Sinossi

Titolo del protocollo: Studio clinico in doppio cieco, controllato con placebo, randomizzato, di fase 2/3 volto a valutare l'efficacia, la sicurezza e la farmacocinetica di MK-4482 in adulti ospedalizzati affetti da COVID-19

Titolo breve: Studio di fase 2/3 su MK-4482 in adulti ospedalizzati con COVID-19

Acronimo: N/D

Ipotesi, obiettivi ed endpoint:

Le ipotesi sono allineate con gli obiettivi nella tabella Obiettivi ed Endpoint.

I seguenti obiettivi saranno valutati in partecipanti ospedalizzati di ≥18 anni di età con COVID-19.

Obiettivi primari	Endpoint primari
• Valutare l'efficacia di MK-4482 rispetto al placebo, come stimato in base al tasso di recupero sostenuto dalla data della randomizzazione fino al Giorno 29. Ipotesi (H1): MK-4482 è superiore al placebo, come valutato dal tasso di recupero sostenuto fino al Giorno 29.	• Tempo al recupero sostenuto
• Valutare la sicurezza e la tollerabilità di MK-4482 rispetto al placebo	• Eventi avversi • Eventi avversi che determinano l'interruzione dell'intervento dello studio
Secondari	Endpoint Secondari
• Valutare l'efficacia di MK-4482 rispetto al placebo, come stimato in base alla percentuale di partecipanti che sono deceduti fino al Giorno 29. **Ipotesi (H2)**: MK-4482 è superiore al placebo, come valutato dalla percentuale di partecipanti che muoiono fino al Giorno 29.	• Mortalità per tutte le cause
• Valutare l'efficacia di of MK-4482 rispetto al placebo, come stimato in base alle probabilità di una risposta più favorevole sulle scale dell'esito ordinale selezionate nel Giorno 3, EOT, Giorno 10, Giorno 15 e Giorno 29.	• Punteggio polmonare • Punteggio polmonare+
• Valutare l'efficacia di MK-4482 rispetto al placebo, come stimato in base alle probabilità di una risposta	• National Early Warning Score

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più favorevole in relazione al rischio clinico della categoria di mortalità basata sul National Early Warning Score all'EOT (End Of Treatment, Fine del trattamento).	
• Valutare l'efficacia di MK-4482 rispetto al placebo, valutata in base alle probabilità di una risposta più favorevole sulla scala ordinale dell'OMS a 11 punti nel Giorno 3, EOT, Giorno 10, Giorno 15 e Giorno 29.	• Punteggio della scala a 11 punti dell'OMS

Disegno complessivo

Fase di studio	Fase 2/Fase 3
Scopo primario	Trattamento
Indicazione	COVID-19
Popolazione	Partecipanti di ≥18 anni di età ospedalizzati con COVID-19
Tipo di studio	Interventistico
Modello interventistico	In parallelo Questo è uno studio multicentrico.
Tipo di controllo	Controllato con placebo
Cecità dello studio	In doppio cieco con mascheramento in-house
Ruoli nel cieco	Partecipanti o soggetti Sperimentatore Sponsor
Durata stimata dello studio	Lo Sponsor stima che lo studio richiederà circa 12 mesi dalla data nella quale il primo partecipante (o il suo rappresentante legalmente accettabile) fornisce il consenso informato documentato fino all'ultimo contatto correlato allo studio dell'ultimo partecipante.

Numero di partecipanti:
Circa 1300 partecipanti in totale saranno randomizzati nello studio.

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Gruppi di intervento e durata:

<table>
<tr><td>Gruppi di intervento</td><td>
<table>
<tr><th>Nome del gruppo di intervento</th><th>Farmaco</th><th>Intensità della dose</th><th>Frequenza della dose</th><th>Via di somministrazione</th><th>Periodo di trattamento</th></tr>
<tr><td colspan="6">Parte 1 (N~300)</td></tr>
<tr><td>MK-4482 (200 mg)</td><td>MK-4482</td><td>200 mg</td><td>Q12H</td><td>Orale</td><td>5 giorni (10 dosi in totale)</td></tr>
<tr><td>MK-4482 (400 mg)</td><td>MK-4482</td><td>400 mg</td><td>Q12H</td><td>Orale</td><td>5 giorni (10 dosi in totale)</td></tr>
<tr><td>MK-4482 (800 mg)</td><td>MK-4482</td><td>800 mg</td><td>Q12H</td><td>Orale</td><td>5 giorni (10 dosi in totale)</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>0 mg</td><td>Q12H</td><td>Orale</td><td>5 giorni (10 dosi in totale)</td></tr>
<tr><td colspan="6">Parte 2 (N~1000)</td></tr>
<tr><td>MK-4482</td><td>MK-4482</td><td>mg da definire</td><td>Q12H</td><td>Orale</td><td>5 giorni (10 dosi in totale)</td></tr>
<tr><td>Placebo</td><td>Placebo</td><td>0 mg</td><td>Q12H</td><td>Orale</td><td>5 giorni (10 dosi in totale)</td></tr>
<tr><td colspan="6">N = numero di partecipanti da arruolare in ciascuna parte dello studio; Q12H = una volta ogni 12 ore; TBD = da determinare in base alla dose selezionata nella Parte 1 dello studio.</td></tr>
</table>
</td></tr>
<tr><td>Numero totale di gruppi/bracci di intervento</td><td>Parte 1: 4 gruppi
Parte 2: 2 gruppi</td></tr>
<tr><td>Durata della partecipazione</td><td>Ciascun partecipante resterà nello studio per circa un massimo di circa 7 mesi dalla data nella quale il primo partecipante fornisce il consenso informato documentato fino al contatto finale. I partecipanti riceveranno 10 dosi dell'intervento dello studio assegnato (somministrato Q12H) e saranno seguiti per 28 giorni dopo la randomizzazione. Inoltre, i partecipanti saranno contattati circa 7 mesi dopo l’ultima dose di intervento dello studio.</td></tr>
<tr><td>Comitato direttivo</td><td>No</td></tr>
<tr><td>Comitato di controllo esecutivo</td><td>Sì</td></tr>
<tr><td>Comitati di monitoraggio dei dati</td><td>Sì</td></tr>
<tr><td>Comitato di valutazione clinica</td><td>No</td></tr>
<tr><td colspan="2">Le considerazioni relative alla sorveglianza dello studio sono riportate nell’Appendice 1 del protocollo.</td></tr>
</table>

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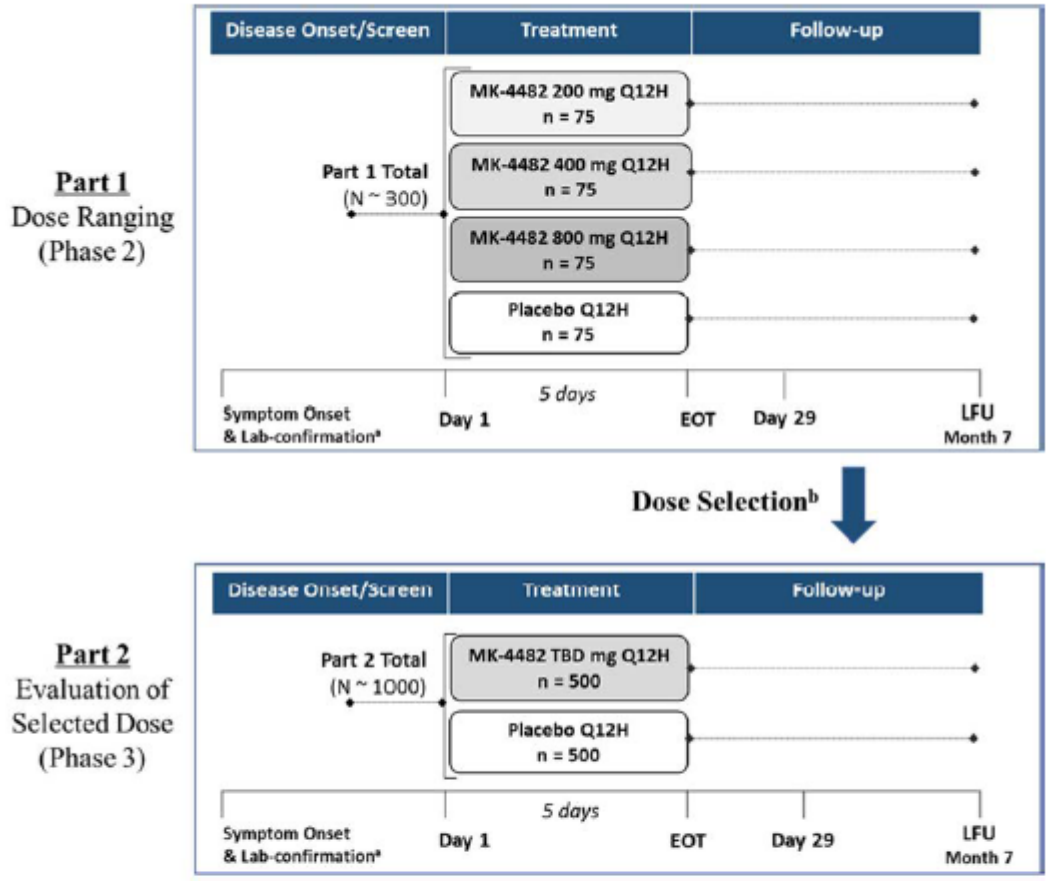
Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema and Treatment Plan



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

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

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

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1.3 Schedule of Activities

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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