Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia
Study Number:	MS200569-0026
Merck Compound Number:	M5049
Study Phase:	II
Short Title:	A Phase II Study of M5049 in COVID-19 Pneumonia (ANEMONE)
Coordinating Investigator:	PPD
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Clinical Trials.gov registry identifier:	NCT04448756

Clinical Study Protocol Version: 01 March 2021 / Version 4.0

Replaces Clinical Study Protocol Version: 13 October 2020 / Version 3.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
4.0	Global	01 Mar 2021
3.0	Global	13 Oct 2020
2.0	Global	24 Jul 2020
1.0	Original Protocol	26 May 2020

Protocol Version 4.0 (01 March 2021)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The three major purposes of the amendment are to (1) replace the primary efficacy endpoint, (2) adapt the protocol to the changing landscape and local standard of care for COVID-19 pneumonia, and (3) to align with the new version of the Investigator's Brochure CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Title Page; Appx. 6 Sponsor Signature Page	Updated Medical Responsible	Change of Medical Responsible.
1.1 Synopsis; 3.2 Part B Objectives; 9.1.2 Efficacy Assessments; 10 Statistical Considerations	Replaced primary efficacy endpoint to "time to recovery" and reorganized the statistical considerations, since the original primary endpoint is covered within a secondary endpoint.	At the beginning of the pandemic (data collected from 18 Jan 2020 to 03 Feb 2020), patients hospitalized due to COVID-19 pneumonia on standard of care (SoC) had both a median duration of hospitalization and median time to clinical improvement (≥ 2 points improvement on a 7-category ordinal scale) of 16 days (Cao 2020). In Nov 2020 the final report on the use of remdesivir for treatment of COVID-19 showed that the median time to recovery for patients receiving remdesivir was 10 days (compared to 15-days for patients receiving SoC), and the median time to recovery in patients hospitalized requiring any supplemental oxygen was 7 to 9 days (Beigel 2020).

Section # and Name	Description of Change	Brief Rationale
		In light of this rapidly changing COVID-19 SoC (e.g., remdesivir, other treatment options currently available and those that might be available within the next months), the current primary efficacy endpoint "alive and not requiring supplemental oxygenation at Day 14" may not allow a differentiation between the ANEMONE treatment groups. By contrast, time to recovery is an endpoint that would capture an earlier hospital discharge or shorter duration of hospitalization compared to the beginning of the pandemic. Moreover, time to recovery being a widely used endpoint in COVID-19 clinical trials would facilitate the interpretation of the ANEMONE results. In addition, this new primary endpoint is derived from the same WHO ordinal scale for clinical status assessment as the former primary endpoint, but now all data points collected will be used.
1.1 Synopsis; 3.2 Part B Objectives; 10.4.3.9 Analysis of Total Days in the Hospital and Time to Hospital Discharge	For the objective "to assess the length of hospital stay", a new endpoint "time to hospital discharge from Day 1 through Day 28" was added.	To conduct additional analysis with the collected data and gain a better understanding on hospitalization length.
1.2 SoA.	Emphasized the requirement for study sites to record daily the clinical status by the WHO 9-point ordinal scale during participants hospitalization and the clinical status change after hospital discharge. Added Day 3 and Day 5 as examples of additional study visits to take place if participant is discharge by then (at applicable assessments).	To avoid confusion, making sure that the study sites record data required per protocol.
1.2 SoA.	Added clarification that print-out or paper copy of ECG telemetry is required as source document.	To provide instructions on correct source documentation.
1.2 SoA; Appx. 4 Clinical Laboratory Tests.	Specified electrolytes to be measured, specified time window for Day 1 laboratory tests and added glucose and deleted reticulocytes.	To provide detailed information to sites and clarify discrepancies.
1.2 SoA; 4.1. Overall Design; 5 Study Population; 5.1 Inclusion Criteria; 9.2. Safety and Other Assessments; 13 References.	Added clarification to allow oxygen saturation measurement by pulse oximeter for SpO_2/FiO_2 assessment instead of arterial blood gas (including references) for PaO_2/FiO_2 assessment in sites where arterial blood gas is not standard of care or available.	To adapt to the SoC without impacting on the safety of participants nor study outcome. The correlation between SpO_2/FiO_2 ratio and measured PaO_2/FiO_2 ratio is high when restricted to patients with $SpO_2 \leq 96\%$, as substantial variation of PaO_2 is present in higher SpO_2 range (Brown 2016).

Section # and Name	Description of Change	Brief Rationale
2.2 Background; 4.1 Overall Design; 13 References.	Updated with changes in COVID-19 landscape (e.g., number of SARS-CoV-2 cases).	Update the protocol to the rapid changing COVID-19 landscape.
2.3.1 Risk assessment	CCI	Align with updated Investigator's Brochure.
5.2 Exclusion Criteria; 7.4 Concomitant Therapy; Appx. 3 Medication Guidance	Included SARS-CoV-2 vaccination as exclusion criteria and prohibited therapy through Day 28 (earlier vaccination might be permitted after consultation with Medical Monitor or designee).	SARS-CoV-2 vaccines were not available at the time of previous protocol amendment. Several efficacy endpoints are measured up to Day 28. SARS-CoV-2 vaccination prior to Day 28 could potentially confound the clinical outcome of participants (e.g., less severe disease if vaccinated). Flexibility to allow prior vaccination is however kept by Sponsor, in case of further developments in the rapidly changing COVID-19 landscape.
5.2 Exclusion Criteria	Specified the exclusion of septicemia, as an example of the exclusion criteria (already present in prior versions) uncontrolled active infection.	Clarification to avoid protocol deviations.
5.2 Exclusion Criteria	Included clarification that Investigator might perform tuberculosis test as per clinical judgement.	Clarify that, although not required as Screening assessment, Investigator has flexibility to test for tuberculosis infection as per clinical judgement.
5.2 Exclusion Criteria; 7.4.2 Hemoperfusion; Appx. 3 Medication Guidance	Included hemoperfusion as exclusion criteria and prohibited therapy	Hemoperfusion could reduce the levels of IL-6, Type I IFN or TNFα, which is the expected treatment effect of M5049. Therefore, hemoperfusion would confound the study treatment outcome and therefore is exclusionary and prohibited for this study.
6.1.1.2 Dosing and Administration	Added clarification regarding number of doses and tablets.	To avoid confusion, especially for participants with first dose during the evening.
CCI		
7.4.1 Corticosteroids	Added within Table 3 (Prednisone Equivalent Calculation), the equivalent of 15 mg prednisone and maximum allowed daily dose for other oral corticosteroids.	To facilitate the work of sites, by avoiding calculations to determine prednisone equivalents.
9.4. Treatment of Overdose	Added new section describing the definition and management of overdose	To provide instruction on definition and management of overdose.

Section # and Name	Description of Change	Brief Rationale
10.3 Populations for Analyses; 10.4.3 Analysis of the Secondary Endpoints	Updated the in Intent-to-Treat analyses set, from randomized to treated participants, being analyzed according to the actual treatment received, instead of the treatment randomized to. Changed the time definition for analyses, accordingly, from first dose instead of from randomization.	To account for the eventuality that participants have been treated without being randomized.

ECG = electrocardiogram, COVID 19 = coronavirus disease 2019, FiO2 = fraction of inspired oxygen, PaO2= partial pressure of oxygen, SARS-CoV-2 = severe acute respiratory syndrome coronavirus, SoA = schedule of activities, SpO2 = peripheral capillary oxygen saturation, TNF = tumor necrosis factor.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia

Short Title: A Phase II Study of M5049 in COVID-19 Pneumonia (ANEMONE)

Rationale: Coronavirus disease 2019 (COVID-19) is a new pandemic disease characterized by pulmonary inflammation from infection with severe acute respiratory syndrome coronavirus 2. While antiviral therapies to treat COVID-19 are urgently needed, treatments for severe disease with excessive pulmonary inflammation are also critical to reduce COVID-19 complications leading to increased mortality and to decrease the burden of the rapidly evolving pandemic on the health care system.

In this study, M5049 taken for 14 days will be evaluated in participants who are hospitalized with moderate to severe COVID-19 pneumonia but not on mechanical ventilation. The exploratory Phase II study will evaluate if M5049 inhibition of the host inflammatory response targets, a potential mechanism of virus-associated cytokine storm in COVID-19. Treatment of COVID-19 pneumonia after the immediate host innate and early adaptive immune responses (hospitalization on average occurring 10 days after infectious exposure) could potentially halt progression to severe immunopathology without compromising viral clearance.

Participants will be maintained on standard of care/supportive measures (excluding prohibited medications), and the study will begin with an assessment of safety in 15 participants (Part A) before expanding to a full Phase II clinical evaluation of the study intervention in an additional 135 participants (Part B); the clinical outcomes of participants from Part A will be included in the analyses for Part B.

Objectives and Endpoints:

Part A Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To assess the safety of M5049 compared to placebo.	• Incidence of TEAEs, AESIs, TEAEs leading to treatment discontinuation, and SAEs from Day 1 through Day 60. • Clinically significant changes in laboratory parameters and ECGs from Day 1 through Day 28.
Secondary	
To evaluate clinical deterioration with M5049 compared to placebo.	• Time to ICU (Day 1 through Day 28). • Time to invasive mechanical ventilation (Day 1 through Day 28).

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
To evaluate the change in clinical status with M5049 compared to placebo.	Clinical status from Day 1 through Day 60 (on a 9-point ordinal scale): 0. Uninfected: no clinical or virological evidence of infection. 1. Ambulatory: no limitation of activities. 2. Ambulatory: limitation of activities. 3. Hospitalized, mild disease: hospitalized, no oxygen therapy. 4. Hospitalized, mild disease: oxygen by mask or nasal prongs. 5. Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen. 6. Hospitalized, severe disease: intubation and mechanical ventilation. 7. Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO. 8. Death.
To assess the PK of M5049.	Pharmacokinetic parameters: C_{max}, t_{max}, λ_z, $t_{1/2}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}\infty}$, CL/F, V_z/F, C_{max}/D, $AUC_{0\text{-last}}$/D, $AUC_{0\text{-}12h}$/D, $AUC_{0\text{-}\infty}$/D, $R_{acc}(AUC_{0\text{-}12h})$, and $R_{acc}(C_{max})$ on Day 1 and Day 7.

AESI = adverse event of special interest; CL/F = apparent total body clearance of study intervention following extravascular administration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; PK = pharmacokinetic; R_{acc} = accumulation ratio; RRT = rapid response team; SAE = serious adverse event; TEAE = treatment-emergent adverse event; V_z/F = apparent volume of distribution.

Part B Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary Efficacy	
To evaluate the time to recovery in participants hospitalized due to COVID-19 pneumonia with M5049 compared to placebo.	Time to recovery from Day 1 through Day 28, defined as time from Day 1 to first occurrence of WHO 9-point ordinal scale 3 or less.
Primary Safety	
To assess the safety of M5049 compared to placebo.	• Incidence of TEAEs, AESIs, TEAEs leading to treatment discontinuation, and SAEs from Day 1 through Day 60. • Clinically significant changes in laboratory parameters and ECGs from Day 1 through Day 28.
Secondary	
To assess the proportion of participants free of respiratory support with M5049 compared to placebo.	Alive and not requiring supplemental oxygenation (including any supplemental oxygen, noninvasive or mechanical ventilation and ECMO) through Day 28.
To evaluate the change in clinical status with M5049 compared to placebo.	Clinical status from Day 1 through Day 60 (on a 9-point ordinal scale): 0. Uninfected: no clinical or virological evidence of infection. 1. Ambulatory: no limitation of activities.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	2. Ambulatory: limitation of activities. 3. Hospitalized, mild disease: hospitalized, no oxygen therapy. 4. Hospitalized, mild disease: oxygen by mask or nasal prongs. 5. Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen. 6. Hospitalized, severe disease: intubation and mechanical ventilation. 7. Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO. 8. Death.
To assess normalization of oxygenation status with M5049 compared to placebo in participants who are alive and not on mechanical ventilation.	Time to SpO_2 of ≥ 94% sustained for at least 24 hours in room air from Day 1 through Day 28.
To evaluate the numbers of deaths with M5049 compared to placebo.	All-cause mortality (Day 1 through Day 60).
To evaluate clinical deterioration with M5049 compared to placebo.	• Time to ICU (Day 1 through Day 28). • Time to invasive mechanical ventilation (Day 1 through Day 28). • Time to noninvasive mechanical ventilation (Day 1 through Day 28).
To assess the length of stay in the ICU with M5049 compared to placebo.	Total days in ICU from Day 1 through Day 60.
To assess the length of hospital stay with M5049 compared to placebo.	• Total days in the hospital from Day 1 through Day 60. • Time to hospital discharge from Day 1 through Day 28.
To evaluate modulation of biomarkers of COVID-19 inflammation with M5049 compared to placebo.	Inflammatory biomarkers (CRP, d-dimer, and ferritin) during study period (Day 1 through Day 28).
To evaluate modulation of select biomarkers with M5049 compared to placebo.	Biomarkers (IL-6, TNFα, IL-8) during study period (Day 1 through Day 28).
To evaluate occurrence of relapse with M5049 compared to placebo.	Occurrence of relapse in participants during the study period (if first discharged within the 60-day study period). Relapse refers to worsening oxygenation, with either a positive result of any respiratory pathogenic nucleic acid test, or worsening lesions on chest imaging with re-hospitalization.
To assess occurrence of re-hospitalizations due to COVID-19 disease complications.	Occurrence of re-hospitalization in participants during the study period (if first discharged within the 28-day study period) due to COVID-19 disease complications (Day 5 through Day 60).

AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; RRT = rapid response team; SAE = serious adverse event; SpO_2 = peripheral capillary oxygen saturation; TEAE = treatment-emergent adverse event.

Overall Design: This is a 2-part, Phase II double-blind, randomized, placebo-controlled study to evaluate the safety of and clinical response to M5049 tablets taken orally twice daily for 14 days in participants initially hospitalized because of moderate to severe COVID-19 pneumonia. Participants will be randomized 1:1:1 to receive M5049 50 mg, M5049 100 mg, or placebo twice daily. Part A and Part B of this exploratory study will each consist of an up to 48-hour Screening Period, a 14-day treatment period within a 28-day inpatient and/or outpatient Surveillance period, and then a 32-day inpatient and/or outpatient Safety Follow-up Period. Study participants should be provided the local standard/supportive care but cannot be on antimalarial (chloroquine-related) medications or other immunomodulating drugs (except for corticosteroids – see eligibility and coadministrations specifications). Participants on RECOVERY Trial dexamethasone dosing equivalent of corticosteroids and initiated on antiviral therapy and/or convalescent plasma for treatment of COVID-19 may be eligible for enrollment.

Sites: Site selection will be determined as information becomes available about the epidemiology of COVID-19, and sites will be activated based on the number of local/regional cases and the willingness of local Investigators to participate in the study. More specifically, epidemiology is defined by the evolving number of COVID-19 cases, the number of hospitalizations, and the number of intensive care unit admissions at each site.

Study Duration: The study will last approximately 15 months. Each participant is expected to be on study/in follow-up for 60 to 62 days.

Involvement of Special Committee(s): An internal Independent Data Monitoring Committee will be monitoring safety.

1.2 Schedule of Assessments

Table 1 Schedule of Assessments

All data are to be collected from the participant's clinical chart. If the data are not collected, document circumstances. As per notes column in the table below, data specific to eligibility and the primary endpoints must be collected from the participant if not available from the participant's chart.

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Screening and Randomization-only Assessments															
Informed consent	X														
Inclusion/ exclusion criteria	X	X													Participant eligibility to be confirmed on Day 1, if Screening and Day 1 occur on different dates.
Demographics	X														
Past and current medical conditions (includes substance usage), medications	X														Substances: drugs, marijuana, alcohol, and tobacco. Medication history in the 1 month prior to Screening should be collected.
Influenza testing	X													X	Collected per local guidelines (e.g., influenza season).

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Tuberculosis assessment	X													X	Data collected from chart: TB status is to be documented per local guidelines. Evaluations to be performed by local laboratory.
IWRS	X	X													Will be used to assign unique participant numbers, allocate participants to study intervention group, and allocate study intervention at the randomization visit.
Randomization		X													On Day 1, eligibility review of data completed, if the participant remains eligible, randomization occurs followed by receipt of blinded study intervention assignment.
Serum virology (hepatitis B and C screening, HIV)	X														Data collected from chart: virology status is to be documented per local guidelines. A positive test result is NOT exclusionary but for participant management. Evaluations to be performed by local laboratory.
Urine for drugs of abuse	X													X	Data collected from chart: status to be documented per local guidelines. A positive test result for nonprescribed drugs is NOT exclusionary but for participant management. Evaluations to be performed by local laboratory.

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Clinical Assessments and Study Intervention															
Study intervention administration		←Throughout 14 days→							X					X	Every 12 hours ± 2 hours for 14 days (4 tablets in the morning and 4 tablets in the evening).
Study intervention accountability		←----------Throughout (daily)---------→												X	Date and time of study intervention administration should be recorded daily, if discharged before EoT, date and time to be recorded on diary card.
Clinical surveillance scoring (9-point ordinal scale)		←----------**Once daily during hospitalization** (incl. predose on Day 1) **and at the time of hospital discharge**. After hospital discharge, then at study visits (e.g., Days 3, 5, 7, 10, 14, 21, 28, 44, and 60) and clinical status change----------→													Record each day throughout hospitalization at the first assessment of a given study day and at the time of hospital discharge; after participant is discharged, either via telemedicine contact or by return to study site at the times indicated only. The scale includes information such as hospitalization discharge, ICU stay, mechanical ventilation.
Adverse event review	←----------Throughout----------→														Record each day at approximately the same time throughout hospitalization; if participant is discharged, either via telemedicine contact or by return to study site at the times indicated only.
Concomitant medication/ procedure review	←----------Once daily during hospitalization. If discharged, then at study visits (e.g., Days 3, 5, 7, 10, 14, 21, 28, 44, and 60)----------→														Document what is available from the participant's chart. Record each day at approximately the same time throughout hospitalization; if participant is discharged, either via telemedicine contact or by return to study site at the times indicated only.

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Complete physical examination	X	X						X	X					X	Data may be collected from chart but must be verified by Clinical Investigator.
Brief physical examination			X		X	X	X			X	X				Data may be collected from the chart but must be verified by a Clinical Investigator (unless participant is discharged).
Vital signs, weight, height	←---**Once daily** during hospitalization (incl. predose on Day 1). --→ If discharged, then at study visits (e.g., Days 3, 5, 7, 10, 14, 21, and 28)											X	X	X	Vital signs: body temperature, blood pressure, respiration rate, pulse (unless participant is discharged). Weight will be recorded at Screening, relapse admission, and Day 28 (if feasible). Height will be recorded at Screening only. Record each day at approximately the same time throughout hospitalization. All data collected from the chart. After discharge, record only at times indicated if/when participant returns to study site.
SpO_2 saturation and FiO_2 (or liters of O_2)	←---**Once daily** during hospitalization (incl. predose on Day 1). --→ If discharged, then at study visits (e.g., Days 3, 5, 7, 10, 14, 21, and 28)													X	SpO_2 measured by pulse oximetry; record each day at approximately the same time of day throughout hospitalization and after discharge, at times indicated only if participant returns to study site (refer to Section 5).
SpO_2 saturation in room air for 24 hours	←-----Record SpO_2 measures after the first SpO_2 ≥ 94% in room air during hospitalization----------→													X	At any time prior to hospital discharge when SpO_2 ≥ 94% in room air for the first time, **document if participant maintains this status 24 hours later** (unless participant is discharged).

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Laboratory Assessments															
COVID-19 NAT	X	←----------Throughout----------→													Documentation of COVID-19 + laboratory test on hospital admission, whenever collected throughout the study, and at discharge if participant has any symptoms consistent with COVID-19 disease per hospital guidelines. Evaluations to be performed by local laboratory.
Serum or urine pregnancy test	X							X			X		X[a]	X	Women of childbearing potential only. Evaluations to be performed by local laboratory. [a]Done only if seen at study site.
Arterial blood gas	X							X	X		X			X	Arterial blood gas must be performed, according to SoC per local guidance, at Screening only if not available from the participant chart; at other times will be collected from the chart, if available.
Chest imaging documentation	X		←----------Throughout if imaging results available for documentation----------→											X	Chest imaging (chest X-ray, CT scan) per local guidelines is acceptable. If chest imaging is not available during Screening, please discuss with Medical Monitor or designee regarding evidence of probable COVID-19 pneumonia for study participant eligibility.

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
12-lead ECG	X	X		X		X		X	X		X				Screening ECG, Day 1, Day 3, and Day 7 are required. ECG should be performed 1 to 2 hours postdose during the treatment period. After Screening, telemetry is allowed for QTc measurement; print-out or a paper copy is required as source document.
12-lead ECG	←----------Throughout----------→														Record, document, and store when legible all clinically indicated ECG tracings at any time.
Routine hematology, chemistry	X	←----**Once daily** during hospitalization (incl. predose on Day 1). If discharged, then at study visits (e.g., Days 3, 5, 7, 10, 14, 21, 28) if participant returns to study site-------→												X	WBC with differential: numbers and percentage, Hgb, HCT, platelets; electrolytes, BUN, Cr, eGFR, albumin, glucose, TP, ALT, AST, CK (unless participant is discharged). See Appendix 4. Labs obtained within 24 hours of Day 1 can be used for Day 1 assessments. Record results daily from the participant's chart (unless participant is discharged). Evaluations to be performed by local laboratory.
Inflammatory biomarkers tested in COVID-19 (CRP, d-dimer, and ferritin)	X	X		X		X	X	X	X		X			X	Record any available results (and time sample collected) from the participant's chart on days indicated (unless participant is discharged). **Part A and Part B**: Evaluations to be performed by local laboratory.

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Predose PK		X		X		X									PK blood collection must be done within 60 minutes prior to dose administration. Identify and record the time of the closest meal consumed prior to the study intervention administration, i.e., when the last meal was finished before the study intervention administration (unless participant is discharged). PK evaluations to be performed by central laboratory.

Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Postdose PK		X		X		X									See PK instructions for sampling window. **Part A** Day 1: 1, 2, 6, and 12 hours postdose (12 hours postdose sampling must be done prior to the second dose on Day 1). **Part A** Day 7: 1, 2, and 6 hours postdose. **Part B** Day 1: 1-2 hours postdose, 4-6 hours postdose and 8-12 hours postdose (8-12 hours postdose sampling must be done prior to the second dose on Day 1). **Part B** Day 3 and Day 7: 1-2 hours postdose and 4-6 hours postdose. For 1-hour postdose PK, identify and record the time of the closest meal consumed after the study intervention administration, i.e., when the first meal started after study intervention administration (unless participant is discharged). PK evaluations to be performed by central laboratory. **Note:** Selected sites for **Part A and Part B** will not perform sampling at 4 to 6 hours and 8 to 12 hours postdose on Day 1, Day 3, or Day 7.

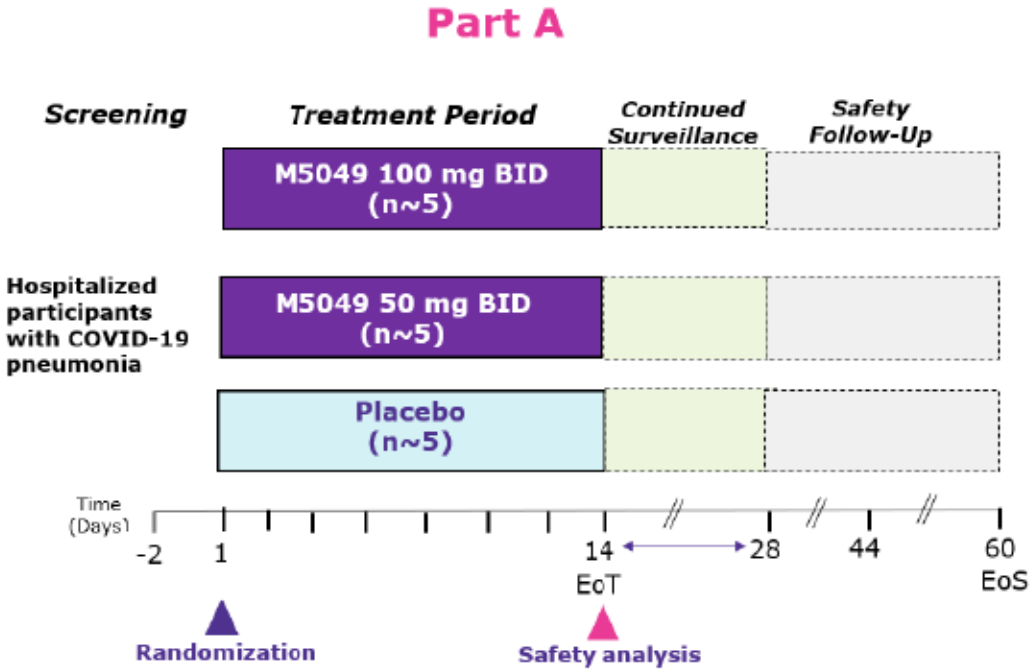
Assessments and Procedures	SCR	Intervention Period (Days)								Continued Surveillance		Safety Follow-up			Notes
	(up to 48 hours before Day 1)							HD/ ET	EoT			☎	EoS ☎	Relapse Admission[a]	HD assessments should occur if participant discharged after Day 3 and before Day 14. ET (early termination of treatment) Visit should occur within + 24 hours of treatment discontinuation.
Study Day		1	2	3	5	7	10		14	21	28	44	60	5 to 60	
Visit Window			± 6 h		± 12 h		± 24 h			+ 2 days		± 5 days	± 7 days	± 6 h	
Serum biomarkers		X		X		X		X	X		X			X	Evaluations to be performed by central laboratory. Day 1 sample must be collected prior to study intervention administration. Record time each sample collected. E.g., other cytokines, anti-SARS-CoV-2 antibodies; collect unless participant is discharged and not seen at study site. **Day 3 sample collected in Part B only.**
CCI															

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CK = creatinine kinase, COVID-19 = coronavirus disease 2019, Cr = creatinine, CRP = C-reactive protein, CT = computed tomography, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate; EoS = End of Study, EoT = End of Treatment, ET = Early Termination of treatment, FiO_2 = fraction of inspired oxygen, HCT = hematocrit, HD = hospital discharge, Hgb = hemoglobin, HIV = human immunodeficiency virus, ICU = intensive care unit; IFN = interferon, IWRS = Interactive Web Response System, NAT = nucleic acid test, PK = pharmacokinetic, RNA = ribonucleic acid, SARS-CoV-2 = severe acute respiratory syndrome coronavirus, SCR = Screening, SoC = standard of care, SpO_2 = peripheral capillary oxygen saturation, TB = tuberculosis, TP = total protein, WBC = white blood cell.

a See Section 4.8 for relapse definition.

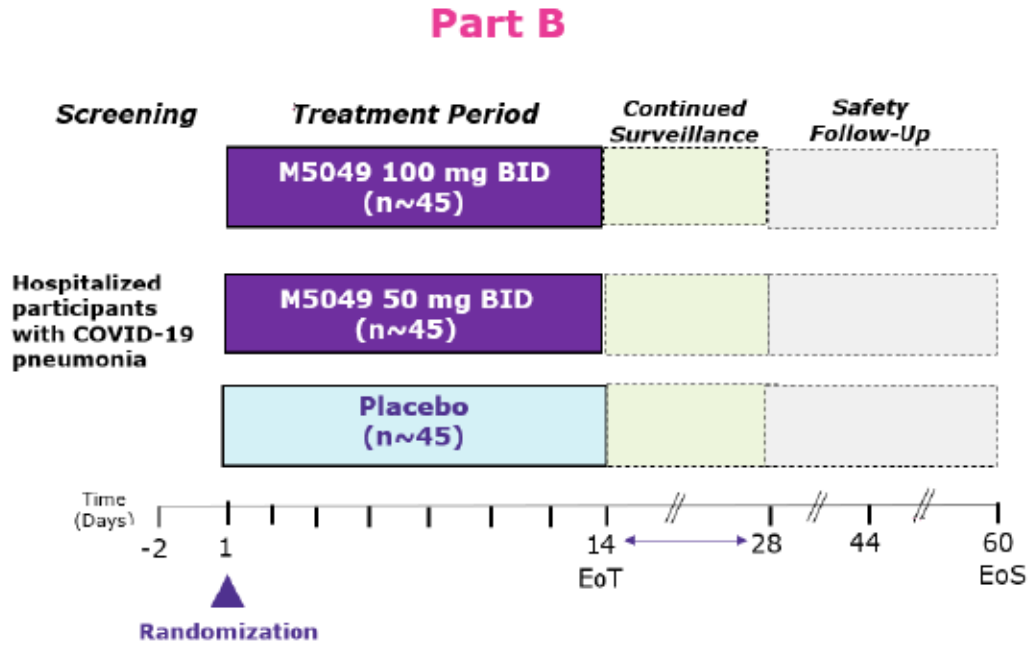
1.3 Study Schema

Figure 1 Study Schema (Part A)



BID = twice daily; COVID-19 = coronavirus disease 2019; EoS = End of Study; EoT = End of Treatment.

Figure 2 Study Schema (Part B)



BID = twice daily; COVID-19 = coronavirus disease 2019; EoS = End of Study; EoT = End of Treatment.

2 Introduction

2.1 Study Rationale

Coronavirus disease 2019 (COVID-19) is a new pandemic disease characterized by pulmonary inflammation from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a single-stranded ribonucleic acid (ssRNA) virus related to both SARS-CoV-1, which caused severe acute respiratory syndrome (SARS) disease in 2002/03, and Middle East respiratory syndrome coronavirus. While antiviral therapies to treat the COVID-19 are urgently needed, treatments for severe disease with excessive pulmonary inflammation are also critical to reduce COVID-19 complications leading to increased mortality and to decrease the burden of the rapidly evolving pandemic on the health care system (Feldmann 2020). Given that the immunopathology in reaction to SARS-CoV-2 infection is contributing to the high rate of morbidity and mortality, host-directed immunomodulatory approaches are also being evaluated (Mehta 2020, Stebbing 2020).

In this exploratory Phase II study, a 14-day course of M5049, a potent, selective toll-like receptor (TLR) 7/8 antagonist will be evaluated. The optimal timing of M5049 dosing is hypothesized to be after the participant's initial antiviral response (so as to not interfere with initial host control or clearance of the virus) and when increasing pulmonary inflammation is signaling an overly amplified host inflammatory response. Treatment of COVID-19 pneumonia after the immediate host innate and early adaptive immune responses could potentially halt progression to severe immunopathology without compromising viral clearance (Siddiqui 2020).

The safety and clinical response to orally-administered M5049 will be evaluated for 14 days in participants with moderated to severe COVID-19 pneumonia who are maintained on local standard of care and hospitalized without the need for mechanical ventilation. The 2-part study is a randomized, double-blind, placebo-controlled design. The study design and participant safety monitoring are based on M5049 data obtained from the first-in-human (FIH) Phase I single ascending dose and 14-day multiple ascending dose healthy volunteer study, nonclinical evaluations of M5049, and the timing of other anti-inflammatory agents for treatment of COVID-19 pneumonia. M5049 demonstrates dose-proportional pharmacokinetics (PK), has a half-life of approximately 7 to 11 hours, and is mainly metabolized by aldehyde oxidase, not the common cytochrome P450 enzymes.

The small molecule, M5049, is a dual TLR7/8 antagonist shown to specifically inhibit the activity of various TLR7/8 ligands such as ssRNA, certain GU-rich micro ribonucleic acid (RNA), and small molecule receptor agonists. TLR7/8 is expressed in the endosomes of cells with innate immune function, where activation by ssRNA viruses (e.g., SARS-CoV-2) stimulates secretion of Type I interferons (IFNs) and proinflammatory cytokines (interleukin [IL] 6, tumor necrosis factor alpha [TNFα], and others), cellular maturation and activation of other host immune mechanisms (Chow 2018, Li 2013).

Two dose levels of M5049, 100 mg twice daily and 50 mg twice daily, will be evaluated against placebo. The dose selection is guided by PK and CCI [redacted] data from the Phase I healthy volunteer study and by the doses found to be efficacious in preclinical lupus animal

models. In the Phase I study, M5049 suppressed secretion of ex vivo-stimulated cytokines including IL-6, TNFα, and IFNα in an exposure-dependent manner. Based on these data, preliminary modeling and simulations projected 100 mg twice daily would suppress ex vivo-stimulated IL-6 production by 90% in 87% of healthy volunteers, and 50 mg twice daily would suppress IL-6 production by 50% in 90% of healthy volunteers. As the magnitude of TLR7/8 inhibition required for suppression of the cytokine production in COVID-19 patients is unknown, and the M5049 safety profile has not been described in this patient population, clinical and pharmacologic evaluation of both the 50 mg and 100 mg twice daily doses in participants with COVID-19 pneumonia is viewed as justified.

Given the available data for M5049 in humans, a 2-part, placebo-controlled study is deemed necessary. The study will begin with an assessment of safety in 15 participants (Part A) before expanding to a full Phase II clinical evaluation of the study intervention in an additional 135 participants (Part B). Study participants may be maintained on supportive care but should not be simultaneously enrolled in other COVID-19 studies. Other immunomodulating drugs should not be used with M5049 (with the exception of corticosteroids per eligibility and concomitant medications requirements) unless the participant decompensates, (e.g., requires mechanical ventilation).

Addition of an antimalarial or anti-inflammatory medication would undermine the evaluation on the role of M5049 for COVID-19 pneumonia and the validity of the study. The study participant's primary managing clinician may place the participant on the locally preferred antiviral therapy and/or convalescent plasma (as previously determined at a site level and with Sponsor notification before study implementation). Part A participants will be stratified by presence/absence of obstructive lung disease. Part B participants will be stratified based on (1) the use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, (2) the use of antiviral therapy including convalescent plasma (presence or absence) within 48 hours prior to randomization, and (3) country.

This exploratory, Phase II, proof-of-concept study will evaluate participants with moderate to severe COVID-19 pneumonia receiving M5049 compared to placebo on the clinical response defined as the proportion of participants who are alive and not requiring supplemental oxygenation (including noninvasive or mechanical ventilation and ECMO) at Day 14. The participants will continue to be followed to document their vital status and need for oxygen or ventilatory support through Day 28 in the M5049 compared to placebo groups. In addition to following other clinical parameters, such as WHO ordinal scale, data on time to peripheral capillary oxygen saturation (SpO_2) $\geq 94\%$ sustained for at least 24 hours in room air through Day 28 will also be collected and evaluated to better inform future study intervention evaluation in this population. Participants will be followed through Day 60 for vital signs.

2.2 Background

2.2.1 Purpose of Study

Coronaviruses are positive-sense single-stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic coronaviruses capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus.

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS-CoV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (Chan 2020). SARS-CoV-2 has now resulted in a pandemic infecting over 100 million people worldwide with a case fatality rate of around 2.1% as of end of January 2021 (WHO 2021).

There is an urgent public health need for rapid development of novel interventions. Efforts continue to expand in evaluating existing and novel antivirals and therapeutic strategies that could be successful in treating COVID-19 disease.

2.2.2 Potential Therapeutics

There are several antivirals and immunomodulating drugs under investigation for COVID-19. The medical science is rapidly evolving. and e.g., the US FDA approved the use of remdesivir for the treatment of SARS-CoV-2 infection in October 2020 and has provided Emergency Use Authorization to a number of treatments (e.g., monoclonal antibodies as antiviral treatments targeting SARS-CoV-2 infection), however, access to these medications for all hospitalized patients with COVID-19 pneumonia is yet to be determined.

M5049 is hypothesized to be complementary to antiviral therapies and to be evaluated for prevention and treatment of the cytokine storm phase of disease in participants hospitalized with moderate to severe COVID-19 pneumonia; other investigational anti-inflammatories are contraindicated unless the participant requires invasive mechanical ventilation. Antivirals including convalescent plasma will be allowed as background therapy (according to local standard of care and with previous approval by the site Principal Investigator [PI] and the Sponsor per each site).

2.3 Risk/Benefit Assessment

CCI

[redacted]

2.3.2 Risks to Privacy

Participants will be asked to provide personal health information. All attempts will be made to keep this information confidential within the limits of the law. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical site. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the personal health information that is collected.

Any publications from this study will not use information that will identify participants by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), Sponsor, and the pertinent Regulatory Authorities.

2.3.3 Known Potential Benefits

The candidate therapeutic under evaluation may or may not improve clinical outcome of an individual adult participant with COVID-19 who participates in this study. However, there is potential benefit to society from their participation in this study resulting from insights gained about the study intervention and whether or not the mechanism of action of the drug impacts the natural history of the disease.

3 Objectives and Endpoints

3.1 Part A Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To assess the safety of M5049 compared to placebo.	• Incidence of TEAEs, AESIs, TEAEs leading to treatment discontinuation, and SAEs from Day 1 through Day 60. • Clinically significant changes in laboratory parameters and ECGs from Day 1 through Day 28.
Secondary	
To evaluate clinical deterioration with M5049 compared to placebo.	• Time to ICU (Day 1 through Day 28). • Time to invasive mechanical ventilation (Day 1 through Day 28).
To evaluate the change in clinical status with M5049 compared to placebo.	Clinical status from Day 1 through Day 60 (on a 9-point ordinal scale): 0. Uninfected: no clinical or virological evidence of infection. 1. Ambulatory: no limitation of activities. 2. Ambulatory: limitation of activities.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	3. Hospitalized, mild disease: hospitalized, no oxygen therapy. 4. Hospitalized, mild disease: oxygen by mask or nasal prongs. 5. Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen. 6. Hospitalized, severe disease: intubation and mechanical ventilation. 7. Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO. 8. Death.
To assess the PK of M5049.	Pharmacokinetic parameters: C_{max}, t_{max}, λ_z, $t_{1/2}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}\infty}$, CL/F, V_z/F, C_{max}/D, $AUC_{0\text{-last}}$/D, $AUC_{0\text{-}12h}$/D, $AUC_{0\text{-}\infty}$/D, $R_{acc}(AUC_{0\text{-}12h})$, and $R_{acc}(C_{max})$ on Day 1 and Day 7.

AESI = adverse event of special interest; CL/F = apparent total body clearance of study intervention following extravascular administration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; PK = pharmacokinetic; R_{acc} = accumulation ratio; RRT = rapid response team; SAE = serious adverse event; TEAE = treatment-emergent adverse event; V_z/F = apparent volume of distribution.

3.2 Part B Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary Efficacy	
To evaluate the time to recovery in participants hospitalized due to COVID-19 pneumonia with M5049 compared to placebo.	Time to recovery from Day 1 through Day 28, defined as time from Day 1 to first occurrence of WHO 9-point ordinal scale 3 or less.
Primary Safety	
To assess the safety of M5049 compared to placebo.	• Incidence of TEAEs, AESIs, TEAEs leading to treatment discontinuation, and SAEs from Day 1 through Day 60. • Clinically significant changes in laboratory parameters and ECGs from Day 1 through Day 28.
Secondary	
To assess the proportion of participants free of respiratory support with M5049 compared to placebo.	Alive and not requiring supplemental oxygenation (including any supplemental oxygen, noninvasive or mechanical ventilation and ECMO) through Day 28.
To evaluate the change in clinical status with M5049 compared to placebo.	Clinical status from Day 1 through Day 60 (on a 9-point ordinal scale): 9. Uninfected: no clinical or virological evidence of infection. 10. Ambulatory: no limitation of activities. 11. Ambulatory: limitation of activities. 12. Hospitalized, mild disease: hospitalized, no oxygen therapy. 13. Hospitalized, mild disease: oxygen by mask or nasal prongs.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	14. Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen. 15. Hospitalized, severe disease: intubation and mechanical ventilation. 16. Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO. 17. Death.
To assess normalization of oxygenation status with M5049 compared to placebo in participants who are alive and not on mechanical ventilation.	Time to SpO_2 of ≥ 94% sustained for at least 24 hours in room air from Day 1 through Day 28.
To evaluate the numbers of deaths with M5049 compared to placebo.	All-cause mortality (Day 1 through Day 60).
To evaluate clinical deterioration with M5049 compared to placebo.	• Time to ICU (Day 1 through Day 28). • Time to invasive mechanical ventilation (Day 1 through Day 28). • Time to noninvasive mechanical ventilation (Day 1 through Day 28).
To assess the length of stay in the ICU with M5049 compared to placebo.	Total days in ICU from Day 1 through Day 60.
To assess the length of hospital stay with M5049 compared to placebo.	• Total days in the hospital from Day 1 through Day 60. • Time to hospital discharge from Day 1 through Day 28.
To evaluate modulation of biomarkers of COVID-19 inflammation with M5049 compared to placebo.	Inflammatory biomarkers (CRP, d-dimer, and ferritin) during study period (Day 1 through Day 28).
To evaluate modulation of select biomarkers with M5049 compared to placebo.	Biomarkers (IL-6, TNFα, IL-8) during study period (Day 1 through Day 28).
To evaluate occurrence of relapse with M5049 compared to placebo.	Occurrence of relapse in participants during the study period (if first discharged within the 60-day study period). Relapse refers to worsening oxygenation, with either a positive result of any respiratory pathogenic nucleic acid test, or worsening lesions on chest imaging with re-hospitalization.
To assess occurrence of re-hospitalizations due to COVID-19 disease complications.	Occurrence of re-hospitalization in participants during the study period (if first discharged within the 28-day study period) due to COVID-19 disease complications (Day 5 through Day 60).
[redacted]	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
evaluate WBC as markers for disease severity.	

AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; C_{trough} = predose observed concentration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IFN = interferon; CCI; PK = pharmacokinetic; CCI RRT = rapid response team; SAE = serious adverse event; SARS-CoV = severe acute respiratory syndrome coronavirus; SpO_2 = peripheral capillary oxygen saturation; TEAE = treatment-emergent adverse event; WBC = white blood cell.

4 Study Design

4.1 Overall Design

This is a 2-part, Phase II double-blind, randomized, placebo-controlled study to evaluate the safety of and clinical response to M5049 tablets taken orally twice daily for 14 days in participants initially hospitalized because of moderate to severe COVID-19 pneumonia. Participants will be followed to assess those who are alive and not requiring supplemental oxygenation (including noninvasive or mechanical ventilation and ECMO) at Day 14 in the M5049 compared to placebo groups. Participants will continue to be followed to document their need for oxygen or ventilation support and clinical status through Day 28, and complete safety follow-up (and vital signs) through Day 60.

Eligible study participants, who test SARS-CoV-2 positive as established by local guidelines, will not be on mechanical ventilation and must have an $SpO_2 < 94\%$ in room air and partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≥ 150 with a maximum FiO_2 0.4.

Part A participants will be stratified by presence/absence of obstructive lung disease. Part B participants will be stratified based on (1) the use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, (2) the use of antiviral therapy including convalescent plasma (presence or absence) within 48 hours prior to randomization, and (3) country.

If the attending hospital physician anticipates the participant may require mechanical ventilation in the first 24 hours of entering in the study, the participant should not be approached for consent. Study participants should be provided the local standard/supportive care but cannot be on chloroquine-related medications or other immunomodulating drugs to enter the study (the exception is that if corticosteroids are initiated prior to or during the study Screening period [and prior to randomization], they are allowed but they must not be higher than 40 mg prednisone per day based on the dosing regimen and schedule used in the RECOVERY Trial (NCT04381936; Horby 2020). If the local standard of care includes use of an antiviral therapy (and/or convalescent plasma), which has been uniformly agreed to by the site, has the permission of the local Principal Investigator, and the Sponsor has been notified, participants on antiviral therapy may be eligible for enrollment.

Participants will be randomized 1:1:1 to receive M5049 50 mg, M5049 100 mg, or placebo tablets orally twice daily (every 12 hours). Part A and Part B of this exploratory study will each consist of an up to 48-hour Screening Period, a 14-day treatment period at the start of the overarching 28-day inpatient and/or outpatient Surveillance period, and up to a 32-day inpatient and/or outpatient Safety Follow-up Period. Details of management of potential drug toxicity and study intervention discontinuation for the participant are provided in Section 8.1.

Part A of the study will pause enrollment after 15 participants have been randomized to the study-defined intervention (see Figure 1). Unless a participant is terminated from the study as a treatment failure or for safety reasons, and after consultation with the Sponsor, participants randomized in Part A may be replaced if they have discontinued the study before completing 14 days of treatment. An internal Independent Data Monitoring Committee (IDMC) that provides ongoing surveillance of participant safety will review available safety and clinical outcomes data and will provide a recommendation whether or not the study is safe to proceed to Part B. Details of the review may be found in the IDMC charter.

Part B of the study will enroll approximately 135 participants (see Figure 2). Detail analyses performed for the purpose of risk/benefit monitoring, the full membership, mandate, and processes of the IDMC may be found in the IDMC charter. The IDMC will decide whether or not to continue the study as per protocol or make recommendations as specified in the IDMC charter. Unless there is reason to halt the study based on IDMC recommendations, a total of 150 participants are planned to be randomized and followed in Part A and Part B of this study.

After consent of the participant (and/or if necessary, the participant's legally designated guardian by teleconference as allowable by local laws), data for this study will be obtained from the participant's outpatient, emergency room and/or hospital records. Data to assess eligibility will be obtained in this manner unless the data are unavailable; then the procedures as specified in Table 1 must be performed to determine eligibility. Other data not available from the participant's records may be obtained from the participant, only without interference in the participant's clinical management and with permission of the participant's primary attending clinician (e.g., physician, physician assistant, or nurse practitioner). If data are not obtainable, documentation as to why should be provided.

Participants will be administered one of two dose levels of the study intervention, M5049, or matching placebo tablets, orally every 12 hours, after any required study safety assessments/procedures (other than post-treatment PK sampling and ECGs) are performed. Unless otherwise specified (e.g., arterial blood gas at Screening according to standard of care per local guidance), all scheduled blood and clinical assessments will be obtained from the study participant's record as the assessment would be part of standard of care for managing COVID-19 pneumonia in the hospital. A small number of research blood samples (e.g., PK, serum, and CCI biomarker samples) will be collected at Day 1, Day 3, Day 7, Day 14, and Day 28 (at the time points indicated in Table 1) only if the participant remains in the hospital. As those assessments are to guide further study intervention development and evaluation and are not part of standard of care for COVID-19, the sample assessments will not be performed real-time.

All participants who are discharged before Day 14 will be provided with a diary card (see Section 6.1.1.2) and have telemedicine visits in locales where it is legally acceptable and if an

outpatient return visit is not feasible. Outpatient participants, who prematurely discontinue the study intervention, upon notification of their study site, should preferably continue the study follow-up schedule for safety; or if necessary, return as soon as possible for an Early Termination (ET) Visit.

4.2 Scientific Rationale for Study Design

This Phase II study aims to evaluate the potential of M5049 to treat participants hospitalized with moderate to severe COVID-19 pneumonia before requiring mechanical ventilation. M5049, a selective TLR7/8 inhibitor, could potentially suppress excess cytokine production (e.g., IL-6, TNFα) that is induced by ssRNA SARS-CoV-2 in participants with COVID-19 pneumonia. The timing of M5049 intervention is proposed to be after the participant's initial antiviral response (so as to not interfere with initial host control or clearance of the virus) in those who subsequently have increasing pulmonary inflammation and distress, when the study intervention may decrease an overly amplified host inflammatory response representing antibody-dependent elaboration of cytokine storm (Siddiqui 2020). The study design is informed by the data on M5049 generated in the FIH Phase I healthy volunteer PK study and preclinical animal model experiments.

Observation of an association of M5049 treatment with improvement of clinical status (e.g., no longer requiring supplemental oxygenation or ventilation support, hospital discharge, etc.) in participants with COVID-19 pneumonia would provide support for further clinical development of M5049 for COVID-19 (Cao 2020, Van den Boom 2020, Wang 2020, Zhou 2020, Guan 2019).

4.3 Justification for Dose

The proposed doses of M5049 for the study are 50 mg or 100 mg twice daily in a new tablet formulation without food restriction. The dose levels to be evaluated are selected based on safety, PK, and PD (inhibition of ex vivo-stimulated IL-6 cytokine secretion) observed in the single and multiple ascending dose (FIH) study in healthy participants. Pharmacokinetic results indicated dose-proportionality of maximal concentrations and overall exposure (AUC) in the investigated dose range (1 to 200 mg single or as daily dose) with a terminal half-life of 7 to 11 hours.

The following data were considered when determining the doses of M5049 for this study:

- Preliminary modeling and simulations based on the observed PK and PD (inhibition of ex vivo-stimulated IL-6 cytokine secretion) in the FIH study suggest that M5049 trough concentrations at steady-state ($C_{min,ss}$) will remain above the IC_{90} in 87.3% of the participants who receive a 100 mg twice daily dose and 31.2% of participants who receive a 50 mg twice daily dose. For both the 50 mg and 100 mg twice daily doses, M5049 trough concentrations will remain above the IC_{50} in more than 90% of participants.
- The FIH healthy volunteer study evaluated an oral M5049 solution under fasted condition except for a small food effect cohort. The current study will use a tablet formulation without food restriction. M5049 is considered as a Biopharmaceutics Classification System Class 1 compound and tablet formulation showed very rapid dissolution profile. It is expected that the new tablet formulation has similar exposure compared to the oral solution used in the FIH study.

- The expected $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ at 100 mg twice daily without food restriction remains well below the exposures at the no observed adverse effect levels in 4-week nonclinical toxicology study in dog with at least 10-fold safety margin.
- The AUC was increased by 33% and C_{max} was decreased by 11% under fed condition compared to fasted conditions.

Based on the above considerations, both the 50 mg and 100 mg twice daily doses in the new tablet formulation without food restrictions may provide the opportunity to observe a PD effect (i.e., suppression of inflammatory biomarkers, e.g., IL-6) and clinical response in participants with COVID-19 pneumonia while also maintaining acceptable safety margin.

4.4 Early Hospital Discharge Assessments

A participant who is discharged from the hospital after Day 3 and before Day 14 should have the same assessments as ET of study treatments as per the schedule of assessments (Section 1.2), but continue study treatment as an outpatient until Day 14.

4.5 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in Table 1.

The end of the study is defined as the date of the last visit of the last participant or the last scheduled procedure shown in Table 1 for the last participant globally.

4.6 Early Termination of Treatment

When a participant is discontinued or withdraws from treatment before Day 14, the participant should complete the ET assessments as soon as possible and revert to the same study schedule (Table 1) based on the participant's Day 1; the participant should be encouraged to continue follow-up for safety and clinical assessments outlined in Table 1 through Day 60.

4.7 Surveillance, Safety and End of Study Visits

Since important secondary endpoints are evaluated at Day 28, surveillance assessments occur between Day 14 and Day 28, which may be distinguished from continued safety follow-up to Day 60. If a participant is discharged and not seen at the study site (as may be the requirement of the state and/or local hospital/clinic), every effort should be made to collect what information is available over the phone or through a telemedicine contact after hospital discharge.

As the majority of study participants should be discharged by Day 28, assessments for visits at Day 44 and Day 60 (End of Study) are anticipated to be by telemedicine or phone contact.

4.8 Relapse Definition

A participant who has been discharged from the hospital with an SpO_2 of $\geq 94\%$ sustained for at least 24 hours in room air, but who must be re-admitted before Day 60 due to worsening oxygenation (an $SpO_2 < 94\%$ in room air), with either a positive result of respiratory pathogenic nucleic acid test (NAT) or worsening lesions on chest imaging (compared to the participant's same modality of chest imaging [chest X-ray or computed tomography {CT}] at discharge, if available) will be counted as a respiratory relapse. For SARS-CoV-2 or any other infection, record the anatomic site from which the infection was assessed in addition to the infecting agent. The assessments in Table 1 for the Relapse Visit will be performed, and assessments in Table 1 will be resumed based on the participant's Day 1 of study entry.

5 Study Population

Hospitalized patients (≥ 18 to ≤ 75 years of age) with COVID-19 pneumonia not on mechanical ventilation with an $SpO_2 < 94\%$ in room air AND able to maintain a $PaO_2/FiO_2 \geq 150$ (or equivalent $SpO_2/FiO_2 \geq 190$) with a maximum FiO_2 0.4. These readings may be obtained after exertion by the participant. Patients on continuous positive airway pressure should have assessments for eligibility performed while awake.

The correlation between SpO_2/FiO_2 ratio and measured PaO_2/FiO_2 ratio is high when restricted to patients with $SpO_2 \leq 96\%$, as substantial variation of PaO_2 is present in higher SpO_2 range (Brown 2016). The relationship between SpO_2/FiO_2 and PaO_2/FiO_2 was described by the following equation: $S/F = 64 + 0.84 \times (PaO_2/FiO_2)$ (Rice 2007). Maximum inhaled percentage oxygenation (FiO_2 0.4) means patients should be on a nasal cannula or face mask without nonrebreather at ≤ 5 L/min (see guidance Table 2). (Note: face mask with nonrebreather will have a higher estimated FiO_2 [i.e., > 0.40] and therefore would be ineligible).

Table 2 Flow Rates Translated as Inhaled Oxygen Percentage (i.e., Fraction of Inspired Oxygen)

Device	Flow Rates	Delivered O_2[a]
Nasal cannula	1 L/min	21%-24%
	2 L/min	25%-28%
	3 L/min	29%-32%
	4 L/min	33%-36%
	5 L/min	37%-40%
	6 L/min	41%-44%
Simple oxygen face mask	6-10 L/min	35%-60%
Face mask with O_2 reservoir (nonrebreathing mask)	6 L/min	60%
	7 L/min	70%
	8 L/min	80%
	9 L/min	90%
	10-15 L/min	95%-100%
Venturi mask	4-8 L/min	24%-40%
	10-12 L/min	40%-50%

a Percentage is approximate.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply during the 48-hour study Screening Period:

Informed Consent

1. Participant (or legally authorized representative) provides signed informed consent prior to the initiation of any study assessments for participation in the study.

Age

2. Are ≥ 18 to ≤ 75 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

3. Has laboratory-confirmed SARS-CoV-2 infection as determined by nucleic acid amplification test, polymerase chain reaction, antigen test, or other commercial or public health assay (based on locally accepted guidelines) in a sample collected < 10 days prior to randomization.

4. Documentation of chest imaging consistent with COVID-19 pneumonia (as per locally accepted guidelines). If chest imaging is not available during Screening, please discuss with

Medical Monitor or designee regarding evidence of probable COVID-19 pneumonia for study participant eligibility.

5. Not on mechanical ventilation (invasive or noninvasive), or ventilation, or ECMO, nor (based on medical judgement of admitting physician) anticipated to be in the next 24 hours.

6. An $SpO_2 < 94\%$ in room air AND able to maintain a $PaO_2/FiO_2 \geq 150$ (or equivalent $SpO_2/FiO_2 \geq 190$) with a maximum FiO_2 0.4. These readings may be obtained after exertion by the participant. Note: if participant is on chronic low O_2 therapy (≤ 2 L), assess their current baseline O_2 requirements for eligibility.

7. Requiring hospitalization (i.e., in the process of hospital admission or already admitted).

Birth Control based on Sex at Birth

8. a. Female Participants:

- Not a woman of childbearing potential (See Appendix 2).

OR

- If a woman of childbearing potential:
  - Is using a depot contraceptive or extended cycle oral contraceptive from before the first dose of the study intervention(s).
  - Agree not to become pregnant or donate eggs (ova, oocytes) for reproduction for a full 60 days.
  - Use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year) as described in Appendix 2 for the duration of the study (a full 60 days), either with:
    - A daily use hormonal contraception from before the first dose of the study intervention(s),

      OR

    - Uses a barrier method during the length of the study (a full 60 days).

b. Male Participants:

- Agree to refrain from donating sperm for at least 90 days.

PLUS, either

- Abstain from intercourse with a woman of childbearing potential.

OR

- Use a male condom for at least 90 days:

When having sexual intercourse with a woman of childbearing potential, who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year (see Appendix 2), since a condom may break or leak.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any condition that could interfere with the study objectives, conduct or evaluation in the opinion of the Investigator or Sponsor or designee.

2. If pregnant (by positive high-sensitivity pregnancy test) or breastfeeding.

3. Clinically significant (i.e., active) cardiovascular disease: cerebrovascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class ≥ III), or serious cardiac arrhythmia requiring medication (including corrected QT interval prolongation of > 470 ms and/or pacemaker) or prior diagnosis of congenital long QT syndrome. Note: documented, longstanding Left Bundle Branch Block (LBBB) resulting in a long QTc using Fridericia's formula, is not exclusionary if corrected by the QTc-LBBB {[QT – (0.7 × QRS – 50)]/square root RR} or JTc (QTc – QRS duration) formula.

4. History of uncontrolled illness (in the opinion of the Investigator) prior to SARS-CoV-2 infection, within the 3 months prior to Screening, including but not limited to:
   a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower), or
   b. Uncontrolled active infection (e.g., septicemia), or
   c. Significantly uncontrolled diabetes mellitus or any diabetes that has resulted in severe end organ damage, or
   d. Uncontrolled or severe asthma or other chronic obstructive pulmonary disease. Note: uncontrolled asthma/chronic obstructive pulmonary disease is defined as more than 1 exacerbation in the previous 12 months that required an emergency room visit or hospitalization. Note: chronic low O_2 (≤ 2 L) therapy is allowed as long as the participant meets the criteria outlined in Inclusion Criterion 6.

5. History of epilepsy, other neurological disorder associated with seizures (e.g., cerebrovascular accident/stroke, acute brain infection, traumatic brain injury, progressive brain disease, congenital brain disease), or currently active and uncontrolled neuropsychiatric condition (in the opinion of the Investigator) including depression or current suicidal ideation.

6. History of interstitial lung disease prior to Screening or current thrombosis or embolism present during Screening.

7. History of a primary immunodeficiency, organ transplant, splenectomy or functional asplenia.

8. History of the following prior to Screening:
   a. Human immunodeficiency virus infection.
   b. Untreated hepatitis C (i.e., if hepatitis C antibody positive, hepatitis C DNA is detectable).
   c. Untreated hepatitis B (positive for hepatitis B surface antigen or if hepatitis core antibody positive, hepatitis B DNA is detectable).
   d. Recurrent herpes zoster (two or more episodes within a 10-year period).
   e. Known active tuberculosis (TB) or untreated latent TB infection.

   Note: laboratory confirmation of inactive infection status is not required for study eligibility. Appropriate TB test can be performed to diagnose TB infection per clinical judgement.

9. History of malignancy (hematologic or solid tumor) that is not currently under control or in remission prior to Screening.

10. History of known alcohol or drug abuse in the 3 months prior to Screening as per Investigator opinion.

Prior/Concomitant Therapy

11. Known hypersensitivity to any study treatment, component, or placebo.

12. History of vaccination against SARS-CoV-2. Vaccination is allowed after Day 28 as per local standard of care and/or as per the Investigator's clinical judgment and might be permitted before Day 28 after consultation with the Medical Monitor or designee.

13. Daily use of the following medications associated with serotonin syndrome within 14 days prior to randomization:
   a. Antidepressants: selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, St. John's wort. Exception: fluoxetine within 8 weeks prior to randomization.
   b. Analgesics: tramadol, fentanyl (i.e., intermittent use as needed prior to randomization is allowed).
   c. Long-acting anti-emetics e.g., palonosetron, dolasetron. Short-acting anti-emetics, e.g, ondansetron, potentially associated with serotonin syndrome may be prescribed on an as needed basis. If short-acting antiemetics require around the clock administration for more than 1 day, please contact your Medical Monitor or designee to ensure safety of the study participant. Short-acting anti-emetics should not be administered within 3 hours of study treatment.
   d. Linezolid, tryptophan, buspirone, tedizolid.

14. The initiation, use or change in therapies within 14 days prior to randomization:

a. Use of raloxifene, tamoxifen, estradiol, clozapine, chlorpromazine (strong aldehyde oxidase inhibitors).

b. Use of corticosteroids exceeding 40 mg daily prednisone equivalent (e.g., dexamethasone 6 mg). Use of 40 mg daily prednisone equivalent (e.g., dexamethasone 6 mg) for more than 10 days during the study.

c. Any vaccination included but not limited to subunit or inactivated vaccines.

d. Use of Chinese herbal/non-herbal medications (e.g., tripterygium, total glucosides of peony, etc.).

e. Use of plasmapheresis or hemoperfusion (see Section 7.4.2).

15. The initiation, or use of therapies within 1 month prior to randomization:

a. Vaccination with live or live attenuated virus vaccine.

b. Use of any medication considered to have immunomodulating and/or immunosuppressant properties including but not limited to the following: antimalarials, (e.g., chloroquine, hydroxychloroquine, mefloquine), leflunomide, methotrexate, 6-mercaptopurine, sulfasalazine, mycophenolate mofetil or sodium, azathioprine, cyclophosphamide, dapsone, retinoids, abatacept, anifrolumab, thalidomide, lenalidomide, anti-TNFα agents, systemic calcineurin inhibitors (e.g., cyclosporine, tacrolimus) (although topical use of calcineurin inhibitors are allowed), Bruton's tyrosine kinase inhibitors, other small molecules such as tofacitinib (i.e., Janus kinase/signal transducers, activators of transcription pathway inhibitors), IL-1 and IL-6 pathway inhibitors, TNFα pathway inhibitors, IL-12/IL-23 pathway inhibitors, (e.g., ustekinumab), or other disease modifying, immunosuppressive or immunomodulatory therapies not otherwise specified in protocol.

c. Use of B cell depleting/modulating therapy such as anti-CD20 agents including but not limited to rituximab, ocrelizumab, ofatumumab, obinutuzumab, ocaratuzumab, veltuzumab, or biosimilars thereof, belimumab, or dual or other anti-B Lymphocyte Stimulator/a proliferation inducing ligand neutralizing therapies (e.g., RCT 18).

16. Concurrent interventional clinical study participation prior to study randomization through Day 28. After Day 28, approval to participate must be requested from the Sponsor when there exists the intent of participation in a concurrent study.

Diagnostic Assessments

17. Clinically significant or predefined abnormalities in laboratory tests (serum chemistries: aspartate aminotransferase [AST], alanine aminotransferase [ALT] or alkaline phosphatase level > 5.0 × upper limit of normal [ULN]), or hematologic test (hemoglobin < 5.0 mmol/L [9 g/dL], white blood cells $< 1.5 \times 10^9$/L, absolute neutrophil count $< 750/mm^3$, platelets $< 50 \times 10^9$/L) at Screening.

18. Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation:

eGFR = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if race is black)

5.3 Lifestyle Considerations

No restrictions pertaining to lifestyle and/or diet beyond the details indicated in Section 5.2.

5.4 Screen Failures

After the Screening evaluations have been completed, the Investigator or designee is to review the inclusion/exclusion criteria and determine the participant's eligibility for the study. Only the reason for ineligibility will be collected on screen failures. Participants who are found to be ineligible will be told the reason for ineligibility. Participants who do not meet the criteria for inclusion in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number and will undergo Screening procedures as determined by the Sponsor and Investigator.

5.5 Strategies for Recruitment and Retention

5.5.1 Recruitment

It is anticipated that participants with COVID-19 will present to participating hospitals and that no other efforts to recruit potential participants are needed. Recruitment efforts may also include dissemination of information about this study to other medical professionals/hospitals.

Participants who are confirmed to have SARS-CoV-2 and in the process of hospital admission or already in the hospital will be assessed for eligibility.

Screening will begin with a brief discussion with study staff. Some participants will be excluded based on demographic data and medical history (i.e., pregnant, < 18 or > 75 years of age, severe or uncontrolled chronic obstructive pulmonary disease including asthma, heart disease, central nervous system disease, renal failure, etc.). Information about the study will be presented to potential participants (or legally authorized representative) and questions will be asked to determine potential eligibility. Assessments completed for participation in the study can begin only after informed consent is obtained.

5.5.2 Costs

There is no cost to participants for the research tests, procedures/evaluations and study intervention while participating in this study. Procedures and treatment for clinical care, including costs associated with hospital stay, may be billed to the participant, participant's insurance, or third party, if and as appropriate.

5.5.3 Study Follow-up

All participants will be followed as an inpatient or outpatient for up to 60 days after study entry for any COVID-19 disease comorbidities, any other AEs requiring changes in concomitant

medications, serious adverse events (SAEs) including any re-admissions to the hospital, and changes in vital status assessments including the WHO ordinal scale.

Participants who are found to have active hepatitis, human immunodeficiency virus, or tuberculosis infection after enrollment into the study (based on anticipated delays in diagnostic labs), will be assessed and managed according to Section 8.1.

5.5.4 Hospital Discharge

All participants should be encouraged to maintain the study schedule of assessments (Table 1), if not by returning to the study site then through telemedicine visits. Record all available assessments per Table 1 including nucleic acid testing for SARS-CoV-2 and any assessments for continuation of viral shedding per local procedures. A participant who is discharged from the hospital after Day 3 and before Day 14 should have the same assessments as ET of study treatments as per the schedule of assessments (Section 1.2).

6 Study Intervention

6.1 Study Intervention and Administration

6.1.1 Investigational Therapeutic and Matching Placebo

The supplied matching placebo M5049 tablet is identical in physical appearance to the active M5049 tablet.

6.1.1.1 Study Intervention Description

Study Intervention Name:	M5049	Matching Placebo
Dose Formulation:	Film-coated yellowish to yellow tablet	Film-coated yellowish to yellow tablet
Unit Dose Strength(s):	25 mg	Placebo
Dosage Level(s):	50 mg, 100 mg	Placebo

6.1.1.2 Dosing and Administration

Four study intervention tablets will be taken orally with water twice daily (every 12 hours, morning and evening) for 14 days (a total of 28 doses, 4 tablets each dose). Dosing should occur within a 2-hour window. Those participants who enter the intensive care unit (ICU), may still receive the study intervention if able to take the tablets by mouth. If participants in the ICU may receive medicines only by nasogastric tube (NGT), refer to the Pharmacy Manual for instructions on preparing the study intervention tablets for administration via NGT. No other medication should be given at the same time as the study intervention via NGT.

For participants who are discharged prior to treatment completion, a diary card will be provided to record the number of study intervention tablets administered daily as well as any symptoms the participant may be experiencing. This diary card may be returned by mail or electronically to the study site. Date and time of study intervention administration will be recorded in the diary card/electronic case report form (eCRF).

CCI [redacted]

6.1.2.1 Acquisition and Accountability

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

Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may provide it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff. Further guidance and information for the study intervention accountability are provided in the Pharmacy Manual.

Before the study is initiated, the log-in information and directions for the Interactive Web Response System (IWRS) will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each participant.

Blinded treatment kit numbers will be obtained through the IWRS. The IWRS will be used to assign unique participant numbers, allocate participants to study intervention group and allocate study intervention at the randomization visit.

6.1.2.2 Destruction

Destruction of used and unused stock will be performed locally by the site at the end of the study as per institutions procedures and standard operating procedures. Confirmation and record of destruction will be provided to the Sponsor.

[redacted]

CCI

6.1.5 Preparation

M5049 film-coated tablets and placebo film-coated tablets are ready for oral use. No special handling is required unless the participant is unable to receive study intervention by mouth.

For those participants who cannot take the tablets by mouth during Part B of the study, e.g., participants who are mechanically intubated, refer to the Pharmacy Manual for information on preparation of the tablets (study intervention) and application via an NGT. Participants in Part A of the study will need to discontinue study intervention if/when they are no longer able to take tablets by mouth.

7 Measures to Minimize Bias: Randomization and Blinding

Once the participant meets inclusion and exclusion criteria, the Investigator or delegate will request the blinded study intervention treatment assignment using the IWRS. The study will randomize participants 1:1:1 to M5049 50 mg, M5049 100 mg, or placebo twice daily.

Part A participants will be stratified by presence/absence of obstructive lung disease. Part B participants will be stratified based on (1) the use of corticosteroids at a prednisone equivalent daily dosage of $\leq$ 15 mg or > 15 mg within 48 hours prior to randomization, (2) the use of antiviral therapy including convalescent plasma (presence or absence) within 48 hours prior to randomization, and (3) country.

Participant numbers will be assigned in the appropriate format and will reflect study number, site number and participant identification. Participant numbers will not be reassigned to other participants or reused in this study. If a participant is replaced, the replacement will be enrolled with a unique participant number.

7.1 Blinding

The study will be double-blinded with the participant, the Investigator, monitors, and study site staff being blinded to the study intervention administered. However, if a participant is receiving medications only via NGT, the pharmacist will possibly be unblinded in preparing the tablets for administration via NGT. Refer to the Pharmacy Manual for methods to prevent unblinding of other hospital staff when participants are receiving the study intervention via NGT.

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either M5049 or placebo in a 1:1:1 ratio using an IWRS and per a computer-generated randomization list. The IWRS will be used to assign unique participant numbers and to allocate participants to a study intervention group

at Day 1. Before the study is initiated, the directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each participant.

Only the internal IDMC may request review of unblinded data as needed. If a safety concern arises, the IDMC members are allowed to request immediate unblinding of the partial or complete dataset. The recommendations of the IDMC will not contain unblinded data or other information that could lead to the Investigator or study staff becoming unblinded. An independent statistician, not involved with study conduct nor a member of the IDMC, will be responsible for producing the unblinded safety data for the IDMC review. Functioning of the IDMC will be described in the IDMC Charter.

All breaks of the study blind must be adequately documented.

The bioanalytical laboratory(ies) responsible for the bioanalysis of the PK samples (requiring shipment of laboratory samples from the site) will be unblinded during study conduct to perform PK bioanalysis on samples from participants who received active study intervention. The laboratory applies masked subject identifiers to prevent association of treatment codes with any other clinical data such as efficacy and safety data.

7.2 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the responsible Medical Monitor/Sponsor prior to the unblinding, unless this could delay emergency treatment. The Medical Monitor/Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor with the reason for unblinding without revealing the study intervention, except to the designated drug safety representative via the Emergency Unblinding Notification Form. The date of, and reason for unblinding must be recorded in the source documents and eCRF.

7.3 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered at the study site will be recorded in the source documents and recorded in the eCRF.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each telemedicine or study site visit. Compliance will be assessed by counting returned tablets during the site visits or if possible, participant showing remaining tablets via telemedicine visit (e.g., screen of phone, computer, etc.); site will document numbers in the source documents and eCRF. Any deviation(s) from the prescribed dosage regimen are recorded in the eCRF.

A record of the number of study intervention tablets dispensed to and taken by each participant will 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 be recorded in the eCRF.

7.4 Concomitant Therapy

All concomitant therapies (e.g., medicines and nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes (see Appendix 3), must be recorded in the eCRF. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Co-enrollment in another interventional study evaluating COVID-19 treatments or SARS-CoV-2 vaccines is not allowed until after Day 28, and only with permission of the Sponsor. Off-label use of antiviral therapy and/or convalescent plasma is permitted if the therapy was identified as part of the standard of care for the site prior to its enrolling participants into the study. Other supportive care including off-label use of other drugs, devices, or interventions that might be used to manage COVID-19 (e.g., anticoagulants) should also be recorded.

The list of on-study contraindicated medications is the same as those contradicted for study eligibility and can be found in Appendix 3 through Study Day 28. Standard of care vaccinations are recommended to be provided from Day 28 on unless there is an immediate clinical need (e.g., rabies vaccination). After Study Day 28, any drug is allowed for participant treatment. Administration of SARS-CoV-2 vaccines, as per standard of care and/or as per the Investigator's clinical judgement, is permitted after Day 28; earlier administration might be permitted after consultation with the Medical Monitor or designee.

7.4.1 Corticosteroids

Corticosteroids should not be initiated or their dose changed once the participant has entered the study so as to not interfere with the primary objective of this study - evaluation of the anti-inflammatory effects of the study drug.

Corticosteroids initiated prior to or during the study Screening period (and prior to randomization) must not be higher than 40 mg prednisone per day based on the dosing regimen and schedule used in the RECOVERY Trial (NCT04381936) performed by the University of Oxford, United Kingdom (Horby 2002) The corticosteroid dosing (6 mg of dexamethasone, ≤ 40 mg prednisone, refer to Table 3) schedule must be completed within 10 days of corticosteroids initiation as per the RECOVERY Trial (mean days of corticosteroid use was 6 days).

Table 3 Prednisone Equivalence Calculation (Total Daily Dose)

Oral Corticosteroid Medication	Equivalent (mg) to 1 mg Prednisone	Equivalent (mg) to 15 mg Prednisone[a]	Maximum allowed daily dose (mg)
Betamethasone	0.15	2.3	6
Cortisone	5	75	200
Deflazacort	1.2	18	48
Dexamethasone	0.15	2.3	6
Hydrocortisone	4	60	160
Meprednisone	0.8	12	32
Methylprednisolone	0.8	12	32
Prednisolone	1	15	40
Triamcinolone	0.8	12	32

a In Part B, participants will be stratified based on the use of corticosteroids within 48 hours prior to randomization: prednisone equivalent daily dose of ≤ 15 mg or > 15 mg.

However, if the participant requires invasive mechanical ventilation AND the hospital standard of care recommends use of corticosteroids (up to 40 mg prednisone-equivalent daily) and/or other anti-inflammatory medications, these drugs will be permitted. Any additional anti-inflammatory use initiated at the same time of mechanical ventilation should also be recorded, i.e., the name, reason for use, dates administered, and dosing information.

7.4.2 Hemoperfusion

The FDA has granted temporary authorization under the Emergency Use Authorization program for four hemoperfusion devices for treatment of patients with severe COVID-19, defined as hospitalization, ICU admission, intubation or mechanical ventilation. However, as the intent of hemoperfusion is to remove inflammatory cytokines from the circulation, this procedure could reduce the levels of IL-6, Type I IFN or TNFα, which is the expected treatment effect of M5049. Therefore, hemoperfusion would confound the study treatment outcome and therefore is exclusionary and prohibited for this study. Specifically, if a participant is on hemoperfusion at Screening, this participant will not be eligible for enrollment in this study. If an enrolled study participant on study intervention needs to receive hemoperfusion as per Investigator judgement, then it should be discussed with the study monitor. This participant should discontinue the study intervention.

8 Discontinuation the Study Intervention or from the Study and Premature Study Closure

8.1 Temporary or Permanent Discontinuation of the Study Intervention for Toxicity

Any new clinically relevant finding is reported as an AE graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Participants who have their study intervention held for suspected drug toxicity, may have the study intervention restarted with approval of the Sponsor if the potential benefit of the study intervention outweighs the risk of the toxicity. More specifically, if a clinically significant finding is identified after enrollment, the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed in discussion with the Medical Monitor and Sponsor.

The study intervention may not be restarted if any SAE, clinically significant AE, persistent Grade 4 laboratory abnormality, intercurrent illness, or other medical condition occurs indicating to the Investigator that continued participation is not in the best interest of the participant.

- The study intervention will not be restarted if the following occurs: serious infection other than COVID-19, seizure, clinically significant arrhythmia, or serotonin syndrome.
- The study intervention should be withheld if the participant develops Grade 3 liver function tests (i.e., an increase in transaminases [ALT or AST] > 5.0 to 20.0 × ULN if Baseline was normal or > 5.0 to 20.0 × Baseline if Baseline was abnormal regardless of the participants bilirubin level). If the ALT and AST do not immediately trend to the participant's Baseline values within 24 hours, the study intervention must be held until the liver function tests return to the participant's Baseline values. If the ALT and AST return to the participant's Baseline values before Day 15, the study intervention may be restarted.
- For participants whose eGFR < 40 mL/min/1.73 m^2 for 24 hours, experience a Grade 3 increase in serum creatinine (> 3.0 × Baseline or > 3.0 to 6.0 × ULN) for 24 hours or who develop Acute Kidney Injury (requiring hemodialysis), the study intervention must be permanently discontinued.
- If the ECG QTc interval (corrected by Fridericia's formula) increases to > 480 msec, an immediate investigation into potential drug causes should be performed, and the study intervention temporarily withheld. If the participant is not on any known drugs to prolong QTc, then kidney function should be reviewed and also a potential drug interaction should be considered. The contraindicated drug list should be reviewed for study contraindicated medications (e.g., aldehyde oxidase inhibitors) and the offending drug discontinued unless no alternatives are available for management of the participant. If the QTc returns to the participant's Baseline or the prolongation is assessed as related to the underlying SARS-CoV-2 infection of the perimyocardium, in the opinion of the Investigator, the study intervention may be restarted any time before Day 15.

8.2 Reasons for Discontinuation of Study Intervention

A participant may discontinue study intervention (early termination of study intervention) for any of the following reasons:

- Unacceptable toxicity.
- Occurrence of pregnancy.
- The participant requests to discontinue study intervention.
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol.
- The participant is assessed as at risk for reactivation of TB.
- The participant fails to comply with protocol requirements or study-related procedures.

Unless the participant withdraws consent, those who discontinue study intervention before completing the 14-day course should be encouraged to remain in the study for further safety evaluations and to ascertain vital status to Day 60. It is critical to the study data integrity that vital status be collected at Days 14, 21, 28, and 60 either through telemedicine contacts or phone calls if the participant is unable to return to the study site (i.e., hospital area or clinic). The reason for participant discontinuation of study intervention should be documented in the eCRF.

8.3 Withdrawal from the Study by the Participant

The participant will discontinue the study if:

- Participant withdraws consent, participant's legally authorized representative withdraws consent, or the participant requests discontinuation from the study for any reason.
- Participant dies.
- Participant is lost to follow-up.
- Participants are free to withdraw from the study at any time upon request without any consequence. In the case of a participants becoming lost to follow-up, attempts to contact the participant should be made and documented in the participant's medical records.

After hospital discharge, a participant will be considered lost to follow-up if he or she fails to appear for a follow-up telemedicine conference or in-person assessment at the study site. The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.

Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls and 2) if

necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address. These efforts will be documented in the participant's record.

Participants who withdraw from this study or are lost to follow-up after signing the informed consent form (ICF) and administration of the study intervention will be replaced in Part A only with Sponsor approval. The reason for participant discontinuation from Part A and B of the study will be recorded on the appropriate eCRF.

8.4 Study Termination and Closure

This study may be prematurely terminated for reasons including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or not evaluable.
- As determined by the Sponsor, Regulatory Authorities or the local IRB/IEC.

If the study is prematurely terminated, the site PI will promptly inform study participants and the IRB/IEC as applicable. The site PI will assure appropriate follow-up for the participants, as necessary. If there is cause for emergently notifying participants for safety reasons before the IRB/IEC has reviewed the information, the PI may do so.

The Sponsor will notify Regulatory Authorities as applicable.

9 Study Assessments and Procedures

9.1 Screening and Efficacy Assessments

9.1.1 Screening Procedures

After participants gave informed consent, Screening assessments will be completed as indicated in Table 1.

Clinical screening assessments will be performed locally by the site laboratory. The overall eligibility of the participant to participate in the study will be assessed once all screening assessments are completed and reviewed to confirm that potential participants meet all eligibility criteria. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team. Study participants who meet all eligibility criteria will be immediately randomized. Screening will be halted when enrollment numbers have been reached while allowing for eligible participants in Screening to still enroll.

9.1.2 Efficacy Assessments

For all Baseline assessments and Follow-up Visits, refer to Table 1 for procedures to be done and details for each assessment. The respiratory status is assessed on a daily basis together with the clinical status on the WHO ordinal scale. The clinical response (efficacy assessment) is based on data collected from the primary endpoint time to recovery from first dose (Day 1) through Day 28 (defined as first occurrence of WHO scale 3 or less) and assessments of respiratory status and the clinical ordinal scale for secondary endpoints are performed on Days 1 through Day 28.

The FiO_2 score and method of respiratory support will be obtained (e.g., nasal cannula, high flow oxygenation, noninvasive ventilation, mechanical ventilation, etc.) from the hospital chart and recorded for the day obtained (i.e., on Day 4, Day 4 respiratory status is obtained and recorded as Day 4). For participants who are placed on invasive mechanical ventilation, document the reason for intubation and the local institutional protocol for intubation.

In addition, both SpO_2 measured by pulse oximetry and FiO_2 will be recorded at the time SpO_2 is documented on a daily basis while the participant is hospitalized. When SpO_2 reaches $\geq 94\%$ in room air and is maintained for 24 hours, the day and time are recorded at the beginning and conclusion of the 24 hours, as documentation is supportive of the primary endpoint (i.e., alive and free of respiratory support).

9.1.3 Secondary Endpoint Assessments

9.1.3.1 Clinical Status

The clinical status will be assessed with an ordinal scale as the second assessment of a given study day. The score can be obtained from the hospital chart using the last score prior to the time of assessment. This is recorded for the day obtained (i.e., on Day 3, Day 3 score is obtained and recorded as Day 3).

The WHO ordinal scale is as follows:

0. Uninfected: no clinical or virological evidence of infection.
1. Ambulatory: no limitation of activities.
2. Ambulatory: limitation of activities.
3. Hospitalized, mild disease: hospitalized, no oxygen therapy.
4. Hospitalized, mild disease: oxygen by mask or nasal prongs.
5. Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen.
6. Hospitalized, severe disease: intubation and mechanical ventilation.
7. Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, rapid response team, ECMO.
8. Death.

When deaths are recorded, data should be collected on whether the death occurred after withdrawal of care and, if so, the reason for withdrawal of care.

9.1.3.2 Additional Clinical Endpoints, COVID-19 Inflammatory Biomarkers, and Select Serum Biomarkers

Data collected for other clinical endpoint and inflammatory biomarkers will be obtained from the participant's hospital chart and should be recorded for the day obtained. Where relevant, data will also be cross-checked with the SAE and AE reported data (e.g., all-cause mortality as an SAE report).

As part of the secondary clinical endpoint assessments, data on all-cause mortality (Day 1 through Day 60), the time to ICU (Day 1 through Day 28), the time to invasive mechanical ventilation (Day 1 through Day 28), the time to noninvasive mechanical ventilation (Day 1 through Day 28), the total days in ICU from Day 1 through Day 60, and the total days in the hospital from Day 1 through Day 60 will be collected for analysis.

Inflammatory biomarker data (C-reactive protein, d-dimer, and ferritin) collected by the site during the study period (Day 1 through Day 28) will also be recorded as indicated in Table 1 in the study clinical database. Other biomarker data and research samples analyzed at the central laboratory are not established as standard of care and will not be available for participant management.

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Hospital re-admissions (if the participant was first discharged within the 60-day study period) should be reported as SAEs (unless the admission is elective). Specifically, hospital re-admission will be considered as a COVID-19 relapse if the participant is re-admitted due to worsening oxygenation and either a positive result of any respiratory pathogen test or worsening lesions on chest imaging.

9.1.3.3 Pharmacokinetics

Pharmacokinetic data will be analyzed at a central laboratory and are not available for participant management.

- The following PK parameters for M5049 will be calculated for Part A, when available data permits:

Symbol	Definition
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve (AUC) from time of dosing to the time of the last observation
$AUC_{0\text{-last}}/D$	Dose-normalized $AUC_{0\text{-last}}$
$AUC_{0\text{-12h}}$	AUC from time of dosing to 12 hours postdose
$AUC_{0\text{-12h}}/D$	Dose-normalized $AUC_{0\text{-12h}}$

Symbol	Definition
$AUC_{0-\infty}$	AUC from time of dosing to infinity
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$
CL/F	The apparent total body clearance of study intervention following extravascular administration. CL/F = Dose/$AUC_{0-\infty}$
C_{max}	Maximum observed concentration (Part A and B)
C_{max}/D	Dose-normalized C_{max}
C_{trough}	Predose observed concentration (Part A and B, Day 7 only)
λ_z	Terminal rate constant
$R_{acc}(AUC_{0-12h})$	The accumulation ratio of AUC_{0-12h} from Day 1 to Day 7. $R_{acc}(AUC_{0-12h})$ = AUC_{0-12h} (Day 7)/AUC_{0-12h} (Day 1)
$R_{acc}(C_{max})$	The accumulation ratio of C_{max} from Day 1 to Day 7. $R_{acc}(C_{max})$ = C_{max} (Day 7)/C_{max} (Day 1)
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent elimination half-life
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration. V_z/F = Dose/($AUC_{0-\infty} \times \lambda_z$)

- Whole blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of M5049, as specified in Table 1. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. Acceptable windows for PK collection are indicated in Table 4.
- The exact date/time of sample collection and study intervention administration must be recorded in the eCRF and will be used in the calculation of PK parameters. Time deviations from planned PK sampling times will not be considered a protocol deviation provided the exact date/time of sample collection and study intervention administration are recorded in the eCRF. For Day 1, Day 3 (Part B only), and Day 7 PK sampling, the time of the meal consumed closest to administration of the study intervention should also be recorded on this eCRF, i.e., the time the last meal is finished before or the first meal is started after study intervention administration, whichever time is closest to sampling.
- The quantification of M5049 in plasma will be performed using a validated liquid chromatography-mass spectrometry assay method. Concentrations will be used to evaluate the PK of M5049.
- Remaining samples collected for analyses of M5049 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- All samples collected for PK (except from placebo participants), as specified in Table 1, still within the known stability of the M5049 at the time of receipt by the bioanalytical laboratory may be analyzed.

See Section 10.4.5 for further details on the PK analysis.

Table 4 Acceptable Pharmacokinetic Windows for M5049 (Part A)

Sampling Time	Time from Scheduled Sampling Allowed
1 and 2 hours postdose	± 20 minutes
6 hours postdose	± 30 minutes
12 hours postdose	± 120 minutes

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9.1.4.1 Serum Biomarkers

Blood will be collected as indicated in Table 1 for measurement of serum biomarkers, e.g., additional cytokines (from IL-6, IL-8, and CCI, anti-SARS-CoV-2 antibodies.

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9.1.4.3 Part B: Pharmacokinetic Parameters

Blood will be collected as indicated in Table 1 for drug concentration measurements and/or descriptive population PK analysis.

9.2 Safety and Other Assessments

Time points for study procedures are specified in Table 1. A study physician licensed to make medical diagnoses will be responsible for all study-related medical decisions.

The following safety assessments will be performed:

- AEs (see Section 9.3).
- Concomitant medications.
- Brief physical examination: a brief, symptom-directed (targeted) physical examination will be performed to evaluate for any possible AE throughout the study.
- Clinical laboratory evaluations: data will be recorded from the participant's chart at the time points indicated in Table 1. If the data is not available, blood will be collected without interference in the participant's clinical care. Refer to Appendix 4 for clinical laboratory assessments.
- Vital signs: including respiration rate, pulse, diastolic and systolic blood pressure, body temperature. Height and weight will be recorded as indicated in Table 1.
- ECG: standard 12-lead resting ECG will be obtained after the participant has been in semi-supine position for at least 5 minutes at the time points indicated in Table 1. The ECG

tracing must be clear for computer transfer and analysis and will be stored digitally by the Sponsor.

- Arterial blood gas: will be performed, according to standard of care per local guidance, at Screening only if not available from the participant's chart and recorded from the participant's chart if performed at other times as indicated in Table 1, including normalization of SpO_2 in room air and discharge.
- SpO_2 and FiO_2.
- Chest imaging will be obtained as per local guidelines and recorded from the participant's chart if performed at other times as indicated in Table 1.
- Tuberculosis, human immunodeficiency virus and hepatitis assessment: data will be collected as per local guidelines from the participant's chart.
- Presence of other infections or continued SARS-CoV-2 shedding as per local guidelines.

9.2.1 On-study Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The care of hospitalized participants will be under the management of the attendant floor physician; thus, clinical findings and laboratory data are to be collected from the participant's clinical chart. If the data are not collected, document circumstances. If a physiologic parameter, e.g., vital signs, or laboratory value is outside of the local laboratory-specified range, and the attendant physician has repeated the laboratory measurement, both measurements should be recorded and an accompanying note as to why, in the judgment of the Investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error and should not be reported as an AE.

A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized blood pressure cuff).

9.3 Adverse Events and Serious Adverse Events

9.3.1 Definition of an Adverse Event

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study intervention.

Any medical condition that is present at the time that the participant is screened will be considered as Baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Given the nature of severity of the underlying illness, participants will have many symptoms and abnormalities in vitals and laboratory. All clinically important events will be captured as AEs in this study.

9.3.2 Definition of Serious Adverse Event

An SAE is defined as an AE or suspected adverse reaction which is considered serious if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization or re-hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a participant. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the appropriate SAE eCRF.

All SAEs will be reviewed and evaluated and will be sent to the IDMC for periodic review.

All SAEs will be followed through resolution or stabilization by a licensed study physician (for Investigational New Drug (IND) studies, a physician listed on the Form FDA 1572 as the site Principal or Sub-Investigator).

9.3.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is any SAE where a causal relationship with the study intervention is at least reasonably possible but is not listed in the Investigator's Brochure. The Sponsor's drug safety department will submit any SUSAR reports to Regulatory Authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

9.3.4 Adverse Events of Special Interest

Adverse events of special interests are infections (serious and opportunistic infections), seizure, serotonin syndrome, and clinically significant cardiac arrythmias. All nonserious AESIs must be additionally documented and reported.

9.3.4.1 Infection

Any CTCAE Grade ≥ 3 or SAEs of infection and opportunistic infection will be considered an AESI.

9.3.4.2 Seizure

Any type of seizures/epilepsy of any grade or its consequences are classified as AESIs.

9.3.4.3 Serotonin Syndrome

Serotonin syndrome and its spectrum of symptoms are a product of the overactivation of both the central and peripheral serotonin receptors as a result of high levels of serotonin. Symptoms usually begin within 24 hours of an increased dose of a serotonergic agent, the addition of another serotonergic agent to a drug regimen or overdosing.

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9.3.5 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site Investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

9.3.5.1 Severity of Adverse Events

The Investigator is required to grade the severity or toxicity of each AE. Investigators will reference the CTCAE, Version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by CTCAE, the Investigator is to use the general CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the participant's usual activities of daily living.
- Moderate (Grade 2): events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Life-threatening (Grade 4): Events that represent an immediate risk of death to a participant.
- Death (Grade 5).

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop duration of each reported AE will be recorded on the appropriate eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity. A laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

9.3.5.2 Relationship to Study Intervention

For each reported AE, the PI or designee must assess the relationship of the event to the study intervention using the following guideline:

- Related: the AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related: there is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.3.6 Time Period and Frequency for Event Assessment and Follow-up

For this study, all Grade 1 through Grade 4 AEs and all SAEs will be documented, recorded and reported. All AEs and SAEs occurring from the time the informed consent is signed through the Day 60 (End of Study) visit will be assessed for relationship to the study intervention.

9.3.6.1 Investigators Reporting of Adverse Events

Information on all AEs should be recorded on the appropriate eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped

together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study intervention, action(s) taken, and outcome.

9.3.7 AESI and SAE Reporting

9.3.7.1 Investigators Reporting of Serious Adverse Events

Any AE that meets a protocol-defined criterion as a SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the designated Pharmacovigilance Group, at the following contact details:

E-mail address PPD

Fax number: PPD

Serious adverse event reporting will be submitted via paper forms and will also be entered in the electronic data capturing system. Other supporting documentation of the event may be requested by the designated Pharmacovigilance Group and should be provided as soon as possible. The designated Medical Monitor will review and assess the SAE for potential impact on study participant safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate Sub-Investigator becomes aware of an SAE, the site PI or appropriate Sub-Investigator will report the event to the designated Pharmacovigilance Group.

9.3.7.2 Investigators Reporting of Adverse Event of Special Interest

For a nonserious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.

For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, as specified in Section 9.3.7.1.

9.3.8 Regulatory Reporting of Serious Adverse Events

Following notification from the site PI or appropriate Sub-Investigator, as the IND Sponsor, will report any SUSAR in an IND safety report to the Regulatory Authority and will notify all participating site PIs as soon as possible. Any unexpected fatal or life-threatening suspected adverse reaction will be reported to the Regulatory Authority as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the Sponsor determines that the information qualifies for reporting. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from Regulatory Authority, the Sponsor will submit any additional data or information that the

agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Serious adverse events that are not SUSARs will be reported to the Regulatory Authority at least annually in a summary format which includes all SAEs.

Sites may have additional local reporting requirements (to the IRB/IEC and/or national Regulatory Authority).

9.3.9 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be recorded in the appropriate eCRF and submitted to the Sponsor on the appropriate paper reporting form within 24 hours of learning of the pregnancy. Pregnancy should be followed to outcome.

The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be recorded and reported to the Sponsor accordingly.

9.4 Treatment of Overdose

For this study, any dose of study intervention greater than the planned total daily dose (8 tablets of study intervention per day) within 24-hour time period (midnight to midnight) or total 14-day cumulative study dose (see Section 6.1.1.2) for a participant in the study will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

Even if not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Section 9.3.

9.5 Unanticipated Problems

9.5.1 Definition of Unanticipated Problems

An unanticipated problem is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB/IEC-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.5.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are SAEs will be reported to the study Sponsor within 24 hours of the Investigator becoming aware of the event per the above describe SAE reporting process.
- Any other unanticipated problem will be reported to the study Sponsor within 3 days of the Investigator becoming aware of the problem.

9.5.3 Reporting Unanticipated Problems to Participants

Participants will be informed of any unanticipated problems that occur as part of their participation in this study.

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10.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Set	Description
Enrolled	All participants who sign informed consent.
Intent-to-Treat	The Intent-to-Treat Analysis Set consists of all treated participants. Participants will be analyzed according to the actual treatment received. The Intent-to-Treat Analysis Set will be used for the primary efficacy analysis.
Safety	The Safety Analysis Set consists of all participants who receive at least one dose of study intervention and is used for evaluation of safety endpoints. Participants will be analyzed according to the actual treatment they receive.
Pharmacokinetics	The Pharmacokinetic Analysis population will include all participants who received at least 1 dose of active treatment, for whom at least 1 quantifiable plasma concentration of M5049 is obtained, and without any relevant protocol deviations and absence of factor that may have an influence on pharmacokinetics.
Pharmacodynamics	The Pharmacodynamic Analysis population will include all participants who received at least 1 dose of study intervention, for whom at least 1 postbaseline biomarker assessment was obtained and without any relevant protocol deviations or event that may have an influence on pharmacodynamics.

10.4 Statistical Analyses

10.4.1 General Approach

This study is exploratory.

For each treatment group, continuous variables will be summarized using descriptive statistics, while qualitative variables will be summarized by counts and percentages.

An Integrated Analysis Plan (IAP) will be developed and finalized before the first IDMC meeting.

Analysis will present the clinical outcomes of participants from Part A and Part B combined.

10.4.2 Analysis of the Primary Efficacy Endpoint

The primary endpoint, time to recovery, is defined as the time from first dose (Day 1) through Day 28 to first occurrence of WHO 9-point ordinal scale 3 or less. For participants who die and those considered as failure (that includes use of mechanical ventilation, ICU admission leading to treatment discontinuation, and relapse), the time to recovery will be censored at Day 28. For participants completing the study without recovering or failure, the time to recovery will be censored at Day 28. Participants withdrawn before the End of Study Visit without recovering or failure will be censored at the last date of available clinical status assessment.

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Cumulative distribution function for time to recovery will be estimated via the Kaplan-Meier (product-limit estimates) method by treatment group and presented together with associated statistics (median time to recovery, recovery rates at Day 7, Day 14, and Day 28) including the corresponding two-sided 95% CI.

The potential intercurrent events that could confound the primary endpoint are:

- Intensive care unit admission/invasive mechanical ventilation/death.
- Treatment discontinuation due to AE.
- Concomitant medication: antiviral therapy including convalescent plasma, corticosteroids.
- Forbidden concomitant medication (e.g., chloroquine-related medications, immunomodulating drugs).

Specific analyses to account for intercurrent events and stratification factors will be described in the IAP.

10.4.3 Analysis of the Secondary Endpoints

10.4.3.1 Analysis of Alive and Not Requiring Supplemental Oxygenation through Day 28

The number and proportion of participants alive and do not require supplemental oxygenation or ventilatory support (including mechanical ventilation and ECMO) will be described at Day 7, Day 14, and at regular intervals.

The difference of each dose versus placebo in proportion of participants who are alive and do not require supplemental oxygenation or ventilatory support on Day 7, on Day 14 and on Day 28 will

be provided graphically together with two-sided 95% CIs. The CIs will be based on the Miettinen & Nurminen method (Miettinen 1985).

10.4.3.2 Analysis of Clinical Status

The number and percentage of participants in each clinical status category will be presented by treatment group and by time point in a graphical manner.

An ordinal logistic regression model will be used to compare the clinical status from Day 1 through Day 60 of M5049 groups to placebo. Under the assumption of proportional odds, a summary odds ratio and its 95% CI will be estimated for each M5049 group versus placebo. A test for the proportionality assumption will also be made.

Separate odds ratios will also be estimated for dichotomized version of the health status:

- Death versus any other category.
- Worsening versus stable/improvement.
- Not discharge versus hospital discharged.

An exploratory longitudinal analysis will be run to account for all of the time points and present estimates of treatment effect by time point.

10.4.3.3 Analysis of Time to SpO_2 of ≥ 94% Sustained for at Least 24 hours in Room Air

The time to response is defined as the time from first dose (Day 1) to the date of the first SpO_2 ≥ 94% sustained for at least 24 hours in room air up to Day 28. For participants who die and those considered as failure (that includes use of mechanical ventilation, ICU admission leading to treatment discontinuation, and relapse) the time to response will be censored at Day 28. For participants completing the study without meeting response or failure, the time to response will be censored at Day 28. Participants withdrawn before the End of Study Visit without meeting response or failure will be censored at the last date of SpO_2 assessment in room air temperature.

Cumulative distribution function for time to response will be estimated via the Kaplan-Meier (product-limit estimates) method by treatment group and presented together with associated statistics (median time to response, response rates at Day 7, Day 14, and Day 28) including the corresponding two-sided 95% CI.

10.4.3.4 Analysis of All-cause Mortality Through Day 60

Number and percentage of death through Day 60 with 95% CI will be presented by treatment group.

10.4.3.5 Analysis of Time to Intensive Care Unit Admission (Day 1 Through Day 28)

Time to ICU admission (hereafter, "event") is defined as the time from first dose (Day 1) to the date of event up to Day 28. Participants completing or withdrawing from the study without experiencing the event, will be censored at the time of completion or withdrawal. If death occurs before the event, it will be counted as an event.

Analysis will be based on a stratified log-rank test of distribution of time to event with strata defined by (1) the use of corticosteroids at a prednisone equivalent daily dose of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, (2) the use of antiviral therapy including convalescent plasma (presence or absence) within 48 hours prior to randomization, and (3) country.

Estimation of treatment effect by dose (and 95% two-sided CI) compared to placebo will be based on hazard ratio from a stratified Cox-model of response hazard rate, with terms for treatment group and strata defined as above.

Event-free survival function for time to event will be estimated via the Kaplan-Meier method by treatment group and presented together with associated statistics (median time to event, response rates at Day 9, Day 14 and Day 28) including the corresponding two-sided 95% CI.

10.4.3.6 Analysis of Time to Invasive Mechanical Ventilation (Day 1 Through Day 28)

Time to invasive mechanical ventilation will be analyzed in the same manner as time to ICU.

10.4.3.7 Analysis of Time to Noninvasive Mechanical Ventilation (Day 1 Through Day 28)

Time to noninvasive mechanical ventilation will be analyzed in the same manner as time to ICU.

10.4.3.8 Analysis of Total Days in ICU

The total number of days in ICU from Day 1 through Day 60 will be described together with 95% CI by treatment group.

10.4.3.9 Analysis of Total Days in the Hospital and Time to Hospital Discharge

The total number of days in the hospital from Day 1 through Day 60 will be described together with 95% CI by treatment group.

In addition, time to hospital discharge will be analyzed. The time to hospital discharge is defined as the time from first dose (Day 1) through Day 28 to hospital discharge. For participants who die and those considered as failure (that includes use of mechanical ventilation, ICU admission leading to treatment discontinuation, and relapse), the time to hospital discharge will be censored at Day 28. For participants completing the study without being discharged or failure, the time to hospital discharge will be censored at Day 28. Participants withdrawn before the End of Study Visit without hospital discharge or failure will be censored at the last date of available clinical status assessment.

Cumulative distribution function for time to hospital discharge will be estimated via the Kaplan-Meier (product-limit estimates) method by treatment group and presented together with associated statistics (median time to hospital discharge, hospital discharge rates at Day 7, Day 14, and Day 28) including the corresponding two-sided 95% CI.

10.4.3.10 Analysis of Inflammatory Biomarkers

Absolute values, absolute changes, and percent changes from Baseline to each time point in inflammatory biomarkers will be summarized by treatment group.

Descriptive statistics will be displayed using Box and Whisker plots.

Spaghetti plots with percent change from Baseline as well as absolute change from Baseline will also be provided by treatment group.

10.4.3.12 Analysis of Occurrence of Relapse in Participants During the Study Period (if First Discharged Within the 60-day Study Period)

Count and percentage of participants with relapse (see Section 4.8 for definition) among participants discharged before Day 28 with 95% CI will be presented by treatment group.

10.4.3.13 Analysis of Occurrence of Re-hospitalization in Participants During the Study Period (if First Discharged Within the 60-day Study Period) Due to COVID-19 Disease Complications

Count and percentage of participants who are re-hospitalized before Day 28 with 95% CI will be presented by treatment group and whether or not due to COVID-19 disease complications.

10.4.4 Safety Analysis

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants experiencing 1 or more treatment-emergent adverse events (TEAEs) will be summarized according to MedDRA system organ classes and preferred terms by treatment group, relationship to study intervention, and severity.

Deaths, SAEs, AESIs, TEAEs leading to treatment discontinuation, and TEAEs leading to treatment interruption will be summarized by treatment group.

Summary statistics will be used to present observed values and changes from Baseline in vital signs, ECG parameters, and abnormal laboratory parameters.

10.4.5 Pharmacokinetic Parameters

Pharmacokinetic analyses will be specified in the IAP, which will be finalized before database lock. The PK of M5049 and exposure-response relationships with respect to biomarkers/clinical endpoints will be described using modeling and simulation. Full details of the relevant (integrated) population modeling and simulation activities (including objectives, relevant endpoints, methodology, software, etc.) will be defined in a separate pharmacometric analysis plan for Part B in addition to Part A.

Part A

The concentrations and derived PK parameters of M5049 will be summarized descriptively by time point and dose group.

Individual and mean concentration profiles over time will be provided by participant/dose group.

Boxplots will be prepared for C_{max}, $AUC_{0\text{-}12h}$, C_{max}/D and $AUC_{0\text{-}12h}/D$ by dose group.

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10.4.6 Baseline Descriptive Statistics

Baseline characteristics will be summarized by treatment group. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

10.4.7 Planned Safety Analyses

The study will pause enrollment after 15 participants in Part A have been randomized to the study-defined intervention. An internal IDMC that provides ongoing surveillance of participant safety will review all available safety and clinical outcomes data, and will recommend whether the study is safe to proceed to Part B.

During Part B, the IDMC will provide ongoing surveillance of participant safety, will review available safety and clinical outcomes data, and will recommend whether the study is safe to continue.

Purpose, membership, mandate, and processes of the IDMC will be detailed in the IDMC charter.

11 Supporting Documentation and Operational Considerations

11.1 Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research and the International Council for Harmonisation (ICH) E6(R2).

IRBs/IECs will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the participants, prior to the recruitment, screening, and enrollment of participants. Site IRBs/IECs may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. The Investigator will notify the IRB/IEC of deviations from the protocol and SAEs, as applicable to the IRB/IEC policy.

When applicable, amendments will be submitted to the appropriate Health Authorities.

11.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continuing throughout the individual's study participation. Investigators or designated research staff will obtain a participant's informed consent in accordance with the requirements of 45 Code of Federal Regulations (CFR) 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed.

Participants will receive a concise and focused presentation of key information about the clinical study, verbally and with a written consent form. The key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

ICFs will be IRB/IEC-approved, and participants will be asked to read and review the consent form. Participants (or legally authorize representatives) must sign the ICF prior to starting any study procedures being done specifically for this study. Once signed, a copy of the ICF will be given to the participant for their records.

New information will be communicated by the site PI to participants who consent to participate in this study in accordance with IRB/IEC requirements. The informed consent document will be updated, and participants will be re-consented per IRB/IEC requirements, if necessary.

11.1.2 Confidentiality and Privacy

Participant confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to participants, test results of biological samples and genetic tests, and all other information

generated during participation in the study. No identifiable information concerning participants in the study will be released to any unauthorized third party. Participant confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC, and/or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records including remote access where applicable.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

11.1.3 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ''primary'' or ''initial'' activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB/IEC approval.

Each sample will be labelled only with a barcode and a unique tracking number to protect participant confidentiality. Secondary research with coded samples and data may occur, however, participant confidentiality will be maintained as described for this protocol. An IRB/IEC review of the secondary research using coded specimens is required.

The participant's decision can be changed at any time by notifying the study doctors or nurses in writing. If the participant subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

11.1.4 Safety Oversight

11.1.4.1 Independent Data Monitoring Committee

Safety oversight will be conducted by an internal IDMC consisting of members who are independent of the study team and are experts in clinical trials, risk/benefit, safety, statistical considerations and the relevant medical expertise. The internal IDMC may also request the conduct of a futility analysis, when applicable (e.g., overly prolonged study enrollment with requirement of additional resources to support study conduct).

The IDMC will operate under the guidelines of a charter which will detail analyses performed for the purpose of risk/benefit monitoring by the IDMC, the full membership, mandate, and processes of the IDMC.

11.1.5 Data Handling and Record Keeping

11.1.5.1 Data Collection and Management Responsibilities

All participant study data will be recorded in eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by electronically signing the eCRF.

The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.

The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.

The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.

Study Monitors will perform ongoing remote source data review to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.1.5.2 Study Record Retention

The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

11.1.5.3 Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this study, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of participants is sufficient for obtaining medical history. Solicitation of medical records from the participant's primary care provider is not required.

11.1.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in participant study records.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB/IEC requirements. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the participant's chart if the deviation is participant specific.

11.1.7 Publication and Data Sharing Policy

To avoid premature release of data, this protocol specifies that efficacy data from a study that has not yet been completed due to insufficient enrollment should not be released.

An independent monitoring committee would review results from an interim analysis of study data to make recommendations regarding whether the study should continue or stop for safety as guided by the prespecified monitoring plan.

11.1.8 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. Policies and procedures are established for all study group members to disclose all conflicts of interest as well as a mechanism for the management of all reported dualities of interest.

12 Additional Considerations

12.1 Research-related Injuries

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

For any potential research-related injury, the site PI or designee will assess the participant. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating study site.

As needed, referrals to appropriate health care facilities will be provided to the participant. The site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this study.

If it is determined by the participating site PI that an injury occurred to a participant as a direct result of the tests or treatments that are done for this study, then referrals to appropriate health care facilities will be provided to the participant.

Study personnel will try to reduce, control and treat any complications from this study. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions.

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14 Appendices

Appendix 1 Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the plasma concentration-time curve
CFR	Code of Federal Regulations
CL/F	Apparent total body clearance of study intervention following extravascular administration
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Predose observed concentration
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ET	Early termination of treatment
FIH	First-in-human
FiO_2	fraction of inspired oxygen
HRT	Hormonal replacement therapy
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LBBB	Left Bundle Branch Block

NAT	Nucleic acid test
NGT	Nasogastric tube
PaO_2	Partial pressure of oxygen
CCI	[redacted]
PI	Principal Investigator
PK	Pharmacokinetic
QTc	Corrected QT interval
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
ssRNA	Single-stranded ribonucleic acid
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
V_Z/F	Apparent volume of distribution during the terminal phase following extravascular administration

Appendix 2 Contraception

Definitions:

Women of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

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

A woman of childbearing potential is not:

1. Premenarchal.
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.
3. A postmenopausal female.
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 follicle-stimulating hormone measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a woman of childbearing potential and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
  - Oral.
  - Intravaginal.
  - Transdermal.
  - Injectable.
- Progestogen-only hormone contraception associated with inhibition of ovulation.
  - Oral.
  - Injectable.
- Sexual abstinence: a highly effective method only if defined as refraining from 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.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 3 Medication Guidance

Medication Type	Medications	Discontinuation (Weeks) Before Randomization and Through Day 28
Immunomodulators/ Immunosuppressants	Antimalarials: hydroxychloroquine, chloroquine, mefloquine	4
	Dapsone or retinoids	
	Sulfasalazine	
	Methotrexate	
	Leflunomide	
	Azathioprine	
	6-mercaptopurine	
	Mycophenolate mofetil or sodium	
	Thalidomide or lenalidomide	
	JAK inhibitors: e.g., tofacitinib, baricitinib	
	BTK inhibitors: e.g., ibrutinib	
	Cyclophosphamide	
	Calcineurin inhibitors: e.g., cyclosporine, tacrolimus, voclosporin. Including topical use (e.g., tacrolimus, pimecrolimus)	
	Plasmapheresis	
Biologics	Abatacept	4
	Anti-IL-6 receptor (tocilizumab, sarilumab) or anti-IL6 (siltuximab)	
	IL-12/IL-23 inhibitor: ustekinumab	
	Anti-IL-1	
	IVIG	
	Anti-TNFα: e.g., etanercept, adalimumab	
	Belimumab, dual or other anti-B Lymphocyte Stimulator/a proliferation inducing ligand neutralizing therapies (e.g., RCT 18)	
	Anti-CD20: e.g., rituximab, ocrelizumab, ofatumumab, obinutuzumab, ocaratuzumab, veltuzumab or biosimilars	
	Anti-IFN: e.g., anifrolumab	
Vaccination (Note: participants with previous SARS-CoV-2 vaccination are excluded but might be vaccinated after Day 28, or earlier after consultation with Medical Monitor or designee)	Included but not limited to subunit or inactivated vaccines	2
	Live or live attenuated virus vaccine	4

Medication Type	Medications	Discontinuation (Weeks) Before Randomization and Through Day 28
Chinese Medication/Herbal/Non-herbal supplements	Tripterygium, total glucosides of paeony	2
Antidepressants	Selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, St. John's wort	2
	Fluoxetine	8
Anxiolytic	Buspirone	2
Analgesics	Tramadol and fentanyl, continued use only	2
Anti-emetics (long-acting)	Palonosetron, dolasetron	2
Antibiotics	Linezolid, tedizolid	2
Medications associated with AOX inhibition	Raloxifene, tamoxifen, estradiol, clozapine, chlorpromazine	2
Supplement	Tryptophan	2
Hemoperfusion	Hemoperfusion	2

AOX = aldehyde oxidase; BTK = Bruton tyrosine kinase; JAK = Janus kinase; IL = interleukin; IVIG = intravenous immune globulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; TNFα = tumor necrosis factor alpha.

Appendix 4 Clinical Laboratory Tests

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="3">Hematology</td><td colspan="2">Platelets</td><td>Mean Corpuscular Volume</td><td rowspan="3">WBC Count with Differential:
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils</td></tr>
<tr><td colspan="2">Hemoglobin</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Hematocrit</td></tr>
<tr><td rowspan="3">Biochemistry</td><td>Blood Urea Nitrogen</td><td>Electrolytes (sodium, potassium, chloride, bicarbonate)</td><td>Aspartate Aminotransferase</td><td>Creatinine Kinase</td></tr>
<tr><td>Creatinine</td><td>Albumin</td><td>Alanine Aminotransferase</td><td>Total Protein</td></tr>
<tr><td>eGFR</td><td>Glucose</td><td></td><td></td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">Serum hCG or urine pregnancy test (as needed for a woman of childbearing potential).
All study-required laboratory assessments will be performed by local laboratory. It is required that these local laboratories are certified, perform and document interlaboratory testing at regular time intervals and provide a list of normal range laboratory values including units as defined by international system of units (e.g., CLIA-certified, UK NEQUAS, etc.).</td></tr>
<tr><td>Baseline Tests</td><td colspan="4">• Serum virology (hepatitis B and C screening, HIV) per local guidelines.
• Urine drug screen per local guidelines.</td></tr>
</table>

CLIA = Clinical Laboratory Improvement Amendments of 1988; eGFR = estimated glomerular filtration rate; hCG = human chorionic gonadotrophin; HIV = human immunodeficiency virus; UK NEQUAS = United Kingdom National External Quality Assessment Service; WBC = white blood cell.

Appendix 5 Protocol Amendments History

The information for the current amendment is on the title page.

Changes from Version 2.0 to Version 3.0 Included in the Amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Included that participants on RECOVERY Trial dexamethasone dosing equivalent of corticosteroids may be eligible for enrollment.	Clarification of eligibility for enrollment.
Section 1.1 Synopsis	Increased the duration of the study to 15 months.	Due to protracted enrollment times.
Section 1.2 Schedule of Assessments	Included Hospital Discharge (HD) and HD assessment details. Amended details for requirement for chest imaging documentation. Updated ECG schedule. Updated cross reference.	To gather critical biomarker data and to align with various local standard of care guidance regarding chest imaging. To align ECG schedule with PK sampling.
Section 2.2.2 Potential Therapeutics	Amended details of antivirals and immunomodulating drugs.	Updated to describe recent clinical study results.
Section 3.2 Part B Objectives	Included PK parameters on Day 3 for Part B.	To reflect sampling on Day 3 if discharge is anticipated before Day 7.
Section 4.1 Overall Design Section 9.1.3.3 Pharmacokinetics	Included pre and postdose PK samples on Day 3.	To guarantee collection of Part B PK data if participant is discharged before Day 7.
Section 4.1 Overall Design Section 4.4 Early Hospital Discharge Assessments Section 5.5.4 Hospital Discharge	Clarified that participants discharged prior to Day 14 should have HD assessments performed.	To gather critical biomarker data.
Section 4.4 Early Hospital Discharge Assessments	New section added.	To clarify assessments performed at early discharge.
Section 5 Study Population Section 5.1 Study Population Section 5.5.1 Recruitment	Increased upper age limit for study participants to ≤ 75 years.	Based on study to date, study intervention is well tolerated; therefore, the age restriction is expanded up to 75 years of age, to reflect a higher risk group for COVID-19 pneumonia.
Section 5 Study Population	Included a guidance chart for FiO_2 with regard to O_2 delivery.	To facilitate enrollment.
Section 5.1 Inclusion Criteria	Expanded range of tests for SARS-CoV-2 infection.	To align with the range of tests that have become available.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Clarified inclusion criteria with regard to O_2 therapy.	To facilitate enrollment.
Section 5.2 Exclusion Criteria	Updated exclusion criterion with regard to neurological disorders.	To clarify neurological disorders that are exclusionary for the study.
Section 5.2 Exclusion Criteria	Clarified exclusion criteria with regard to long QTc. Clarified that participants with significantly uncontrolled diabetes mellitus will be excluded. Clarified exclusion criteria with regard to O_2 therapy. Clarified that continued daily use of medications associated with serotonin syndrome within 14 days prior to randomization is exclusionary. Amended criterion to initiation, use, or change in therapy within 14 days of randomization instead of Screening. Clarified exclusion criterion with regard to corticosteroid use during the study. Removal of exclusion criteria for initiation or change in dose of angiotensin converting enzyme inhibitors or receptor blockers. Amended criterion to initiation or use, of therapies within 1 month of randomization instead of Screening. List of medications has been updated and intermittent use of some medications is allowed. Qualified concurrent clinical study participation through Day 28 is exclusionary if the study is evaluating an intervention. Amended exclusion criteria for diagnostic assessments (white blood cells, absolute neutrophil count, and platelets) at Screening. Removal of a history of significant chest imaging abnormalities as an exclusion criterion.	All eligibility criteria are updated to increase potential target population without compromising safety, and based on feedback from sites regarding screen failures.
Section 6.1.1.2 Dosing and Administration	Clarified that diary cards can be returned by mail or electronically.	To enable easier collection of study-required data.
Section 7.4 Concomitant Therapy	Qualified when co-enrollment in another observational only study is allowed. Clarified details for on-study contraindicated medications and vaccinations.	Clarifications of protocol procedures.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.4 Adverse Events of Special Interest	Added clinically significant cardiac arrythmias.	For consistency with Section 2.3.1.
Section 10.3 Populations for Analyses	Removed "randomized" in the definition of Safety Analysis Set.	To allow for all patients receiving study intervention to be evaluated for safety.
Section 10.4.3.11 Analysis of Occurrence of Relapse in Participants During the Study Period (if First Discharged Within the 60-day Study Period)	Updated cross reference.	To reflect document structure.
Appendix 3 Medication Guidance	Clarified that the discontinuation period is the specified number of weeks before and through randomization. Removed discontinuation period for corticosteroids. Amended discontinuation periods for antidepressants, anxiolytics, analgesics, anti-emetics, antibiotics, medications associated with AOX inhibition, and supplements. Removed discontinuation period for investigational agents. Removed details of medications with a required duration of a stable dose.	Clarifications after study drug discontinuation to assist with medical management during the follow-up period.
Throughout	Updated "convalescent serum" to "convalescent plasma". Corrected definition of AOX from "alternative" to "aldehyde" oxidase.	To reflect standard terminology. To reflect correct definition.
	Minor editorial and document formatting revisions.	Minor, therefore these have not been summarized.

AOX = aldehyde oxidase; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; FiO_2 = fraction of inspired oxygen; HD = Hospital Discharge; PK = pharmacokinetic; QTc = corrected QT interval.

Changes from Version 1.0 to Version 2.0 Included in the Amendment

Section # and Name	Description of Change	Brief Rationale
Title page	Added legal entity for all countries, except the US and Canada.	Updated the sponsoring legal entities to provide for study sites in Brazil being included in the study.
	Added Clinical Trials.gov registry number.	Registry number was not available at the time of Version 1.0 finalization.
Section 1.1 Synopsis	Updated PK parameters to be assessed for secondary objectives in Part A.	To ensure consistency across sections and with the IAP.
Section 1.1 Synopsis	Added the evaluation of modulation of select biomarkers as secondary objective in Part B.	Availability of select biomarkers at the same time as the clinical outcome data will guide next steps in clinical development of M5049.
Section 1.2 Schedule of Assessments	Moved serum virology and urine for drugs of abuse assessments to the end of the Screening and Randomization only assessments in Table 1.	To emphasize that these assessments will not be exclusionary but only for participant management.
	Added that arterial blood gas should be performed at Screening if not available from the participant chart.	To clarify that arterial blood gas will be obtained from the participant chart, as available, but should be performed at Screening, if not available from the chart.
	Specified that chest imaging will be done as per local guidelines.	Study sites might be using different radiology guidelines but not ultrasound as not accredited in US or Brazil.
	Added that the time of sample collection for inflammatory biomarkers will be recorded on days as indicated.	To clarify that the date and clock time of sample collection will be recorded as already found on the eCRF.
	For Part B, added a Day 3 sample collection for serum and CCI biomarkers, and documentation at Day 3 of inflammatory biomarkers, if collected.	To better evaluate modulation of select biomarkers.
	For PK sampling, added to both Part A and Part B "at select sites" where post PK sampling may be decreased.	To enable more sites to participate in the study because they can perform only limited PK sampling.
	Add that the time of the closest meal consumed prior to the study intervention administration i.e., when the last meal was finished before the study intervention administration, should be recorded.	To clarify the time to be recorded with regards to meal consumption and study intervention administration.
	Added that the Day 1 samples for serum and CCI biomarkers must be collected prior to study intervention administration and that the time of each collection should be recorded.	To ensure that a Baseline (pretreatment) value is obtained.
CCI		

Section # and Name	Description of Change	Brief Rationale
Section 2.2.2 Potential Therapeutics	Added that convalescent serum will be allowed as background therapy.	To clarify that convalescent serum is allowed if used as in the context of an antiviral.
Section 2.3.1 Potential Risks	Updated potential risk from "QT interval prolongation" to "Clinically significant arrythmia". Added note that documented, longstanding Left Bundle Branch Block variant that corrects with Fridericia's formula, is not exclusionary.	To be consistent with Section 9.3.4.
Section 3.1 Part A Objectives	Updated PK parameters to be assessed for secondary objectives in Part A.	To ensure consistency across sections and with the IAP.
Section 3.2 Part B Objectives	Added the evaluation of modulation of select biomarkers as secondary objective in Part B.	Availability of select biomarkers at the same time as the clinical outcome data will guide next steps in clinical development of M5049.
Section 4.1 Overall Design	Updated stratifications factors for Part B participants.	To include steroid use as a stratification factor for the cases where administered doses are greater than 15 mg and clarify convalescent serum is considered as an antiviral (treated as such on study randomization).
Section 5 Study Population	Added that SpO_2 and PaO_2/FiO_2 readings may be obtained after exertion by the participant.	To clarify that obtaining SpO_2 saturation and FiO_2 measurements after exertion by the participant is allowed.
Section 5.1 Inclusion Criteria	Added that SpO_2 and PaO_2/FiO_2 readings may be obtained after exertion by the participant.	To clarify that obtaining SpO_2 saturation and FiO_2 measurements after exertion by the participant is allowed.
Section 5.2 Exclusion Criteria	Added note that documented, longstanding Left Bundle Branch Block variant that corrects with Fridericia's formula, is not exclusionary.	To address a frequent finding in older participants who otherwise have "normal" ECGs.
	Specified that only participants with severe end organ damage due to uncontrolled diabetes mellitus or any diabetes will be excluded from the study.	To clarify that participants with uncontrolled diabetes mellitus or any diabetes will only be excluded from the study if it has resulted in severe end organ damage.
	Updated definition for uncontrolled asthma/chronic obstructive pulmonary disease.	To clarify the timeframe for hospitalization in case of exacerbation.
	Updated exclusion criteria for the use of therapies within 14 days prior to or during Screening.	To add pheresis and update with respect to corticosteroid use.
	Added that convalescent serum will be allowed if part of the standard of care for the local hospital.	To clarify that convalescent serum is allowed if used as in the context of an antiviral.
	Changed eGRF as calculated by the Modification of Diet in Renal Disease equation, from < 50 mL/min/1.73m^2 to 45 mL/min/1.73m^2.	Changed toxicity criteria for eGFR.
Section 6.1.1.2 Dosing and Administration	Updated text regarding the administration of study intervention via NGT.	To be consistent with instructions in the Pharmacy Manual.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.5 Preparation	Removed text stating that tablets will be crushed if administered via NGT.	To be consistent with instructions in the Pharmacy Manual.
Section 7 Measures to Minimize Bias: Randomization and Blinding	Updated stratifications factors for Part B participants.	To include steroid use as a stratification factor for the cases where administered doses are greater than 15 mg and clarify convalescent serum is allowed if used as in the context of an antiviral.
Section 7.1 Blinding	Updated text to state that the pharmacist will possibly be unblinded in preparing the tablets for administration via NGT. Updated text to state that only the internal IDMC may request review of unblinded data. Removed text describing the unblinding of bioanalytical laboratory(ies) responsible for the bioanalysis of PK samples.	To warn study sites in the event this occurs. Prior language was vague. The text was incorrect.
Section 7.3 Study Intervention Compliance	Removed text stating that a person other than the person administering the study intervention will confirm the dose of study intervention and study participant identification at the time of dosing.	The instructions were incorrect and carryover from WHO template.
Section 7.4 Concomitant Therapy	Added instructions regarding the use and recording of corticosteroids.	To provide guidelines for the use and recording of corticosteroids.
Section 7.4.1.1 Corticosteroids	Added a subsection with instructions regarding the use of corticosteroids.	To provide guidelines for the use of corticosteroids.
Section 8.1 Discontinuation of the Study Intervention for Toxicity	Updated section heading to include temporary or permanent discontinuation. Added text to specify when study intervention may be restarted after Grade 3 liver function tests. Changed toxicity criteria for eGFR. Added toxicity criteria for ECG QTc interval.	Clarified language under which conditions discontinuation of drug occurs with respect to liver function tests, eGR, and ECG QTc.
Section 8.2 Reasons for Discontinuation of Study Intervention	Added text that the vital status for subjects who discontinue study intervention prematurely, will be collected at Days 14, 21, 28, and 60 either through telemedicine contacts or phone calls if the participant is unable to return to the study site.	To minimize missing data, participants who discontinued study intervention prematurely, will be followed for the regularly scheduled efficacy assessments.

Section # and Name	Description of Change	Brief Rationale
Section 9.1.3.2 Additional Clinical Endpoints, COVID-19 Inflammatory Biomarkers, and Select Serum Biomarkers	Updated heading and text regarding the collection of biomarker data.	To clarify timing of data available for statistical analysis.
Section 9.1.3.3 Pharmacokinetics	Added that PK data will be analyzed at a central laboratory and will not be available for participant management. Updated definitions for PK parameters.	To clarify vague language. To ensure consistency across sections and with the IAP.
	Added that the time when the last meal was finished before or the first meal started after study drug administration, whichever is the closest meal consumed, should be recorded.	To clarify the time to be recorded with regards to meal consumption.
CCI		
Section 10.4.2 Analysis of the Primary Efficacy Endpoint	Updated stratifications factors. Updated of the statistical methodology in the sensitivity analysis to take into account the stratification factors.	To include steroid use as a stratification factor for the cases where administered doses are greater than 15 mg.
Section 10.4.3.1 Analysis of Clinical Status	Modified odds ratios to be estimated for dichotomized version of the health status.	Additional analysis deemed to be important.
Section 10.4.3.2 Analysis of Time to SpO_2 of ≥ 94% sustained for at least 24 hours in room air	Updated covariates to reflect the changes in randomization stratification factors.	To account for country and steroid use for the cases where administered doses are greater than 15 mg in the analysis.
Section 10.4.3.4 Analysis of Time to Intensive Care Unit Admission (Day 1 Through Day 28)	Updated covariates to reflect the changes in randomization stratification factors.	To account for country and steroid use for the cases where administered doses are greater than 15 mg in the analysis.
CCI		
Section 10.4.4 Safety Analysis	Updated text regarding the summary statistics for safety analysis.	To clarify statistical procedures.
Section 10.4.5 Pharmacokinetic Parameters	Updated text regarding the presentation of population modeling and simulation activities.	To ensure consistency with the IAP.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Section # and Name	Description of Change	Brief Rationale

COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; FiO2 = fraction of inspired oxygen; IAP = Integrated Analysis Plan; IDMC = Independent Data Monitoring Committee; NGT = nasogastric tube; PaO2 = partial pressure of oxygen; PK = pharmacokinetic; QTc = corrected QT interval; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; SpO2 = peripheral capillary oxygen saturation.

Appendix 6 Sponsor Signature Page

Study Title: A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia

Clinical Study Protocol Version: 01 Mar 2021 / Version 4.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike, Billerica, MA, 01821, USA.
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Appendix 7 Coordinating Investigator Signature Page

Study Title:	A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia
Clinical Study Protocol Version:	01 Mar 2021 / Version 4.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 8 Principal Investigator Signature Page

Study Title:	A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia
Clinical Study Protocol Version:	01 Mar 2021 / Version 4.0
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: