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 non ospedalizzati affetti da COVID-19.

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

Acronimo:N/D
MOVe-OUT

Ipotesi, obiettivi ed endpoint:

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

Nei partecipanti non ospedalizzati di età ≥18 anni con la COVID-19 saranno valutati i seguenti obiettivi.

Obiettivi	Endpoint
Primario	
- Valutare l'efficacia di MK-4482 rispetto al placebo, in base alla percentuale di partecipanti ospedalizzati e/o deceduti dalla randomizzazione fino al Giorno 29. Ipotesi: MK-4482 è superiore al placebo, in base alla percentuale di partecipanti ospedalizzati e/o deceduti fino al Giorno 29	• Ricovero ospedaliero o decesso
• 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	
• Valutare l'efficacia di MK-4482 rispetto al placebo, in base al tempo al miglioramento/risoluzione sostenuta e al tempo alla progressione di ciascun segno/sintomo mirato auto-riportato di COVID-19 dalla randomizzazione fino al Giorno 29.	• Segni/sintomi di COVID-19
- Valutare l'efficacia di MK-4482 rispetto al placebo, in base al tempo al miglioramento/risoluzione e al tempo alla progressione dei segni/sintomi mirati auto-riportati di COVID-19 dalla randomizzazione fino al Giorno 29.	• Punteggio della scala a 11 punti dell'OMS
• - Valutare l'efficacia di MK-4482 rispetto al placebo, in base alle probabilità di una risposta più favorevole sulla scala ordinale a 11 punti dell'OMS al Giorno 3, a fine trattamento, al Giorno 10, al Giorno 15 e al 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 età ≥18 anni con COVID-19,che non necessitano di ricovero ospedaliero
Tipo di studio	Interventistico
Modello interventistico	In parallelo Il presente 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:
Nello studio saranno randomizzati complessivamente circa 1.850 partecipanti.

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

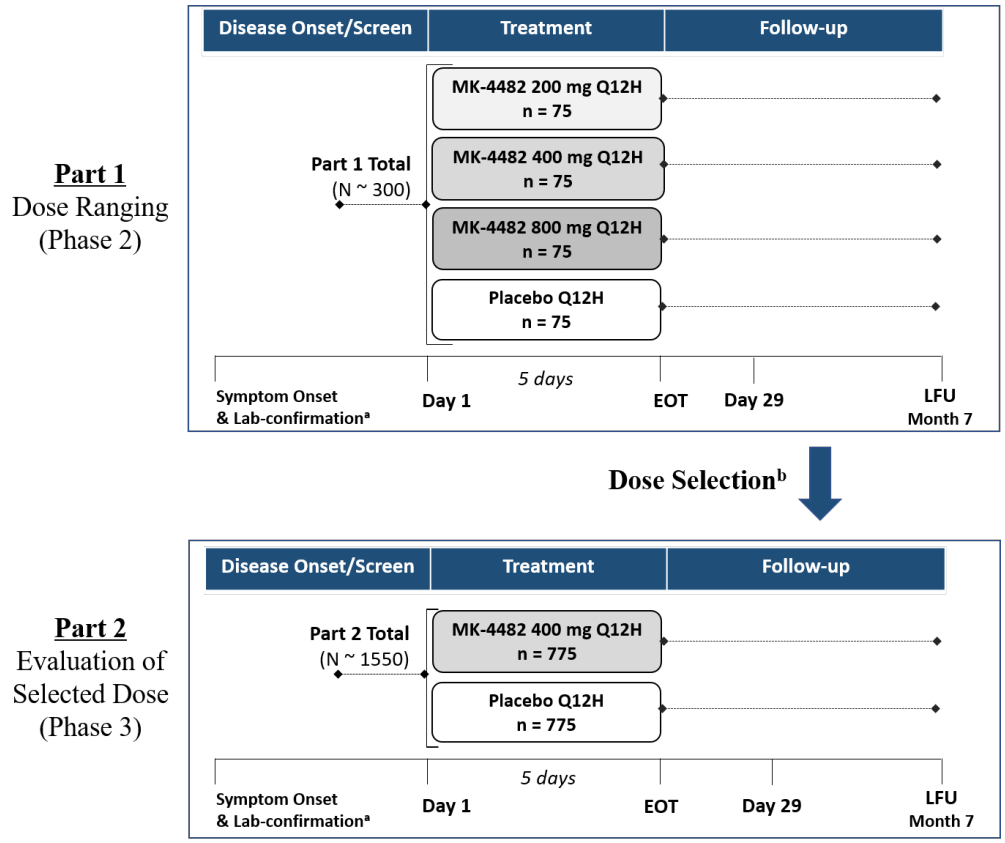
Part 2: 2 groups

Durata della partecipazione:

Ciascun partecipante resterà nello studio per circa un massimo di circa 7 mesi dalla data nella quale 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.

Appendice 1

Disegno di studio



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 ≤5 days prior to randomization (Section 5.1). Calculation of the 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).

Appendice 2

Programma delle attività

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.
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
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),

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]	
											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.
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[g]	SpO_2 and investigator assessment of shortness of breath, and if applicable

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]	
											FiO_2, PaO_2 and supplemental oxygen use.
Hospitalization. Emergency Room, and Other Acute Care Visit Status				X		X	X	X	X	X	
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
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[h]	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

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]	
PK PBMC Sampling[i]						X					Part 1 (PBMC Cohort Only): Pre-dose, 1.5 h post-dose

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

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

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

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

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

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

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

[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 ~50 participants in Part 1 will take part in the PBMC Cohort at selected sites.

Elenco dei centri partecipanti alla sperimentazione		
Titolo Protocollo: "A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Participants ≥18 Years of Age with COVID-19"		
Protocollo Numero: MK-4482-002		**Numero EudraCT** 2020-003368-24
Centro Coordinatore	***Indirizzo***	***Sperimentatore principale***
0600	IRCCS Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani APC Immunodeficienze virali Via Portuense, 292 - 00149 Roma	Dott. Andrea Antinori
Comitato etico unico nazionale dell'INMI Lazzaro Spallanzani – IRCCS c/o Direzione Scientifica dell'I.N.M.I. "Lazzaro Spallanzani" I.R.C.C.S. Via Portuense, 292 - 00149 Roma		Comitato Etico

Centro	***Indirizzo***	***Sperimentatore principale***
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0603	IRCCS Ospedale Policlinico San Martino Clinica Malattie Infettive Largo Rosanna Benzi, 10 - 16132 Genova	Prof. Matteo Bassetti
0604	Policlinico S. Orsola-Malpighi Reparto Malattie Infettive Via Massarenti 11, 40138 - Bologna	Prof. Pierluigi Viale

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0606	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico U.O.C. Malattie Infettive Via Francesco Sforza 35 20122	Dott. Andrea Gori