ 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 m²; 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

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

[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 |
| t _{1/2} | 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 |

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

To revise the dose selection process before initiation of Part 2 (Phase 3), update the benefit/risk assessment, clarify the key secondary efficacy objective regarding COVID-19 signs/symptoms, and add a discontinuation criterion.

Summary of Changes Table:

| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| 1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints 4.2.1.1.2 Secondary Endpoints 9.1 Statistical Analysis Plan Summary 9.4.1.1 Efficacy Endpoints 9.6.1 Statistical Methods for Efficacy Analyses | Key secondary efficacy objective revised to time to sustained resolution or improvement of COVID-19 sign and symptoms | To ensure that a sustained response to study intervention is being measured through this objective |

| Section # and Name | Description of Change | Brief Rationale |
|--|--|--|
| 1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for Study Design 8.1.8 Study Intervention Administration | References to ‘Day 1’ and/or ‘first dose’ were revised to ‘randomization’ and clarification regarding study day numbering (ie, randomization = Day 1) was provided | To add clarity and consistency |
| 1.2 Schema 5.1 Inclusion Criteria | Clarified that 7-day window for assessment of COVID-19 signs/symptoms does not include day of randomization | To clarify the timing of symptom onset prior to randomization for study eligibility |
| 1.3 Schedule of Activities | <ul style="list-style-type: none"> -Included option for clinic or at-home visit in lieu of virtual visits on Days 2 and 4. Corresponding update to Section 8.11.2.3. -Added a footnote to clarify that LFU visit will occur 7 months after the last dose of study intervention -Visit Window for LFU visit changed to ± 1 Month. -Review of inclusion/exclusion criteria added to Day 1 in SoA and Section 8.1.2 -COVID-19 severity must be based on Day 1 pre randomization values. Corresponding updates to Section 8.1.2. | <ul style="list-style-type: none"> -To increase flexibility for visit scheduling -To add clarity -To increase flexibility for visit scheduling -To add clarity for timing of certain screening activities in relation to randomization through the IRT system -To add clarity |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|---|
| | <p>-Added a separate line to the SoA for Blood Collection for Local laboratory Evaluation and revised footnote. Corresponding updates to Section 8.1.2.</p> <p>-Added a separate line to the SoA for collection of serum for antibody exploratory research</p> <p>-Specified that study staff should remind participant to complete the Symptom Diary. Corresponding updates in Section 8.2.5.</p> <p>-Added a separate line to the SoA requiring sites to confirm contraception requirements</p> <p>-Clarified that the first dose of study intervention is preferably administered on Day 1. Corresponding updates in Section 8.1.8.</p> <p>-Clarified that the Study Medication Diary should be collected after the last dose of study intervention. Corresponding updates in Section 8.1.14.</p> | <p>-To add clarity for local laboratory evaluations during screening</p> <p>-To add clarity as a separate laboratory collection kit is needed to collect this sample</p> <p>-To add instructions about reminders to support symptom diary compliance.</p> <p>-To add clarity for confirming contraceptive requirements.</p> <p>-To add clarity</p> <p>-To ensure the diary is not collected prior to the last dose since the EOT visit could occur prior to dose 10</p> |
| <p>2 Introduction 4.1 Overall Design</p> | <p>An additional term and abbreviation for MK-4482 were added</p> | <p>To introduce molnupiravir, and the abbreviation MOV, as the generic name for MK-4482</p> |



| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| 2.2 Background | PK terminal half-life data were updated | To include Phase 1 study results |
| 2.3 Benefit/Risk Assessment | Updated to include preliminary reproductive and developmental toxicity study results. | To include results of a preliminary embryofetal developmental toxicity study |
| 2.3 Benefit/Risk Assessment 5.1 Inclusion Criteria 8.4.1 Time Period and Frequency for Collecting AE, SAEs, and Other Reportable Safety Event Information 8.11.4 Late Follow-up (7 month) Visit | Revised inclusion criteria regarding contraception duration and duration of pregnancy follow up for WOCBP from 7 months after the last day of study intervention to 28 days from the start of study intervention. | MK-4482 was negative in the Big Blue® rat mutagenicity assay, a whole animal model relevant to assessment of human risk for mutagenicity. Based on the totality of the genotoxicity data, MK-4482 is not mutagenic or genotoxic in in vivo mammalian systems. Therefore, the duration of contraception required and pregnancy follow up for WOCBP has been decreased to the end of systemic exposure. The 28 day duration has been selected as a conservative requirement based on the duration of study intervention plus a conservative estimate of systemic exposure. The male requirement for contraception was not amended and is pending availability of testis histomorphology results from an ongoing 3 month toxicity study in rats. |
| 4.1 Overall Design | Added text to clarify that participants will be contacted 7 months after the last dose of study intervention | To add clarity and consistency |

| Section # and Name | Description of Change | Brief Rationale |
|--|--|--|
| 5.1 Inclusion Criteria | -Clarified use of molecular or antigen tests are allowed if authorized for use in the country. Serological tests that detect host antibodies are not allowed to confirm study eligibility. -Updated initial signs/symptoms attributable to COVID-19 -Added note to inclusion criterion #3 -Oxygenation saturation inclusion criterion was deleted | -To clarify appropriate diagnostic testing that can be used for study eligibility -To align the study-qualifying COVID-19 signs/symptoms with mild and moderate signs and symptoms as defined in Appendix 9 -To clarify that Appendix 9 and Appendix 10 must be used to determine this criterion -To streamline the inclusion criterion since oxygen saturation criteria are already included in the assessment of COVID-19 severity per Appendix 9 |
| 5.2 Exclusion Criteria 8.1.2 Inclusion/Exclusion Criteria | Revised exclusion criterion related to HBV or HCV infection. | To allow participants with stable and/or well-controlled HBV/HCV participation in the study |
| 5.2 Exclusion Criteria | Mechanical ventilation criterion edited | To broaden this criterion since participants with a recent history of mechanical ventilation for any reason (not just due to COVID-19) are a higher risk for re-intubation |
| 6.1 Study Interventions Administered | Changed the placebo comparator use from experimental to placebo | To add clarity |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|--|
| 6.3.2 Stratification | Revised wording of stratification criteria. Repeated text present in Section 4.1 regarding planned sample size. | To add clarity and consistency |
| 6.5 Concomitant Therapy | Updated “Investigational Agents” to “Other Non-COVID-19 Investigational Agents” and “medications” to “therapies” in the Prohibited and Allowed Therapies Table | To clarify that this row refers to Investigational Agents not intended for COVID-19 treatment and for wording consistency |
| 7.1 Discontinuation of Study Intervention | <ul style="list-style-type: none"> -Added criteria for participants who meet liver enzyme ECI criteria -Revised criterion for participants with platelet count <50,000 µL that repeat confirmatory testing is needed -Added discontinuation criterion for participants who become pregnant -Repeated discontinuation text present in Sections 8.6.1 and 8.6.2 | <ul style="list-style-type: none"> -To align with ECI criteria for participant safety -To align with ECI criterion - To add criterion for participant and fetal safety -To add clarity and consistency |
| 8.1.8.1 Timing of Dose Administration | <ul style="list-style-type: none"> -Timing of dosing and EOT visit was added - Clarified that if a participant’s renal function deteriorates requiring dialysis, discontinuation is not required | <ul style="list-style-type: none"> -To clarify details regarding the EOT visit requirements -To add clarity |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.1.14 Study Medication Diary | -Added options for recording study intervention in the Study Medication Diary -Included option for collection of the Study Medication Diary at the Day 10 visit if collection at EOT is not feasible. -Clarified capsule count definition. Corresponding updates to Section 9.11. | -To increase flexibility for appropriate methods of recording study intervention administration -To provide flexibility -To provide clarification that capsule count should be recorded on the eCRF |
| 8.2.5 MK-4482 Symptom Diary | -Clarified that the Symptom diary is to be completed by the participant. Study staff may assist in completion if needed. -COVID-19 signs/symptoms were updated | -To increase the flexibility in appropriate methods of symptoms diary data collection -To provide comprehensive list of study-qualifying COVID-19 signs/symptoms |
| 8.3.1 Physical Examination | Revised to indicate the height and weight data will be collected (not measured) | To allow increased flexibility for collection of height and weight data |
| 9.2 Responsibility for Analyses/In-house Blinding 9.7 Interim Analyses | Clarified that Part 2 of the study will not be initiated until Part 1 of the study is completed | To add clarity |
| 9.4.1.1 Efficacy Endpoints | Description of WHO 11-point ordinal scale was added | To provide more detail about the significance of the WHO 11-point ordinal scale |

| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| 9.5.1 Efficacy Analysis Populations 9.5.2 Safety Analysis Populations 9.9.3 Sample Size and Power Calculations for Safety Analyses (Part 2) 9.1 Statistical Analysis Plan Summary | -Clarified that Part 1 (Phase 2) and Part 2 (Phase 3) efficacy endpoints will be analyzed separately -Clarified that Part 1 (Phase 2) and Part 2 (Phase 3) will be combined for the final analysis of safety endpoints | To provide additional details regarding the analysis of efficacy and safety in Part 1 (Phase 2) and Part 2 (Phase 3) |
| 9.6.1 Statistical Methods for Efficacy Analyses | -Removed geographic region as stratification factor for the primary analysis -Text added to describe sensitivity analyses | To clarify primary analysis methodology |
| 9.6.1 Statistical Methods for Efficacy Analyses 9.9.2 Sample Size and Power Calculations for Virology Analyses (Part 1) | -Statistical methods for viral RNA endpoints added -Section added to describe sample size and power calculations for viral RNA endpoints | To provide additional description for the analyses of virology endpoints |
| 9.6.2 Statistical Methods for Safety Analyses | Updated Tier 3 safety endpoint description | To align table with text |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.7 Interim Analyses 9.1 Statistical Analysis Plan Summary | -Revised to state that dose evaluation will occur after 300 participants complete EOT in MK-4482-001 and MK-4482-002 combined, during IA1 -Modifications made to IA1 and IA2 to indicate that dose selection for Phase 3 will not occur until IA2 -Small alpha adjustment added for IA3 | To clarify the timing for dose evaluation |
| 9.7 Interim Analyses | Revised Sponsor siDMC review of IA1 data | To revise purpose of siDMC review of IA1 data |
| 10.2 Appendix 2: Clinical Laboratory Tests | Updated approximate whole blood volumes and visit windows. Corresponding updates in Section 8. | To revise the specimen collection volumes and to clarify windows for specimen collection timepoints |
| 10.9 Appendix 9: COVID-19 Severity Categorization | Table format was modified. Clarified that participants with new oxygen needs not previously on supplemental oxygen are considered to have severe COVID-19. | To add clarity |
| Throughout the document | Corrected minor typographical and grammatical errors | To improve clarity and consistency throughout the document |

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

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).

Summary of Changes Table:

| Section # and Name | Description of Change | Brief Rationale |
|--|--|--|
| 1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.3.3 Dose Selection for Part 2 (Phase 3) 6.1 Study Interventions(s) Administration 6.3.1 Intervention Assignment 9.1 Statistical Analysis Plan Summary | Added text identifying the MK-4482 dose selected for Part 2 (Phase 3) of the study and provided a summary of data used to select the dose. | To identify the MK-4482 dose selected for Part 2 (Phase 3) and the rationale for the dose selection. |
| Title Page | Added NCT number. | To provide the NCT number for the study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|--|
| 1.1 Synopsis 4.1 Overall Design 10.12 Appendix 12 Abbreviations | Included the name of the clinical study (MOVE-OUT). | To provide new clinical study name. |
| 1.1 Synopsis 1.2 Schema 4.1 Overall Design 6.3.1 Intervention Assignment 9.1 Statistical Analysis Plan Summary 9.7 Interim Analyses 9.9 Sample Size and Power Calculations | Updated Part 2 randomization ratio, total sample size, and associated power calculations. | To increase the number of participants exposed to MK-4482 to sufficiently characterize the safety of MK-4482. |
| 1.2 Schema 4.1 Overall Design 4.2.3 Rationale for Selected Participant Population 5.1 Inclusion Criteria | Updated requirements for timing of symptom onset and prior SARS-CoV-2 infection from ≤ 7 to ≤ 5 days prior to randomization | To limit initiation of treatment only to participants early in their disease course, as Part 1 data suggests increased benefit with earlier initiation of treatment. |

| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| 1.2 Schema 4.1 Overall Design 5.1 Inclusion Criteria 10.2 Appendix 2: Clinical Laboratory | Changed “PCR-confirmed” SARS-CoV-2 infection and “PCR-confirmed” COVID-19 to “laboratory-confirmed” SARS-CoV-2 infection and “laboratory-confirmed” COVID-19. | Procedures and methods for laboratory confirmation of SARS-CoV-2 infection are evolving. This change allows for use of other molecular or antigen tests that detect viral RNA or protein in addition to PCR if authorized for use in the country. |
| 1.3 Schedule of Activities | Added timepoint on Day 1 for collection of Medical History | Medical history, including day of onset of COVID-19 signs/symptoms, must be confirmed on day of randomization. |
| 1.3 Schedule of Activities 2.3 Benefit-Risk 4.1 Overall Design 5.1 Inclusion Criteria 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.11.4 Late Follow-up (7 month) Visit | Revised text throughout to reflect change in duration of contraception to at least 4 days after last dose of study intervention: <ul style="list-style-type: none"> • Deleted confirmation of contraception from Visits 8, 9, and 10. • Updated duration of contraception. • Removed collection of, and requirement to review, pregnancy status at LFU. • Updated inclusion criteria to change timeframe for contraception requirements and to delete requirement for male participants to refrain from donating sperm. | To update contraception requirements based on the half-life of NHC (~19 hours) so that the duration of contraception is through the end of systemic exposure (ie, 5 half-lives); and, to remove restriction on sperm donation because sperm donation is washed, therefore, semen (where risk of teratogenicity/fetotoxicity would exist) is not present in the sperm donation. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities 5.2 Exclusion Criteria 8.1.2 Inclusion/Exclusion Criteria | Removed history of acute pancreatitis within 3 months prior to randomization or a history of chronic pancreatitis as an exclusion criterion. | The ECI of elevated amylase or lipase >3X the upper limit of normal was removed for Part 2. |
| 1.3 Schedule of Activities 4.2.1.5 Future Biomedical Research 5.1 Inclusion Criteria 7.2 Participant Withdrawal From the Study 8.1.1 Informed Consent 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 8.1.9.1 Withdrawal From Future Biomedical Research 8.9 Future Biomedical Research Sample Collection 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research | Added or revised text in sections regarding Informed Consent for FBR and specimens and added appendix regarding collection and management of specimens. | To allow for optional research using unused samples collected during the study. |

| Section # and Name | Description of Change | Brief Rationale |
|--|---|---|
| 1.3 Schedule of Activities 8.1.2 Inclusion/Exclusion Criteria | Removed reference to segmented neutrophils and bands for determination of eligibility per local laboratory results. | To allow for calculation of absolute neutrophil count per local standard of care (ie, with or without bands) |
| 1.3 Schedule of Activities 4.2.5 Rationale for Other Exploratory Research Samples 8.2.1 Nasopharyngeal and Oropharyngeal Swabs 8.9 Future Biomedical Research Sample Collection 9.6.1 Statistical Methods for Efficacy Analyses 10.2 Appendix 2 Clinical Laboratory Tests | Removed OP swab collection for Part 2 and clarified relevant text associated with OP swab removal. | Data from Part 1 of the study supports that collection of NP swabs alone are sufficient for evaluation of the study objectives. Removal of OP swab collection will reduce participant burden. |

| Section # and Name | Description of Change | Brief Rationale |
|--|--|---|
| 1.3 Schedule of Activities 3 Hypotheses, Objectives, and Endpoints 8.2.3 Hospitalization 8.10 Medical Resource Utilization and Health Economics 9.4.1.1 Efficacy Endpoints | Added new exploratory objective/endpoint to evaluate the percentage of participants who have any acute care visit, including COVID-19-related acute care visits. Acute care visit is defined as any hospitalization, emergency room visit, or any other acute care visit (including an urgent care visit or visit with any healthcare provider for acute care needs). | To evaluate the efficacy of MK-4482 by assessing the percentage of participants with any acute care visit from randomization through Day 29, including specifically COVID-19-related acute care visits. |
| 2.1 Study Rationale 2.2 Background 2.3 Benefit/Risk Assessment 4.2.1.2 Safety Endpoints 4.3.1 Rationale for Dosing Duration | Revised to update the approved status of remdesivir by the US FDA and European Commission. Updated with currently available preclinical and clinical data. | To update these sections with currently available information. |
| 2.3 Benefit/Risk Assessment | Added text regarding availability of authorized anti-SARS-CoV-2 monoclonal antibodies with demonstrated clinical efficacy. | To provide additional information about the availability and efficacy of authorized anti-SARS-CoV-2 monoclonal antibodies and clarify that participants who chose to receive monoclonal antibodies for treatment of COVID-19 are not eligible for inclusion in the study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|--|
| 3 Hypotheses, Objectives, and Endpoints 4.2.5 Rationale for Other Exploratory Research Samples 9.4.1.1 Efficacy Endpoints 10.2 Appendix 2: Clinical Laboratory Tests | Added text regarding consideration of novel treatment-emergent variants of the original SARS-CoV-2 genotype. | To provide information that multiple viral variants have been identified and continue to circulate worldwide. |
| 4.1 Overall Design 4.2.3 Rationale for the Selected Participant Population 6.3.2 Stratification | <ul style="list-style-type: none"> -Updated enrollment targets for Part 2. • All participants must have at least 1 characteristic or underlying medical conditions associated with being at increased risk for severe illness from COVID-19 • At least 50% of participants must be >60 years of age. <p>-Added text to clarify that the 50% enrollment cap for participants with moderate COVID-19 only applies to Part 1.</p> | <ul style="list-style-type: none"> -To further enrich the study for participants who are at risk for severe illness from COVID-19. -Limiting the number of participants with moderate COVID-19 at baseline is no longer needed due to enrichment of the study for participants who are at risk for severe illness from COVID-19. |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|--|
| 4.2.1.2 Safety Endpoints 8.4.7 Events of Clinical Interest | Removed the ECI of elevated amylase/lipase >3X the upper limit of normal for Part 2. | No safety signals were observed in Part 1 of MK-4482-001 and MK-4482-002 or in other studies in the MK-4482 program. |
| 4.2.5 Rationale for Other Exploratory Research Samples | Added text to clarify the plaque assay. | To add clarity. |
| 5.1 Inclusion Criteria 5.2 Exclusion Criteria | <p>-Changed inclusion criterion from “participants with mild COVID-19” to “all participants” must have at least 1 characteristic or underlying medical conditions associated with being at increased risk for severe illness from COVID-19.</p> <p>-Removed medical condition exclusions of prior chemotherapy and autologous or allogenic hematopoietic stem cell transplant recipient.</p> <p>-Removed exclusion criterion of baseline heart rate of <50 beats per minute at rest.</p> <p>-Removed the CD4 count threshold for HIV exclusion, and added that AIDS-defining illnesses within the past 6 months is exclusionary and that participants with HIV must be on a stable antiretroviral therapy regimen to be enrolled.</p> | <p>-To further enrich the study for participants who are at risk for severe illness from COVID-19.</p> <p>-To allow for enrollment of a higher risk population, and no known DDIs with chemotherapeutic agents or transplant medications.</p> <p>-Results from Part 1 and other studies in the MK-4482 program do not indicate an effect of MK-4482 on cardiac rate or rhythm.</p> <p>-To allow for enrollment of participants with stable and/or well controlled HIV but with a CD4 count <200 cells/mm³.</p> |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|---|
| 6.3.2 Stratification | <p>-Updated stratification factor for timing of symptom onset from $\leq/ > 5$ days to $\leq/ > 3$ days.</p> <p>-Removed stratification for presence of risk factors for Part 2.</p> | <p>-As the requirement for timing of symptom onset and prior SARS-CoV-2 infection was updated from ≤ 7 to ≤ 5 days prior to randomization, stratifying randomization by ≤ 3 days or > 3 days will help ensure that the treatment groups will be well balanced regarding the timing of symptom onset due to likely greater benefit with earlier initiation of treatment.</p> <p>-With the updated requirement for all participants to have at least one risk factor, this stratification variable is no longer applicable.</p> |
| 6.5 Concomitant Therapy | <p>-Added monoclonal antibodies as prohibited therapy.</p> <p>-Removed remdesivir as example of standard of care for treatment for COVID-19</p> <p>-Added a footnote to reference the separate Sponsor-designated standard-of-care document.</p> | <p>-To clarify that monoclonal antibodies for treatment of COVID-19 are not allowed prior to randomization or from randomization through Day 29 due to potential confounding of efficacy.</p> <p>-The Sponsor-designated standard of care document focuses on treatment of non-hospitalized participants with COVID-19, and remdesivir is not indicated in the non-hospitalized setting.</p> <p>-To add clarity.</p> |
| 7.1 Discontinuation of Study Intervention | <p>-Removed need for verification via repeat testing.</p> <p>-Clarified that unscheduled laboratory testing is also used to determine need for discontinuation.</p> | <p>-Repeat testing may not always be feasible and to ensure all events are considered.</p> <p>-To add clarity.</p> |

| Section # and Name | Description of Change | Brief Rationale |
|--|--|---|
| 7.2 Participant Withdrawal From the Study 8.1.1.3 Participants who Discontinue or Withdraw | Added that vital status includes hospitalization status and that vital status through Day 29 and LFU is required for participants who withdraw from the study. | To add clarity regarding vital status collection. |
| 8.1.4 Medical History 10.10 Appendix 10: Individuals at Increased Risk for Severe Illness from COVID-19 | Removed immunocompromised state due to solid organ transplant and sickle cell disease from the list of characteristics or underlying medical conditions considered to be at increased risk for severe illness from COVID-19. | To align with updated CDC data supported by meta-analysis/systematic review for identification of individuals at increased risk for severe illness from COVID-19. |
| 8.1.8.1 Timing of Dose Administration | Deleted instructions regarding timing and recording of dose for participants discharged prior to EOT. | To eliminate potential confusion as all doses will be recorded, regardless of timing of the PK sample collection. |
| 8.2.2 Respiratory/Oxygenation Status | Added “designee” to assessment of shortness of breath. | To add clarity. |
| 8.2.5 MK-4482 Symptom Diary | Added that Day 1 is the same day as randomization. | To add clarity. |
| 8.3.2 Vital Signs | Changed “blood pressure” and “heart rate” to “vital signs.” | To require that all vital signs are measured after 5 minutes of rest. |

| Section # and Name | Description of Change | Brief Rationale |
|--|--|--|
| 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Events | Added exception regarding a positive pregnancy test. | To add clarity. |
| 8.4.7 Events of Clinical Interest | Removed need for verification via repeat testing for platelet ECIs. | Repeat testing may not always be feasible and to ensure all events are captured. |
| 9.6.1 Statistical Methods for Efficacy Analysis | Clarified how unknown hospitalization status will be handled for the primary efficacy endpoint for participants who are lost to follow-up or withdraw from the study prior to Day 29. | To add clarity and account for potential missing data. |
| 9.10 Subgroup Analyses | Clarified time from symptom onset prior to the day of randomization was ≤ 5 days for Part 1 and ≤ 3 days for Part 2, and that increased risk for severe illness from COVID-19 was for Part 1 only. | To add clarity. |
| 10.2 Appendix 2: Clinical Laboratory | Clarified when parallel collection of the sample for central laboratory analysis is not required. | To add clarity. |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|--|
| 10.9 Appendix 9: COVID-19 Severity Categorization | <ul style="list-style-type: none"> -Clarified that vital sign measurements should be preceded by ≥ 5 minutes of rest. -Added “investigator assessed” to shortness of breath assessments. - Updated definition of severe COVID-19 category to change supplemental oxygen requirement consideration from >2 to >4 liters/min. Updated definition of moderate COVID-19 category from on ≤ 2 to ≤ 4 liters/min supplemental oxygen. -Revised the definition of shock for the critical COVID-19 category. | <ul style="list-style-type: none"> -To add clarity. -To add clarity. -For consideration of the potential for slightly more supplemental oxygen use in participants who otherwise meet vital sign criteria in the moderate disease category. -Revised definition of shock to align with WHO criteria. |
| Throughout the document | Corrected minor typographical and grammatical errors | To improve clarity and consistency throughout the document. |

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

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.

Summary of Changes Table:

| Section # and Name | Description of Change | Brief Rationale |
|----------------------------|---|--|
| 1.2 Schema | Revised dose for Part 2 in the schema. | To correct typographical error. |
| 1.3 Schedule of Activities | Added note for Hospitalization, Emergency Room, and Other Acute Care Visit Status. | To clarify that only hospitalization status (not emergency room or acute care visit status) is to be collected at the LFU (Month 7) visit. |
| 2 Introduction | Updated patient population for which MK-4482 is being developed. | MK-4482 is no longer being studied in hospitalized patients. |
| 2.2 Background | Added data about molnupiravir's antiviral activity against SARS-CoV-2 variants. Revised name of the control arm for the MK-4482-005 (AGILE) study. | To update the protocol with new data about the antiviral activity of molnupiravir. To clarify background information. |

| Section # and Name | Description of Change | Brief Rationale |
|--|--|--|
| 2.3 Benefit/Risk Assessment | Added fertility study and rabbit EFD study results and revised mutagenicity study results. | To update the protocol with new preclinical data. |
| 5.1 Inclusion Criteria | Added note to Inclusion Criterion No. 9 regarding the use of monoclonal antibodies. | 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. |
| 6.3.3 Blinding 9.7 Interim Analysis | Added information that a team of select Sponsor personnel not otherwise associated with the clinical study or study team will be unblinded to Part 2 data following the eDMC decision at IA4. | To allow for the preparation and submission of applications by an unblinded team for emergency use and/or marketing authorization based on positive IA4 efficacy and safety data. |
| 6.5 Concomitant Therapy | Removed the statement that monoclonal antibody therapy is permitted in hospitalized participants in Table 2. | SARS-CoV-2 monoclonal antibodies are not authorized for use in hospitalized participants. |
| 8.1.8.1 Timing of Dose Administration | <p>Added Q12H to explain the normal dosing schedule.</p> <p>Added text regarding the potential need for rescheduling the EOT visit to accommodate collection of PK samples in the event the study intervention dosing schedule is changed due to out of window dosing.</p> | <p>To clarify language regarding the normal dosing schedule after a missed dose.</p> <p>To clarify the potential impact of out of window dosing on the EOT visit timing.</p> |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|---|
| 8.2.3 Hospitalization | Clarified that the timeframe for reporting hospitalizations is per Section 8.4.6. | To clarify that not all hospitalizations require a 24-hour reporting timeframe and provide reference to reporting rules in Section 8.4.6. |
| 8.9 Future Biomedical Research Sample Collection | Removed that specimens are collected for Part 1. | Edited to clarify that future biomedical research samples are only collected in Part 2. |
| 9.8 Multiplicity 9.9 Sample Size and Power Calculation | Corrected the absolute difference corresponding to the p-value boundary at final analysis from 0.036 to 0.03 and the observed treatment difference from -3.60 to -3.0 for the statistical criterion for success. | To correct typographical error. |
| 9.10 Subgroup Analyses | Added new subgroup analyses for baseline (Day 1) SARS-CoV-2 VL status and SARS-CoV-2 antibody status. | To prespecify additional subgroup analyses, focusing on baseline SARS-CoV-2 VL status (quantitative and qualitative assays) and baseline SARS-CoV-2 antibody status, as these baseline characteristics could impact efficacy. |
| 10.10 Appendix 10: Individuals at Increased Risk for Severe Illness from COVID-19 | Reworded to clarify what is considered a serious heart condition. | To improve clarity. |
| Throughout the document | Corrected minor typographical and grammatical errors. | To improve clarity and consistency throughout the document. |

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. |