Title Page

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients with COVID-19 Infection

Protocol Number: I4V-MC-KHAA

Protocol Amendment Number: B

Compound: baricitinib (LY3009104)

Study Phase: 3

Acronym: COV-BARRIER

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

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Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	18 May 2020
Amendment A	27 May 2020

Amendment B

This amendment is considered to be substantial based on the criteria set forth 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 main purpose of this protocol amendment is to address regulatory comments regarding the primary endpoint.

Sections # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3.0 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale 8.1.1 COVID-19 Clinical Status Assessment (Primary Endpoint Assessments) 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.4.2 Primary Endpoint	Updated primary endpoint	Response to FDA feedback. The updated primary endpoint is proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 28.
1.3 Schedule of Activities	Added clarification for Vital Signs to be assessed and documented daily.	Response to FDA feedback. Added clarifying test that Vital Signs are assessed and documented daily while hospitalized in the comment box in first position.
4.1 Overall Design 6.5.2 Required and Permitted Concomitant Therapy 11.0 References	Added statement allowing use of hydroxychloroquine and chloroquine only if recommended or required by local COVID-19 treatment guidelines.	Updated given updates in scientific literature.
5.1 Inclusion Criteria	Update to Criterion #3 to provide duration of time between confirmatory testing and enrollment	Response to FDA feedback. The updated criteria provide the duration of time between confirmatory testing and enrollment should not be more than 14 days for SARS-CoV-2 confirmation >72 hours.

Sections # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Update to Criterion #11 with addition of clarifying text for patients that may have ongoing infection	Response to FDA feedback. The updated criterion includes "Note: Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who, in the judgment of the investigator, are at increased risk for serious infections or other safety concerns given the study products should be excluded".
5.2 Exclusion Criteria	Update to Criterion #22 that patients should not be enrolled in any other trials for COVID-19.	Response to FDA feedback. The updated criterion provides the participant should not be enrolled (start) in another clinical trial for the treatment of COVID-19 or SARS CoV-2 through Day 28.
5.2 Exclusion Criteria 6.5.3 Prohibited concomitant therapy	Addition of Exclusion Criterion #25 for the use of extracorporeal blood purification (EBP) device to remove pro-inflammatory cytokines from the blood. Added EBP device to remove pro-inflammatory cytokines from the blood to list of prohibited concomitant therapy.	The new criterion was added and the prohibited concomitant therapy list updated given recent input on current practices and EUA that is in place and use of this modality can confound assessments in KHAA. The new exclusion criterion applies if "Are using or will use extracorporeal blood purification (EBP) device to remove pro-inflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb ®."
5.2 Exclusion Criteria	Addition of Exclusion Criterion #26 to exclude patients that are unlikely to survive participation in the study	The new criterion provides exclusion if the patient, in the opinion of the investigator, unlikely to survive for at least 48 hours after screening.
9.3 Populations for Analyses	Addition of clarification of analyses population	The new language provides that a sensitivity analysis excluding patients who die within 24 hours of randomization and have do not resuscitate (DNR) or do not intubate (DNI) in ITT/PP analyses populations will be conducted.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients with COVID-19 Infection

Rationale:

Baricitinib, an approved therapy for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults, is being proposed as a potential therapy for patients with COVID-19 infection. The proposed mechanism of action in COVID-19 infection includes reduction of cytokine-mediated inflammation and the potential for antiviral activity.

There are currently no approved therapies for the treatment of COVID-19 infection. Management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. The cause of ARDS is a hyperinflammatory state characterized by upregulation of multiple cytokines. Baricitinib, an orally administered inhibitor of JAK1 and JAK2, could be a therapeutic option for this condition because of the potential to inhibit signaling from multiple cytokines that are implicated in COVID-19 ARDS (McInnes et al. 2019). In patients with RA, treatment with the 4-mg dose of baricitinib resulted in a reduction from baseline in serum IL-6 at Week 12 in a Phase 2, randomized, placebo-controlled study of baricitinib (data on file). The potent anti-inflammatory effects of baricitinib have also been demonstrated by the reduction of serum levels of IFN-γ, IP-10, GM-CSF and MCP-1 in pediatric patients with steroid-dependent chronic inflammation, resulting in the ability to wean or taper steroids (Sanchez et al. 2018).

In addition to the anti-cytokine effect, baricitinib has recently been hypothesized (Richardson et al. 2020) and shown (nonclinical data on file) to be a potent inhibitor of numb-associated kinases (NAKs), which include AAK1, GAK, and BIKE. These proteins play a critical role in the host epithelial cell to facilitate propagation of viruses, including SARS-CoV-2, that rely on the scaffold protein known as activator protein 2 (AP2). Inhibiting the NAK proteins that activate the AP2 scaffolding protein vital to viral entry and propagation could be one therapeutic approach to managing COVID-19 infection.

The rationale for study treatment for up to 14 days is based on the known onset of efficacy in the RA population, which is as early as 1 week (Olumiant Summary of Product Characteristics), and on the expected duration of treatment needed for an acute infection such as COVID-19. Recently, data were published on a case series describing a 14-day treatment course of baricitinib in patients with mild to moderate COVID-19 infection (Cantini et al. 2020).

Baricitinib is administered orally once a day. It has a short half-life (approximately 12 hours in RA patients), so treatment can be interrupted or stopped if necessary. It has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies. Baricitinib has a well-established safety profile, based on clinical trial data and postmarketing data in patients with RA.

This profile, together with the observation that baricitinib is a potent AAK1/BIKE/GAK inhibitor with known anti-cytokine profile, provide the rationale to study baricitinib in the context of a randomized, controlled clinical trial in patients with COVID-19 infection.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of baricitinib 4-mg once daily (QD) compared to placebo on disease progression in patients with COVID-19 infection	Proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 28
Key Secondary	
To evaluate the effect of baricitinib 4-mg QD compared to placebo on clinical outcomes in patients with COVID-19 infection	Proportion of patients with at least 1-point improvement on NIAID-OS or live discharge from hospital at Day 4, Day 7, Day 10, Day 14
	Number of ventilator-free days (Day 1 to Day 28)
	Time to recovery (NIAID-OS) (Day 1 to Day 28)
	Overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, Day 14
	Duration of hospitalization (Day 1 to Day 28)
	Proportion of patients with a change in oxygen saturation from <94% to ≥94% from baseline to Day 4, Day 7, Day 10, Day 14
	All-cause mortality (Day 1 to Day 28)

Overall Design

Study I4V-MC-KHAA (KHAA) is Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of baricitinib 4-mg given once daily (QD). The primary endpoint is the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 28.

The study duration will be up to approximately 42 days over 3 study periods:

Screening: on Day 1 prior to dosing

Treatment period: treatment is administered for up to 14 days, or up to the day of hospital discharge, whichever comes first, followed by treatment evaluations up to Day 28

Follow-up: Period starting after treatment evaluation, lasting not less than 28 days after last dose of study drug.

Disclosure Statement: 2-arm parallel treatment period, participant-blinded and investigator-blinded.

Number of Participants: Approximately 400 patients will be randomized.

Intervention Groups:

At baseline, participants will be randomized in a 1:1 ratio to one of two treatments groups:

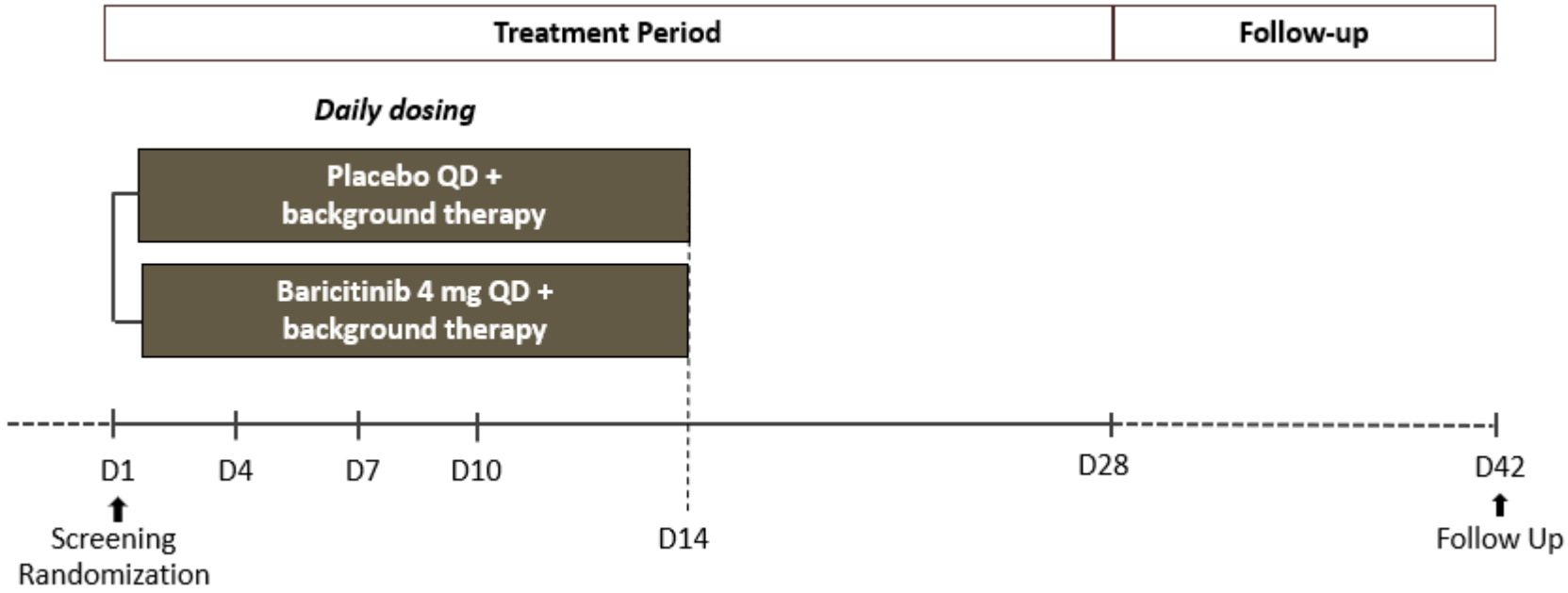
Approximately 200 participants will receive baricitinib, and

Approximately 200 participants will receive placebo.

Both treatment groups will receive background therapy in keeping with local clinical practice for management of COVID-19 infection.

Data Monitoring Committee: Yes

1.2. Schema



Note: Dosing occurs from the day of randomization until Day 14, or until hospital discharge, whichever comes first.
Placebo or baricitinib are given with background therapy in keeping with local clinical practice for management of COVID-19, as defined in the protocol.

Abbreviations: D = study day; QD = once daily.

Figure 1. Schema of Study I4V-MC-KHAA.

1.3. Schedule of Activities (SoA)

Day 1 procedures may be conducted over more than 1 day, as long as all activities are completed within the allowed interval tolerance. Activities at the follow-up visit (28 days after last dose) are required for all randomized patients and can be conducted as a telephone visit. See the Comment Field for details about daily collection of clinical assessments and vital signs.

Study day	**1**	**4**	**7**	**10**	**14**	**28**	**Follow-up (28 Days after Last Dose)**	**ETV**	**Unscheduled**	**Comments**
Interval tolerance (days)	**≤3**	—	—	—	—	—	**±4**	—	—	
Site Visit		**X**	**X**	**X**	**X**	**X**				Site visit is preferred, but telephone visit is acceptable after discharge.
Telephone Visit							**X**			
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographics	X									
Pre-existing conditions and medical history, including relevant surgical history	X									Obtained from interview or available information, for example, medical records.
Prespecified medical history: comorbidities	X									Includes comorbidities such as, but not limited to, diabetes, hypertension, cardiovascular disease, underlying pulmonary disease.
Prespecified medical history: COVID-19	X									Includes COVID-19 diagnosis date and onset of COVID-19 symptoms.
Prior treatments of special interest within last 2 weeks	X									Includes NSAIDs, antivirals, antibiotics, antimalarials, corticosteroids, herpes zoster vaccine, immunosuppressive medications.
Substance use (tobacco use)	X									
Concomitant medications	X	X	X	X	X	X	X	X		Assess daily. Includes medications of interest: background therapy, supportive care, sedating/paralytic drugs, and VTE prophylaxis.
Adverse events (AEs)	X	X	X	X	X	X	X	X		Assess daily. AE collection begins when ICF is signed. For infections and VTEs, additional data are collected (Section 8.3.6).

Study day	1	4	7	10	14	28	Follow-up (28 Days after Last Dose)	ETV	Unscheduled	Comments
Interval tolerance (days)	**≤3**	**—**	**—**	**—**	**—**	**—**	**±4**	**—**	**—**	
Site Visit		**X**	**X**	**X**	**X**	**X**				Site visit is preferred, but telephone visit is acceptable after discharge.
Telephone Visit							**X**			
COVID-19 clinical symptoms	X	X	X	X	X	X	X	X		Assess daily.
Clinical Assessments										
Height	X									May be as measured or reported.
Weight	X									
Vital signs	X	X	X	X	X	X		X		**Assess and document daily while hospitalized.** Includes: respiratory rate and oxygen saturation, blood pressure, body temperature, heart (pulse) rate. See Section 8.2.1.
Physical examination	X									The complete physical exam is performed if feasible; it excludes pelvic, rectal, and breast exams and includes assessment of risk factors for tuberculosis (TB) (Section 8.2.2).
Symptom-directed physical examination		X	X	X	X	X		X		See Section 8.2.2.
Chest imaging (CT scan or x-ray) (local)	X			X				X	X	Assessed by radiologist or pulmonologist (Section 8.2.4). Documentation of hospital-based imaging prior to study entry, obtained up to 24 hours prior to Day 1 is acceptable
12-lead ECG (local)	X									Performed and assessed locally. Documentation of hospital-based ECG prior to study entry, up to 24 hours prior to Day 1 is acceptable (Section 8.2.3).
Clinician-Administered Assessments Paper										
Clinical Status Assessment	X	X	X	X	X	X		X		Document daily through Day 29. Includes status of oxygen/life support procedures and proning.
Assessment for the NEWS	X	X	X	X	X	X		X		Document daily.

Study day	**1**	**4**	**7**	**10**	**14**	**28**	**Follow-up (28 Days after Last Dose)**	**ETV**	**Unscheduled**	**Comments**
Interval tolerance (days)	**≤3**	**—**	**—**	**—**	**—**	**—**	**±4**	**—**	**—**	
Site Visit		**X**	**X**	**X**	**X**	**X**				Site visit is preferred, but telephone visit is acceptable after discharge.
Telephone Visit							**X**			
Laboratory Tests and Sample Collections										For laboratory tests and sample collections, the timing can be +1 day or -1 day from the designated day, unless otherwise specified.
Hematology	X	X	X	X	X	X		X	X	Performed locally. Tests performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
Clinical chemistry, including creatine kinase (CK) and lactate dehydrogenase (LDH)	X	X	X	X	X	X		X	X	Performed locally. Tests performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
Cardiac troponin	X	X	X	X	X	X		X	X	Performed locally. Tests performed in the 24 hours prior to study entry will be accepted. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
eGFR (MDRD)	X	X	X	X	X	X		X	X	Performed locally. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
Serum pregnancy	X									Required prior to randomization. Performed locally. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Only for WOCBP (Section 8.2.5.1, Appendix 10.4).

Study day	**1**	**4**	**7**	**10**	**14**	**28**	**Follow-up (28 Days after Last Dose)**	**ETV**	**Unscheduled**	**Comments**
Interval tolerance (days)	**≤3**	**—**	**—**	**—**	**—**	**—**	**±4**	**—**	**—**	
Site Visit		**X**	**X**	**X**	**X**	**X**				Site visit is preferred, but telephone visit is acceptable after discharge.
Telephone Visit							**X**			
Laboratory Tests and Sample Collections (continued)										For laboratory tests and sample collections, the timing can be +1 day or -1 day from the designated day, unless otherwise specified.
Pharmacokinetic (PK) samples									X	Only for intubated patients in ICU. Timing starts on the first day of mechanical ventilation. Samples on first day of intubation: 15 minutes, 1 hour, and any time between 2-4 hours (all post-dose). Samples on third day of intubation: pre-dose; then 30 minutes, and any time between 6-10 hours post-dose. If collection on the third day of intubation is not possible, PK sample collection can be done on a later day. Central laboratory.
Erythrocyte sedimentation rate (ESR)	X	X	X	X	X	X		X	X	Performed locally. Test performed in the 24 hours prior to study entry will be accepted. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
C-reactive protein (CRP)	X	X	X	X	X	X		X	X	Performed locally. If available, high-sensitivity (hs-CRP) is preferred. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.

Study day	**1**	**4**	**7**	**10**	**14**	**28**	**Follow-up (28 Days after Last Dose)**	**ETV**	**Unscheduled**	**Comments**
Interval tolerance (days)	**≤3**	**—**	**—**	**—**	**—**	**—**	**±4**	**—**	**—**	
Site Visit		**X**	**X**	**X**	**X**	**X**				Site visit is preferred, but telephone visit is acceptable after discharge.
Telephone Visit							**X**			
Laboratory Tests and Sample Collections (continued)										For laboratory tests and sample collections, the timing can be +1 day or -1 day from the designated day, unless otherwise specified.
Ferritin	X	X	X	X	X	X		X	X	Performed locally. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
D-dimer	X	X	X	X	X	X		X	X	Performed locally. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
Procalcitonin	X	X	X	X	X	X		X	X	Performed locally. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
SARS-CoV-2 viral infection confirmation via nasopharyngeal swab	X	X		X	X	X		X	X	Performed locally. Test performed during current hospitalization (prior to study entry) will be accepted for determination of eligibility.
Exploratory biomarker samples: serum, whole blood	X	X	X	X				X		Obtained and sent to the Lilly-designated laboratory.
Exploratory biomarker sample: nasopharyngeal swab	X	X		X	X	X		X		Obtained and sent to the Lilly-designated laboratory.
Randomization	X									Dosing daily from randomization through Day 14, or until patient is discharged from hospital, whichever comes first.

Abbreviations: CT= computerized tomography; eCRF= electronic case report form; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ETV = early termination (discontinuation) visit; ICU = intensive care unit; ICF = informed consent form; MDRD = Modification of Diet in Renal Disease; NEWS = National Early Warning Score; NSAIDs = nonsteroidal anti-inflammatory drugs; VTE = venous thromboembolism; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

Baricitinib, an approved therapy for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults, is being proposed as a potential therapy for patients with COVID-19 infection. The proposed mechanism of action in COVID-19 infection includes reduction of cytokine-mediated inflammation and the potential for antiviral activity.

There are currently no approved therapies for the treatment of COVID-19 infection. Management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. The cause of ARDS is a hyperinflammatory state characterized by upregulation of multiple cytokines. For example, COVID-19 infected patients admitted to the intensive care unit (ICU) in Wuhan, China, exhibited increased plasma concentrations of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP1A, and TNFα, compared to the non-ICU patients (Huang et al 2020). Elevated IL-6 and hyperferritinemia were predictors of death in COVID-19 patients in China (Chen X et al. 2020; Chen T et al. 2020; Mehta et al. 2020; Ruan et al. 2020). Baricitinib, an orally administered inhibitor of JAK1 and JAK2, could be a therapeutic option for this condition because of the potential to inhibit signaling from multiple cytokines that are implicated in COVID-19 ARDS (McInnes et al. 2019). In patients with RA, there was a dose-dependent reduction in plasma IL-6 at Week 12 in a Phase 2, randomized, placebo-controlled, study of baricitinib (data on file). In ex vivo studies, there was a similar dose-dependent effect on inhibition of multiple cytokines implicated in COVID-19 infection. The potent anti-inflammatory effects of baricitinib have also been demonstrated by the reduction of serum levels of IFN-γ, IP-10, GM-CSF and MCP-1 in pediatric patients with steroid-dependent chronic inflammation, resulting in control of disease activity and the ability to wean or taper steroids (Sanchez et al. 2018).

In addition to the anti-cytokine effect, baricitinib has recently been hypothesized (Richardson et al. 2020) and shown (nonclinical data on file) to be a potent inhibitor of numb-associated kinases (NAKs), which include AAK1, GAK, and BIKE. These proteins play a critical role in the host epithelial cell to facilitate propagation of viruses, including SARS-CoV-2, that rely on the scaffold protein known as activator protein 2 (AP2). Inhibiting the NAK proteins that activate the AP2 scaffolding protein vital to viral entry and propagation could be one therapeutic approach to managing COVID-19 infection.

The rationale for study treatment for up to 14 days is based on the known onset of efficacy in the RA population, which is as early as 1 week (Olumiant Summary of Product Characteristics), and on the expected duration of treatment needed for an acute infection such as COVID-19. Recently, data were published on a case series describing a 14-day treatment course of baricitinib in patients with mild to moderate COVID-19 infection (Cantini et al. 2020).

Baricitinib is administered orally once a day. It has a short half-life (approximately 12 hours in RA patients), so treatment can be interrupted or stopped if necessary. It has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies. Baricitinib has a well-established safety profile, based on clinical trial data

and postmarketing data in patients with RA (Olumiant United States package insert, 2019; Olumiant Summary of Product Characteristics).

This profile, together with the observation that baricitinib is a potent AAK1/BIKE/GAK inhibitor and the known anti-cytokine profile, provide the rationale to study baricitinib in the context of a randomized, controlled clinical trial in patients with COVID-19 infection.

2.2. Background

In December 2019, a life-threatening infectious disease first observed in Wuhan, China, and later identified as COVID-19 has rapidly spread, causing a global pandemic. According to the World Health Organization (WHO), as of 20 April 2020, 2,314,621 confirmed cases have been reported worldwide with 157,847 deaths (WHO COVID-19 Situation Report 91).

COVID-19 belongs to the coronavirus family of single-stranded RNA viruses that can cross species barriers and can cause illness ranging from the common cold to more severe diseases such as SARS and MERS. Transmission of COVID-19 is believed to occur through respiratory droplets from coughing and sneezing. The pathogenesis is unclear, but the virus seems capable of producing an excessive immune reaction, which results in extensive tissue damage (Rothan and Byrareddy 2020).

The majority of individuals infected with COVID-19 experience a mild respiratory disease generally affecting the lower airways; symptoms usually appear after an incubation period of approximately 5 days. The most common symptoms at onset include fever, fatigue, and dry cough. Other signs and symptoms include myalgia, headache, diarrhea, nausea, dyspnea, lymphopenia, prolonged thrombin time, elevated lactate dehydrogenase, elevated alanine transaminase, and creatine kinase, and bilateral infiltrates on chest imaging. Patients can deteriorate rapidly. The median time from first symptoms to hospitalization is 7 days (Wang D et al. 2020).

Huang et al. (2020) reported that 27% of hospitalized patients diagnosed with COVID-19 infection in China developed ARDS after 9 days from onset of symptoms requiring oxygen therapy and intensive care. Some patients have laboratory evidence of a severe inflammatory response, similar to the cytokine release syndrome, with persistent fever, elevated inflammatory markers (hs-CRP, D-dimer, ferritin), and multiple organ dysfunction (Guan et al. 2020; Chen T et al. 2020). The major complications during hospitalization include ARDS, arrhythmia, and shock. Disease severity and mortality appears to be associated with those over the age of 70 and individuals with underlying comorbidities such as diabetes, hypertension, cardiovascular disease, chronic renal disease, and chronic lung disease (Chen N et al. 2020; Guan et al. 2020; Rothan and Byrareddy 2020; Wang W et al. 2020).

There is no approved or standard-of-care treatment for COVID-19 infection; medical management is based on supportive care. As stated in the guidelines of the United States Institutes of Health (NIH) and the World Health Organization (WHO), no drug to date has been proven safe and effective for treating COVID-19 infection. Furthermore, there are insufficient data to recommend either for or against the use of any antiviral or immunomodulatory therapy in patients with COVID-19 infection, and neither the WHO nor the NIH recommend the use of corticosteroids unless the patient has an exacerbation of asthma or chronic obstructive pulmonary

disease (WHO 2020; NIH 2020). The use of NSAIDs has been questioned since patients who were treated with NSAIDs early in their course of infection have progressed.

2.3. Benefit/Risk Assessment

Baricitinib, which is an approved therapy for the treatment of moderately to severely active RA in adults, is being proposed as a potential therapy for COVID-19. The proposed mechanism of action includes reduced cytokine-mediated inflammation and the potential for antiviral activity. Patients diagnosed with COVID-19 infection who are candidates for entry into Study KHAA will be at an elevated risk for excess morbidity and mortality due to the underlying SARS-CoV-2 infection and subsequent cytokine activation. Of hospitalized patients with COVID-19 infection in Wuhan, China, 26% were transferred to the intensive care unit (ICU), and of those patients in the ICU, complications included acute respiratory distress syndrome (61.1%), arrhythmia (44.4%), and shock (30.6%) (Wang D et al. 2020). In addition, these patients will inherently be at higher risk for venous thromboembolism (VTE) due to immobilization and the hyperinflammatory state (Klok et al. 2020; Chen N et al. 2020; Huang et al. 2020). As stated in the study rationale, the cytokine storm that may be responsible for the significant complications will potentially be ameliorated by immunomodulators such as the use of baricitinib. The potential benefit of baricitinib in the treatment of COVID-19 infection is described further in the study rationale (Section 2.1).

Baricitinib is a Janus kinase (JAK) inhibitor approved for the treatment of RA. In the US, baricitinib 2-mg is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. In Europe, baricitinib 4-mg is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Baricitinib is currently under development in other autoimmune conditions including atopic dermatitis, alopecia areata, systemic lupus erythematosus, and juvenile idiopathic arthritis.

The United States product labeling indicates a boxed warning for the risk of serious infections, malignancies, and thrombosis, while warnings and precautions include serious infections, thrombosis, gastrointestinal perforations, abnormal laboratory assessments (potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids), and avoidance with the use of live vaccines.

The Summary of Product Characteristics indicates as special warning and precautions for infections, including tuberculosis (TB), hematological abnormalities, viral reactivation, use of live vaccines, increase in blood lipid parameters, increase in hepatic transaminase, malignancy, VTE, hypersensitivity, and use of baricitinib with potent immunosuppressive medications.

Baricitinib has an established safety profile with a positive benefit/risk profile in RA. An integrated analysis of patients with active RA exposed to baricitinib with 3770 patients and 10,127 patient-years for a maximum exposure of 7 years (as of February 2018) was recently published (Genovese et al. 2019). No significant differences were seen for baricitinib 4-mg versus placebo in adverse events leading to permanent drug discontinuation, death, malignancy, serious infection, or major adverse cardiovascular events. Malignancy (excluding non-melanoma skin cancer) incidence rates (IRs) per 100 patient-years were 0.8 (2-mg) and 1.0 (4-mg; as-

randomized analysis). Fewer than 1% of patients discontinued due to abnormal laboratory results.

Specifically regarding VTE, during the 16-week placebo-controlled period of RA studies, the IRs per 100 patient-years for deep vein thrombosis (DVT)/pulmonary embolism (PE) were numerically higher in baricitinib 4-mg (IR=1.7) versus both baricitinib 2-mg and placebo (IR=0). With long-term exposures, the exposure-adjusted IR of VTE for baricitinib-treated patients with RA was similar to the background rates published in the literature for the target population. Cases observed with baricitinib were confounded by 1 or more recognized risk factors for VTE and the time to onset of an event ranged from 37 to 1658 days.

VTE has been classified as an important potential risk for baricitinib and is also an adverse drug reaction. Mitigation of the risk of venous thromboembolism will be managed through the appropriate exclusion and discontinuation criteria which limit participation of patients who are at an increased risk of VTE (Section 5.2, Section 7.1.1). The addition of VTE prophylaxis to all patients enrolled in this study unless there is a contraindication will also reduce the potential risk (Section 6.5.2).

During the 16-week treatment period of RA studies, overall infections were numerically increased with IRs per 100 patient-years of 100.1 events, 99.1 events and 82.1 events in baricitinib 4-mg, baricitinib 2-mg, and placebo respectively. However, serious infections for the 16-week treatment period were similar between baricitinib 4-mg, baricitinib 2-mg, and placebo (IRs per 100 patient-years 3.7, 3.6 and 4.2 respectively). The frequency of Herpes zoster was higher for baricitinib 4-mg versus placebo (1.4 vs 0.4) and for baricitinib 4-mg versus baricitinib 2-mg (1.4 vs 1.0).

There are provisions in the protocol to mitigate risk from potential concurrent infections, including allowance of appropriate use of standard-of-care for treatment of infections and criteria for permanent discontinuation of study drug if the patient is diagnosed with active tuberculosis, hepatitis B, or hepatitis C (Section 6.5.2, Section 7.1.1). Permanent discontinuation of study drug will also occur if a participant develops a serious adverse event which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug (Section 7.1.1).

It is difficult to extrapolate the potential risks of baricitinib in a disease state very different than a chronic autoimmune disease such as RA. However, baricitinib has an established safety profile for RA, with approximately 10,034 patients having received baricitinib in all clinical trials and 150,000 patients estimated to have been treated with baricitinib (based on postmarketing sources) worldwide. In RA, baricitinib was approved for long-term chronic use whereas the duration of baricitinib treatment in this COVID-19 study will be short (up to 14 days). The half-life of the molecule is approximately 12 hours, which will lead to a very short washout period once discontinued and has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies

More detailed information about the known risks and reasonably expected adverse events of baricitinib may be found in the Investigator's Brochure (IB).

In summary, in the context of the cumulative knowledge for baricitinib with respect to the established safety profile, the potential to mitigate the hyperinflammatory state and cytokine storm associated with SARS-CoV-2, and the high unmet need for a treatment to slow the

progression of COVID-19 infection, the benefit/risk balance for this study is assessed to be favorable.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of baricitinib 4-mg once daily (QD) compared to placebo on disease progression in patients with COVID-19 infection	Proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 28
Key Secondary	
To evaluate the effect of baricitinib 4-mg QD compared to placebo on clinical outcomes in patients with COVID-19 infection	Proportion of patients with at least 1-point improvement on NIAID-OS or live discharge from hospital at Day 4, Day 7, Day 10, Day 14
	Number of ventilator-free days (Day 1 to Day 28)
	Time to recovery (NIAID-OS) (Day 1 to Day 28)
	Overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, Day 14
	Duration of hospitalization (Day 1 to Day 28)
	Proportion of patients with a change in oxygen saturation from <94% to ≥94% from baseline to Day 4, Day 7, Day 10, Day 14
	All-cause mortality (Day 1 to Day 28)
Other Secondary	
To evaluate the effect of baricitinib 4-mg QD compared to placebo on other clinical outcomes in patients with COVID-19 infection	<u>Treatment Period – (Day 1 to Day 28, unless otherwise specified)</u> Time to recovery (NIAID-OS) by disease duration of < 7 days or ≥7 days Duration of stay in the intensive care unit (ICU) in days Time to clinical deterioration (one-category increase on the NIAID-OS) Time to clinical improvement in one category of the NIAID-OS Time to resolution of fever, in patients with fever at baseline Overall improvement on the NIAID-OS evaluated at Day 21, Day 28

Objectives	Endpoints
	Mean change in National Early Warning Score (NEWS) Time to definitive extubation Time to independence from non-invasive mechanical ventilation Time to independence from oxygen therapy in days Time to oxygen saturation of ≥94% on room air in days Number of days with supplemental oxygen use Number of days of resting respiratory rate <24 breaths per minute <u>Landmark analysis – Day 4, Day 7, Day 10, Day 14, Day 28</u> Proportion of patients in each severity category on the NIAID-OS Proportion of patients with at least 2-point improvement on the NIAID-OS or live discharge from the hospital Proportion of patients with at least 1-point improvement on NIAID-OS or live discharge from hospital
Exploratory	
Exploratory objectives and endpoints may include the following: C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), ferritin Virologic measures Characterization of the pharmacokinetics of baricitinib in intubated patients with COVID-19 infection	
Notes: The Day 28 Clinical Status Assessment is entered for midnight to midnight for the previous day. Therefore, the Day 28 Clinical Status Assessment is entered on Day 29. Recovery is defined as the first day or time from study start on which the participant satisfies 1 of the following 3 categories from the ordinal scale: Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; Not hospitalized, limitation on activities and/or requiring home oxygen; Not hospitalized, no limitations on activities (applies to live discharge from hospital to home as well).	

4. Study Design

4.1. Overall Design

Study I4V-MC-KHAA (KHAA) is Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of baricitinib 4-mg given once daily (QD). The primary endpoint is the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28.

The study duration will be up to approximately 42 days over 3 study periods:

Screening: on Day 1 prior to dosing

Treatment period: treatment is administered for up to 14 days, or up to the day of hospital discharge, whichever comes first, followed by treatment evaluations up to Day 28

Follow-up: Period starting after treatment period, lasting not less than 28 days after last dose of study drug.

Patients will be enrolled if they are hospitalized with coronavirus (SARS-CoV-2) infection and meet other study entry criteria. Patients requiring invasive mechanical ventilation (including ECMO) at the time of study entry are not eligible.

While hospitalized, enrolled patients will receive either baricitinib or placebo until Day 14 or until the day of hospital discharge, whichever comes first.

Participants may remain on stable background therapy per local guidelines, including antimalarials (hydroxychloroquine), and/or antivirals, and/or azithromycin. Hydroxychloroquine and chloroquine are not approved to treat COVID-19 infection. Recently published data suggest that chloroquine and hydroxychloroquine may be associated with increased risk in patients with COVID-19 infection (Mehra et al. 2020; Tang et al. 2020). Hydroxychloroquine and chloroquine are only permitted as concomitant medication if these are recommended or required by local COVID-19 treatment guidelines. Concomitant biologics (including interferon, tocilizumab, sarilumab, TNFi) or Janus kinase (JAK) inhibitors [except for study drug]) are not permitted (see Section 6.5).

A final follow-up visit approximately 28 days after last dose is required for all randomized patients, including those discharged from hospital before Day 14. Activities at the final visit can be conducted as a telephone visit.

Discharge from the hospital prior to Day 14 is not considered early discontinuation from the study drug or from the study. All randomized patients, including patients meeting criteria for early discontinuation of study drug, as specified in Section 7.1, should be encouraged to remain in the study for the scheduled study assessments specified in the Schedule of Activities (SoA) (Section 1.3). Patients who prematurely discontinue from the study should have an ETV and final follow-up visit, if possible, as shown in the SoA.

The study schema is presented in Section 1.2.

4.2. Scientific Rationale for Study Design

The double-blind, placebo-controlled design of this study limits potential bias in investigator assessments and enables a clearer interpretation of the effects of active drug compared to placebo (background therapy).

The primary endpoint of this study is the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28. Progression to requiring non-invasive or invasive mechanical ventilation is an indicator of critical disease and can occur at any timepoint after hospitalization. Time on ventilation increases the patient's risk of complications, including pneumothorax, airway injury, alveolar damage, ventilator-associated pneumonia, and ventilator-associated tracheobronchitis, which are associated with higher death rates and longer hospital stays (Craven et al. 2009; Hess 2011; Patel 2020). An effective treatment should be able to halt progression of patients to ventilation at any time. A primary endpoint capturing progression to death or non-invasive ventilation/high-flow oxygen or invasive ventilation (including ECMO) *by* Day 28 (rather than *at* Day 28) is clinically meaningful because it utilizes all available data about the course of disease progression or resolution in response to treatment.

In addition, an observation of treatment effect for baricitinib to 28 days is based on US regulatory and WHO recommendations, and allows comparisons across different therapeutic agents in COVID-19 studies.

The rationale for study treatment for up to 14 days is based on the known onset of efficacy in the RA population, which is as early as 1 week (Olumiant Summary of Product Characteristics), and on the expected duration of treatment needed for an acute infection such as COVID-19. Recently, data were published on a case series describing a 14-day course of baricitinib in patients with mild to moderate COVID-19 infection (Cantini et al.2020).

A key secondary objective is improvement on an ordinal scale. The ordinal scale used in this study (NIAID-OS) has been used in the NIAID ACTT study and is similar to the WHO ordinal scale recommended for use in the assessment of therapeutics for the treatment of COVID-19 infection (WHO R&D). Clinical improvement as described by a similar ordinal scale was used in a study comparing the effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection (Wang Y et al. 2019), and was an endpoint recommended by the WHO R&D Blueprint expert group (WHO R&D).

To ensure that sufficient patients enrolled are in the hyperinflammatory state which correlates with progression to severe disease and ventilation requirements, patients are required to have at least one inflammatory marker (CRP, D-dimer, LDH, ferritin) that is greater than the upper limit of normal (ULN).

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the possible need to assess variable response in safety and/or efficacy based on race or ethnicity. Such a need can be addressed only if all the relevant data are collected.

The post-treatment follow-up period allows for continued safety monitoring after the last dose.

4.3. Justification for Dose

The 4-mg QD dose of baricitinib selected for this study in a patient population with COVID-19 infection is based on clinical data showing an effect of baricitinib on inhibition of cytokine signaling. Upregulation of multiple proinflammatory cytokines has been shown in patients with COVID-19 infection admitted to ICU units in Wuhan, China, and elevated IL-6 was a predictor of mortality in COVID-19 patients in another China-based study.

In patients with RA, there was a dose-dependent reduction in plasma IL-6 levels, assessed after 12 weeks of treatment. In ex vivo studies, there was a similar dose-dependent effect on inhibition of multiple cytokines implicated in COVID-19 infection. In a compassionate use program in pediatric patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, patients on a mean dose of baricitinib 6-mg QD showed a striking reduction in cytokine signaling (Sanchez et al. 2018). In healthy volunteers, exposures observed at the baricitinib 4-mg (or higher) doses are associated with reduction of IL-6 induced ex vivo pSTAT3 activation (Shi et al. 2014).

In terms of risk considerations, the proposed duration of treatment with baricitinib 4-mg in the setting of COVID-19 infection is brief (up to 14 days); to date, baricitinib has been studied and approved for long-term use in the setting of chronic autoimmune conditions. In a vaccine response study, individuals treated with baricitinib 4-mg can mount an appropriate immune response to a pneumococcal vaccine, suggesting that transient exposure to baricitinib will not result in clinically meaningful changes to adaptive immunity (Winthrop et al. 2019).

In addition, the choice of the 4-mg dose is supported by efficacy and safety data for baricitinib in Phase 2 and Phase 3 RA studies. In the RA population, there was a dose-dependent reduction in plasma IL-6 levels, assessed after 12 weeks of treatment (data on file). In ex vivo studies, there was a similar dose-dependent effect on inhibition of multiple cytokines. The baricitinib 4-mg dose is approved in multiple regions globally for the treatment of RA and is currently being studied in large ongoing global Phase 3 studies of RA, systemic lupus erythematosus, atopic dermatitis, and alopecia areata.

In summary, the potential benefit of the 4-mg dose in reducing the hyperinflammatory state caused by COVID-19 infection, and the short duration of treatment with this dose with a well-established safety profile, provides the rationale for the assessment of the benefit/risk profile of the baricitinib 4-mg dose in the setting of a randomized, controlled clinical trial in a hospital setting.

Dose Adjustment for Renal Impairment

As detailed in the IB, baricitinib exposure increases with decreased renal function (Study I4V-MC-JADL [JADL]). Based on PK simulations, dose adjustment is not required for patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2. Patients with eGFR >30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 at screening who are randomized to the 4-mg QD dose will receive a 2-mg QD dose, to avoid exposures that exceed those of the 4-mg QD dose in patients with eGFR ≥60 mL/min/1.73 m^2.

4.4. End-of-Study Definition

A participant is considered to have completed the study if he or she has completed the last scheduled procedure shown in the SoA (Section 1.3).

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

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

All screening evaluations must be conducted and reviewed to confirm that potential participants meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Due to the criticality of participant health and the setting of this research study, verbal interview of the potential participant, or his or her legal representative or family member, may be the source for pre-existing conditions and prespecified medical history, unless otherwise specified within the eligibility criteria.

For screen failures and rescreening activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria during the screening period, unless otherwise specified below:

Informed consent

[1] Patient (or legally authorized representative) who gives informed consent as described in Appendix 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Participant characteristics

[2] Are male or female patients from 18 years of age (inclusive), at the time of enrollment.

Note: Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. There are no contraceptive requirements for men. See Appendix 10.4 for contraception requirements.

COVID-19 pulmonary infection-related inclusion criteria

[3] Hospitalized with coronavirus (SARS-CoV-2) infection, confirmed by polymerase chain reaction (PCR) test or other commercial or public health assay in any specimen, as documented by either of the following:

- PCR positive in sample collected <72 hours prior to randomization; OR
- PCR positive in sample collected ≥72 hours prior to randomization (but no more than 14 days prior to randomization), documented inability to obtain a repeat sample (for example, due to lack of testing supplies, limited testing capacity, results taking >24 hours, etc.) AND progressive disease suggestive of ongoing SARS-CoV-2 infection

[4] Have evidence of pneumonia (SpO2 <94 or PaO2/FiO2 [or SpO2/FiO2] ratio <300 mmHg or chest imaging findings consistent with pneumonia), OR have evidence of active COVID infection (with clinical symptoms including any of the following: fever, vomiting, diarrhea, dry cough, tachypnea defined as respiratory rate >24 breaths/min)

[5] Have indicators of risk of progression: at least 1 inflammatory markers >ULN (CRP, D-dimer, LDH, ferritin) with at least 1 instance of elevation >ULN within 2 days before study entry.

5.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria within the screening period, unless otherwise specified:

Prior or concomitant therapy

[6] Are receiving cytotoxic or biologic treatments (such as TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], T-cell or B-cell targeted therapies (rituximab), interferon, or Janus kinase (JAK) inhibitors for any indication at study entry.

Note: A washout period 4 weeks (or 5 half-lives, whichever is longer) is required prior to screening, with the following exceptions:

- B-cell targeted therapies: a washout period of 24 weeks or 5 half-lives (whichever is longer)
- TNF inhibitors: a washout period of 2 weeks or 5 half-lives (whichever is longer), and
- JAK inhibitor: a washout period of 1 week or 5 half-lives (whichever is longer).

See Section 6.5.1 for requirements.

[7] Have ever received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19

[8] Have received high dose corticosteroids at doses >20 mg per day (or prednisone equivalent) administered for ≥14 consecutive days in the month prior to study entry.

[9] Strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry.

Current or historical infections

Note: Documentation from verbal interview or available medical records is acceptable.

[10] Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening tests required).

[11] Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product. Note: Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who, in the judgment of the investigator, are at increased risk for serious infections or other safety concerns given the study products should be excluded.

Vaccines

[12] Have received any live vaccine within 4 weeks before screening, or intend to receive a live vaccine during the study.

Note: Use of nonlive (inactivated) vaccinations is allowed for all participants.

Other medical conditions or history

[13] Require invasive mechanical ventilation, including ECMO at study entry.

[14] Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product.

[15] Have a history of VTE (deep vein thrombosis [DVT] and pulmonary embolism [PE]) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE).

[16] Anticipated discharge from the hospital, or transfer to another hospital (or another unit), which is not a study site within 72 hours after study entry.

Diagnostic assessments

[17] Have neutropenia (absolute neutrophil count <1000 cells/μL) (<1.00 x 10^3/μL or <1.00 GI/L)

[18] Have lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 10^3/μL or <0.20 GI/L)

[19] Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times ULN

[20] eGFR (Modification of Diet in Renal Disease [MDRD]) <30 mL/min/1.73 m^2.

Note: For each aforementioned diagnostic assessment, 1 repeat testing is allowed during the screening period, and values resulting from repeat testing may be accepted for a participant's enrollment eligibility if the other eligibility criteria are met. In addition, these tests performed in the 24 hours prior to study entry will be accepted for determination of eligibility.

Prior or concurrent clinical study experience

[21] Have a known hypersensitivity to baricitinib or any of its excipients.

[22] Are currently enrolled in any other clinical study involving an investigation product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Note: The participant should not be enrolled (start)in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 28.

Other exclusions

[23] Are pregnant, or intend to become pregnant or breastfeed during the study.

[24] Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

[25] Are using or will use extracorporeal blood purification (EBP) device to remove pro-inflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb®.

[26] Are, in the opinion of the investigator, unlikely to survive for at least 48 hours after screening.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

5.4.1. Allowed Retesting of Screening Investigations

Repeating the screening labs associated with criteria [17], [18], [19], and [20] during the screening period does not constitute rescreening.

5.4.2. Rescreening of Individuals Who Failed Screening

Individuals who do not meet the COVID-19 pulmonary infection-related criteria and other diagnostic assessments for participation in this study (screen failures) may be rescreened.

Rescreening 1 time for any eligibility parameter that was not initially met is allowed if patient is expected to meet study requirements per investigator assessment. It is not necessary to repeat all screening requirements. Patient will not be required to reconsent due to rescreening.

Rescreened participants should be assigned a new participant number.

6. Study Intervention

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

6.1. Study Interventions Administered

Study interventions

This study involves baricitinib and placebo, as shown below.

Treatment Name	baricitinib	placebo
Dosage Formulation	tablet	tablet
Dosage Levels	4 mg as two 2-mg tablets*	2 placebo tablets
Routes of Administration	Oral**	Oral**
Dosing Instructions	daily	daily

* Patients with eGFR >30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 at screening who are randomized to the baricitinib 4-mg dose will receive a 2-mg QD dose, to avoid exposures that exceed those of the 4-mg QD dose in patients with eGFR ≥60 mL/min/1.73 m^2. Patients on the baricitinib 2-mg QD dose will receive a single 2-mg tablet.

Patients with eGFR <60 mL/min/1.73 m^2 at screening who are randomized to placebo will receive one placebo tablet.

** Baricitinib will be administered as a 4-mg dose orally (po) (two 2-mg tablets) or crushed for NG tube, given daily, for the duration of the hospitalization up to a 14-day total course. A placebo will be given as 2 tablets po or crushed for NG tube, daily, for the duration of the hospitalization up to a 14-day total course.

Investigational product will be administered to the patient at the study site.

Packaging and labeling

Study interventions (baricitinib and placebo) will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP). Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

6.2. Preparation/Handling/Storage/Accountability

The Pharmacy Manual provides instructions for the preparation, handling, and storage of baricitinib drug product and placebo, and describes site responsibility and accountability for the administered products.

Investigators should consult the information provided in the Pharmacy Manual or the label for specific administration information, including warnings, precautions, contraindications, adverse reactions, and dose modifications.

Handling and storage

Follow the storage and handling instructions on the IP packaging.

Site responsibilities and accountability

The following are responsibilities of the investigator or his or her designee:

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The investigator or designee is also responsible for

- explaining the correct use of the study interventions
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding will be maintained in the Phase 3 study

Method of treatment assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1 ratio (baricitinib 4-mg: placebo) at Day 1.

Randomization will be stratified by these factors:

- disease severity:
  - hospitalized not requiring supplemental oxygen, requiring ongoing medical care
  - hospitalized requiring supplemental oxygen by prongs or mask
  - hospitalized requiring non-invasive ventilation or high-flow oxygen

- age (<65 years; ≥65 years)
- region (United States, Europe, rest of world), and
- symptom onset <7 days or ≥7 days prior to randomization.

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

Emergency unblinding

Emergency unblinding for adverse events may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If a participant's study treatment assignment is unblinded to the investigator, to site personnel performing assessments, or to the participant, the participant must be discontinued from the study, unless the investigator obtains specific approval from the sponsor's medical monitor for the participant to continue in the study (Section 7.1.1).

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment.

In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor for the participant to continue in the study.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator and/or appropriate designee at the study site. The date and time of each dose administered will be recorded in the source documents and recorded in the case report form (eCRF). Deviations from the prescribed dosage regimen should be recorded in the eCRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- dates of administration including start and end dates, and
- dosage information, including dose for concomitant therapies of special interest.

Participants will be instructed to consult the investigator or other appropriate study site personnel before taking any new medications or supplements during the study.

The sponsor's medical monitor should be contacted if there are any questions.

6.5.1. Prior Medications

Participants must have been discontinued from following medications before enrolling in the study, as stated in Section 5.2:

- Biologic therapy (such as anti-IL-1, anti-IL-6 [tocilizumab or sarilumab], T-cell targeted therapies, interferon) must be discontinued 4 weeks or 5 half-lives, whichever is longer, prior to screening
- B-cell targeted therapies (rituximab): a washout period of 24 weeks or 5 half-lives (whichever is longer)
- TNF inhibitors: a washout period of 2 weeks or 5 half-lives (whichever is longer), and
- JAK inhibitor: a washout period of 1 week or 5 half-lives (whichever is longer).

In addition, strong inhibitors of OAT3 (such as probenecid) must be discontinued at study entry.

6.5.2. Required and Permitted Concomitant Therapy

Prophylaxis for VTE is required for all patients unless there is a major contraindication such as active bleeding events or history of heparin-induced thrombosis.

The following will be permitted as concomitant therapy during the study:

- Concomitant antibiotic, antiviral, antifungal, and/or antimalarial (background therapy in keeping with local clinical practice for management of COVID-19). Hydroxychloroquine and chloroquine are only permitted as concomitant medication if these are recommended or required by local COVID-19 treatment guidelines.
- Corticosteroid use should be limited unless indicated per standard of care for a concurrent condition such as, but not limited to, asthma, chronic obstructive pulmonary disease, adrenal insufficiency.

6.5.3. Prohibited Concomitant Therapy

The following will be prohibited as concomitant therapy during the study:

- Any biologic therapy (such as TNF inhibitors, anti- IL-1, anti-IL-6 [tocilizumab or sarilumab], T-cell or B-cell targeted therapies (rituximab), interferon, JAK inhibitors (other than baricitinib), or immunoglobulin (IgG) for any indication.
- Live vaccines, including herpes zoster vaccination. Nonlive seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.
- Strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry.
- Extracorporeal blood purification device to remove pro-inflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb®.

6.6. Dose Modification

Patients with eGFR >30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 at screening who are randomized to the baricitinib 4-mg dose will receive a 2-mg QD dose, to avoid exposures that exceed those of the 4-mg QD dose in patients with eGFR ≥60 mL/min/1.73 m^2.

If after randomization eGFR decreases to less than 60 mL/min/1.73 m^2 but more than 30 mL/min/1.73 m^2, patients will receive a 2-mg QD dose (one tablet) until eGFR returns to eGFR ≥60 mL/min/1.73 m^2.

Baricitinib is not recommended for use in patients with estimated GFR of <30 mL/min/1.73 m^2.

6.7. Intervention after the End of the Study

Baricitinib will not be provided to participants following completion of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

In rare instances, it may be necessary for a participant to permanently discontinue study drug.

These sections describe reasons for a participant's

- permanent or temporary discontinuation of study drug, or
- discontinuation (withdrawal) from the study.

Discontinuation of specific sites or of the trial as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Appendix 10.1, Section 10.1.9.

Note: In this study, discharge from the hospital prior to Day 14 is not considered early discontinuation from the study drug or from the study.

7.1. Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

7.1.1. Criteria for Permanent Discontinuation of Study Drug

Data collection and safety follow-up when study drug is permanently discontinued

If a patient permanently discontinues study drug early (that is, prior to hospital discharge or Day 14, whichever comes first), the patient should remain in the study and have the scheduled study assessments specified in the SoA (Section 1.3). Every effort should be made to encourage participants to remain in the study for the duration of their planned outcome assessments. Participants should be educated on the continued scientific importance of their data, even if they discontinue study drug.

Unless the participant withdraws consent or meets other criteria listed in Section 7.2, those who discontinue study drug early will remain in the study. The reason for participant discontinuation of study drug should be documented in the CRF.

If a patient who is not receiving study drug is unwilling or unable to continue the scheduled study assessments, the site personnel should attempt to collect as much follow-up information as possible, including, at minimum, information specified for an early termination visit (ETV) **and** information for the final follow-up visit occurring approximately 28 days after the last dose.

Criteria for permanent discontinuation of study drug

Possible reasons leading to permanent discontinuation of study drug include, but are not limited to, the following:

Participant decision

- The participant requests to discontinue the study drug.

Prohibited concomitant medication use

- The participant requires treatment with a prohibited medication (Section 6.5.3).

Pregnancy

- The participant becomes pregnant during the study.

Safety considerations

- The participant should be discontinued if the participant develops any of the following conditions during the study:
  - new malignancy
  - human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) infection
  - active TB infection or evidence of latent TB (positive QuantiFERON-TB Gold assay or T-SPOT.TB or greater than 1 "indeterminate" result for QuantiFERON-TB Gold assay or a "borderline" result T-SPOT.TB assay)
  - active hepatitis B (HBV DNA) or hepatitis C (HCV RNA)
  - VTE (DVT/PE)
- The investigator, after consultation with the sponsor's designated medical monitor, determines that a systemic hypersensitivity reaction has occurred and is related to study drug administration.
- The participant experiences any 1 of the following events on 2 consecutive samples taken at least 48 hours, but no more than 1 week, apart.
  - Total white blood cells (WBC) <1000 cells/μL
  - Absolute neutrophil count (ANC) <500 cells/μL
  - Absolute lymphocyte count (ALC) <200 cells/μL
- The participant has an adverse event or serious adverse event or a clinically significant change in a laboratory value that, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.

Hepatic event or liver test abnormality

- Discontinuation of study drug because of abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with the medical monitor (see Section 8.2.6)
  - ALT or AST >8 times ULN or
  - ALT or AST >3 times ULN and (total bilirubin >2 times ULN or PT-INR >1.5)

Other reasons

- Unblinding: If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study drug and continue to post-treatment follow-up. In cases where there are ethical reasons to have the participant continue on study drug, the investigator must obtain specific approval from the sponsor or designee for the participant to continue.

7.1.2. Criteria for Temporary Interruption (Withholding) of Study Drug

Study drug should be interrupted for:

- Absolute neutrophil count (ANC) <500 cells/μL
- Absolute lymphocyte count (ALC) <200 cells/μL
- ALT or AST >5 times ULN
- estimated GFR of <30 mL/min/1.73 m^2

Study drug may be restarted when these criteria are no longer applicable, at the discretion of the investigator. Retest timing and frequency is at the investigator's discretion.

Baricitinib is not recommended for use in patients with estimated GFR of <30 mL/min/1.73 m^2.

7.2. Participant Discontinuation/Withdrawal from the Study

Participant discontinuation (withdrawal from the study) is expected to be uncommon.

A participant may withdraw from the study in the following circumstances:

- at any time at his or her own request, or at the request of his or her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant enrolls in any other clinical study involving an investigational medicinal product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, needs to be transferred to another hospital or another hospital unit
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Data collection and follow-up for participants who discontinue the study

At the time of discontinuing from the study, an ETV and final follow-up visit should be conducted, if possible, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study.

Withdrawal of consent for disclosure

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor's clinical research physician agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational medicinal product. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 ("Safety Assessments"), and Section 8.3 ("Adverse Events and Serious Adverse Events").

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1. Efficacy Assessments

8.1.1. COVID-19 Clinical Status Assessment

The COVID-19 Clinical Status Assessment will be used to collect components needed to derive scores for the ordinal scales used in this study. This assessment will also collect the use of proning and reason for discontinuation of invasive mechanical ventilation.

The assessment will be completed on each day of the study by entering the assessment for the previous day (that is, midnight to midnight; 00:00 – 23:59 [24 hour clock]).

On Day 1, the patient's status at randomization will be reported.

On Day 2 the status will be reported for the period from randomization to midnight on Day 1.

The patient's clinical status will be captured daily.

The hospitalization portion of the patient's clinical status will be completed daily, regardless of patient's discharge status or patient contact.

The patient's clinical status reflecting data for Day 28 (midnight to midnight) will be recorded in the Day 29 eCRF.

Primary Endpoint Assessments

The primary endpoint will assess the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 28. Non-invasive ventilation/high-flow oxygen includes administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). High-flow oxygen consists of breathing support administered through a face mask, nasal mask, or a helmet (including BiPAP, CPAP).

Patients on non-invasive ventilation/high-flow oxygen at baseline will be counted toward the primary endpoint if they progress to invasive mechanical ventilation.

8.1.2. Ordinal Scale

Using data from the COVID-19 Clinical Status Assessment, results will be calculated for ordinal scales currently being used in other studies, and in this study, to measure clinical outcomes in patients treated for COVID-19, in particular the NIAID-OS.

The NIAID-OS is as follows:

Patient State Descriptor
Not hospitalized, no limitations on activities
Not hospitalized, limitation on activities and/or requiring home oxygen
Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care: (This would include those kept in hospital for quarantine/infection control, awaiting bed in rehabilitation facility or homecare, etc).
Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
Hospitalized, requiring supplemental oxygen
Hospitalized, on non-invasive ventilation or high-flow oxygen devices
Hospitalized, on invasive mechanical ventilation or ECMO
Death

Source: Adaptive COVID-19 Treatment Trial (ACTT) [NCT04280705].

In this study, because scores for the ordinal scales will be derived from data already entered into the eCRF, no additional data entry related to the ordinal scales will be required.

8.1.3. Other Efficacy Assessments

Several secondary efficacy endpoints of this study are based on clinical assessments and procedures conducted in hospitalized patients with COVID-19 infection. The following table shows these endpoints, their definitions for this study, and measurement method.

Endpoint	Defined as	Measured by
Ventilator-free days	Patient breathing without mechanical ventilation assistance, if the period of unassisted breathing lasts at least 24 consecutive hours and the patient does not die	—
Recovery	Participant satisfies one of the following three categories from the NIAID-OS: ● Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; ● Not hospitalized, limitation on activities and/or requiring home oxygen; ● Not hospitalized, no limitations on activities (applies to live discharge from hospital to home as well)	score on NIAID-OS
Duration of hospitalization	Period of time the patient is hospitalized	date of admission to date of discharge
Oxygen saturation	Measure of the oxygen level of the blood.	pulse oximetry
All-cause mortality	28-day all-cause mortality	score on NIAID-OS
Duration of stay in the intensive care unit (ICU)	Date of admission to ICU to date of discharge from ICU	—
Clinical deterioration	One-category increase on the ordinal scale (worsening in patient clinical status)	score on NIAID-OS

Endpoint	Defined as	Measured by
Clinical improvement	One-category decrease on the ordinal scale (improvement of patient clinical status)	score on NIAID-OS
Fever	≤36.6°C (axilla) ≤37.2°C (oral), or ≤37.8°C (rectal or tympanic) at least 48 hours	oral, rectal, or tympanic measurements
Definitive extubation	When patient is removed from mechanical ventilation	score on NIAID-OS
Non-invasive ventilation/ high-flow oxygen	Administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). Patients requiring high-flow oxygen breathing support administered through a face mask, nasal mask, or a helmet (includes BiPAP, CPAP)	score on NIAID-OS
Supplemental oxygen use	Patients requiring oxygen by mask or nasal prongs (cannula)	score on NIAID-OS
Respiratory rate	Measure of resting respiratory rate per minute	—
Mechanical ventilation and intubation	Patient requires mechanical ventilation and is intubated during the study	score on NIAID-OS

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

8.1.3.1. Alert Voice Pain Unresponsive (AVPU) and National Early Warning Score (NEWS)

Alert Voice Pain Unresponsive (AVPU)

Level of consciousness is an important parameter in assessing the severity of acute illness. The AVPU scale is used to measure and record a patient's level of consciousness. The AVPU scale used in this study is the one recommended for use in the calculation of NEWS (Royal College of Physicians 2012).

The investigator and/or appropriate designee assesses the patient's current condition in the following sequence, recording only one of these four possible outcomes:

Alert: The patient is fully awake, with spontaneous opening of the eyes, responsiveness to voice, and motor function. The patient may, or may not be, confused or disorientated.

Voice: The patient makes some kind of response when spoken to. The patient's response can be a response of eyes, voice, or motor function, for example, opening eyes when spoken to, or making a grunt or moan or moving a limb when spoken to.

Pain: The patient responds to a pain stimulus. The response may be withdrawal from pain or involuntary flexion or extension of limbs.

Unresponsive: Commonly called "unconscious." This outcome is recorded if the patient gives no eye, voice, or motor response to voice or pain.

National Early Warning Score (NEWS)

In this study, because the scores for the NEWS parameters will be derived from data already entered into the eCRF, no additional NEWS-specific data entry will be required.

The National Early Warning Score (NEWS) is used to detect and report changes in illness severity in patients with acute illness. The score is determined from six physiological parameters readily measured over time in hospitalized patients:

- respiration rate
- oxygen saturation
- temperature
- systolic blood pressure
- heart (pulse) rate, and
- level of consciousness, as measured by AVPU.

A score is assigned to each parameter, with the magnitude of the score representing the extremity of variation from the norm. A weighting score is added for patients needing supplemental oxygen (oxygen delivery by mask or nasal cannula). The aggregate score is reflective of the patient's status (Royal College of Physicians 2012).

8.1.3.2. Laboratory Assessments

Laboratory assessments will be collected at the times shown in the SoA (Section 1.3).

8.2. Safety Assessments

Order of safety assessments

If multiple safety assessments are scheduled to occur during the same visit, the preferred order of completion is

1) vital signs first
2) other safety assessments, including physical examinations and nonleading (spontaneous) adverse event collection, and finally
3) sample collection for clinical laboratory, pharmacodynamic (PD), and biomarker testing.

Data collection and reporting

The adverse event data collection and reporting requirements are described in Section 8.3 and Appendix 10.3.

Any clinically significant findings that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an adverse event via eCRF.

Safety monitoring

The principle investigator will monitor safety and laboratory data throughout the study and should discuss immediate safety concerns with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue the study intervention.

The sponsor will monitor the safety data, including adverse events and serious adverse events (SAEs), discontinuations, medical history, concomitant medications, vital signs, and clinical laboratory results by means of periodic blinded reviews and other appropriate methods. These methods include reviews by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and who reviews applicable clinical safety and epidemiological publications from the literature. If this safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, additional analyses of the safety data can be performed (Section 9.5 and Section 9.6).

8.2.1. Vital Signs

Vitals signs (body temperature [oral, rectal, or tympanic measurements], blood pressure, heart [pulse] rate, respiration rate, oxygen saturation) will be assessed and documented daily, and as clinical indicated, and entered into the eCRF as specified in the SoA (Section 1.3) and as clinically indicated.

These include the minimum/maximum vital signs daily (including temperature, respiratory rate, oxygen saturation).

The most recent measurements prior to study drug administration will be used to calculate the NEWS. Vital signs should be performed at approximately the same time each day.

Additional vital signs may be measured during the study visits if warranted, as determined by the investigator and/or appropriate designee.

8.2.2. Physical Examinations

A complete physical examination will be performed at the screening visit if feasible. This examination excludes pelvic, rectal, and breast examinations unless clinically indicated. The screening visit should include an assessment of TB risk factors.

A symptom-directed physical examination will be performed on other days, as specified in the SoA (Section 1.3) and as clinically indicated.

Height will be measured or collected as reported, and weight will also be measured. Both will be recorded as specified in the SoA.

8.2.3. Electrocardiograms

For each participant, a 12-lead standard ECG will be obtained locally and read by a qualified physician (the investigator or qualified designee) at the site on Day 1, as specified in the SoA (Section 1.3). ECGs obtained within 24 hours of Day 1 are acceptable.

8.2.4. Chest Imaging Studies

A chest x-ray or computerized tomography (CT) scan, assessed by a radiologist pulmonologist, or appropriate physician will be obtained and the result should be recorded in the eCRF, as specified in the SoA (Section 1.3).

A report on imaging (that is, documentation of hospital-based test result) available prior to study entry is acceptable for the Day 1 imaging (up to 24 hours prior to Day 1 is acceptable).

Results for imaging at other timepoints, if carried out, will be provided via the eCRF.

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB, including chest imaging as assessed by a radiologist or pulmonologist.

8.2.5. Laboratory Tests

Appendix 10.2 lists the clinical laboratory tests to be performed, and the SoA (Section 1.3) specifies the study days at which samples are collected for clinical laboratory tests.

Laboratory tests performed in the 24 hours prior to study entry will be accepted for determination of eligibility (except where designated differently in the SoA).

Additional tests may be performed at any time during the study as deemed necessary by the investigator and/or appropriate designee, or as required by local regulations.

All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator and/or appropriate designee (for example, SAE or adverse event or dose modification), then the results must be recorded in the eCRF.

Reviewing and recording test results

The investigator and/or appropriate designee must review the laboratory report, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

Documentation of review by the investigator and/or designee may be completed according to institution processes or by making an entry in the patient's progress notes (medical record) stating that the lab results have been reviewed.

The laboratory reports must be filed with the source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Repeat testing after clinically significant abnormal findings

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the

investigator or the medical monitor during study participation. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Blinding of laboratory test results

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel (Appendix 10.2).

Sample retention

Unless otherwise specified in the subsections of Section 8 or in Appendix 10.1, Section 10.1.12 ("Long-Term Sample Retention"), all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results or according to local laboratory procedures. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.5.1. Pregnancy Testing

Pregnancy testing is to be performed on women of childbearing potential (WOCBP). Participants who are pregnant will be permanently discontinued from study drug (Section 7.1.1). A pregnancy test will be performed at screening only.

8.2.6. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3 times ULN, ALP ≥2 times ULN, or elevated TBL ≥2 times ULN, liver testing should be repeated within 2 to 3 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to appropriate levels for the patient, per investigator assessment.

Discontinuation criteria of investigational products, either temporary interruption or permanent discontinuation, due to abnormal ALT, AST, TBL, or ALP, are detailed in Section 7.1.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or SAE and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study.

Pregnancy after maternal or paternal exposure to investigational product does not meet the definition of an adverse event. However, to fulfill regulatory requirements, any pregnancy should be reported using the SAE process described in Appendix 10.3, Section 10.3.4, to collect data on the outcome for both mother and fetus. See also Section 8.3.5.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All adverse events will be collected from the time of the participant's signing of the ICF until the participant's last post-treatment follow-up visit. Adverse events will be recorded on the Adverse Event eCRF.

Likewise, all SAEs will be collected from the signing of the ICF until the last post-treatment follow-up visit.

Although all adverse events after signing the ICF are recorded by the site in the CRF/electronic data entry tool, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF but prior to receiving study drug, the SAE needs to be reported ONLY if the SAE is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or the sponsor's designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse events or SAEs after the conclusion of study participation, that is, once the participants have discontinued and/or completed the study (the Participant Study Disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has ended his or her study participation, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting adverse events and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained (including death), or the participant is lost to follow-up (Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3, Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

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

8.3.5. Pregnancy

Details about pregnancy will be collected for pregnancies occurring in female study participants and in female partners of male study participants.

If a pregnancy is reported as having occurred during the study or within 1 week after the last dose of study intervention, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4, Section 10.4.3.

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Special Assessments of Infections and Venous Thromboembolic Events

Venous Thromboembolic Events

Completion of the VTE Endpoint eCRF page is required for each VTE reported as an adverse event or SAE. All suspected VTE events will be independently adjudicated by a blinded Clinical Event Committee.

Infections

Completion of the Infection Follow-up eCRF page is required for each infection reported as an adverse event or SAE with site of infection and source of culture provided, if available. The sponsor will identify infections considered to be opportunistic based on Winthrop et al. (2015).

8.3.7. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention. The sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational product so that the situation can be assessed.

Any adverse events/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 10.3.

Time period for detecting product complaints

Product complaints that result in an adverse event will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used. If the investigator learns of any product complaint at any time after a participant has ended his or her study participation, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

Prompt reporting of product complaints to sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint. The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

Follow-up of product complaints

Follow-up applies to all participants, including those who discontinue study intervention. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint. New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, an overdose of baricitinib is considered any dose higher than the dose assigned through randomization. In case of an overdose, the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment. In the event of an overdose, the investigator should contact the sponsor's medical monitor immediately.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor based on clinical evaluation of the participant.

8.5. Pharmacokinetics

For patients who progress to intubation in ICU, venous blood samples will be drawn on the days and times indicated in the SoA (Section 1.3).

These blood samples will be used to determine the plasma concentrations of baricitinib. Concentrations of baricitinib in human plasma will be determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.

The actual date and exact timing (24-hour clock) of sample collection and the date and time of study drug dosing should be recorded.

The sampling schedule should be followed as closely as possible; however, failure to take PK samples at the specified times will not be considered a protocol violation.

Only samples from patients receiving baricitinib will be assayed; samples from patients receiving placebo will not be assayed. PK samples will be kept in storage at a laboratory facility designated by the sponsor. PK results will not be provided to investigative sites.

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.6. Pharmacodynamics

This section is not applicable.

8.7. Genetics

This section is not applicable.

8.8. Biomarkers

Nasopharyngeal swab (to assess viral load and other characterizations), serum, and whole blood for RNA, epigenetic analysis and cellular phenotyping for exploratory nonpharmacogenetic biomarker research will be collected on days specified in the SoA (Section 1.3), where local regulations allow.

Sample use

Exploratory biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and/or clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of viral load, biomolecules, RNA, proteins, lipids, and other cellular elements.

Samples may be used for research on the drug target, disease process, variable response to baricitinib, pathways associated with the studied disease, mechanism of action of baricitinib, and/or research methods or in validating diagnostic tools or assays related to the disease or to baricitinib.

Confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Medical Resource Utilization and Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective of this study is to test the hypothesis that baricitinib 4-mg QD + background therapy is superior to placebo + background therapy in the treatment of hospitalized patients with COVID-19 infection, as assessed by the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28.

9.2. Sample Size Determination

Study KHAA will enroll approximately 400 patients. The sample size will ensure approximately 90% power to detect a superiority of baricitinib 4-mg QD + background therapy versus placebo + background therapy by assuming that the proportion of patients in placebo+background therapy group progressing to death or non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28 is approximately 40% and that the baricitinib-placebo treatment effect is approximately 15%. The assumption was based on topline results of the remdesivir study in China incorporating the proportion of hospital-admitted patients who were eventually discharged (Wang Y et al. 2020). However, there is significant uncertainty with these assumptions given the limited available data. The sample size may be updated in a blinded manner during the study to reflect newly available external study data.

9.3. Populations for Analyses

The following populations are defined for this study:

Population	Description
Entered	All participants who sign the informed consent form
Intent-to-Treat (ITT)	All participants randomly assigned to study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Per Protocol Set (PPS)	The PPS of the ITT population analysis set will include those participants who do not have any identified important protocol violations considered to impact efficacy analyses. Qualifications for, and identification of, significant or important protocol violations will be determined while the study remains blinded, prior to database lock.
Safety	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit. Participants will be analyzed according to the intervention they actually received within each study period.
Follow-up	All randomized participants who received at least 1 dose of investigational product and have entered the post-treatment follow-up period. Participants will be analyzed according to the intervention to which they were assigned in the treatment period.

A sensitivity analysis excluding patients who die within 24 hours of randomization and have Do Not Resuscitate (DNR) or Do Not Intubate (DNI) in ITT/PP analyses populations will be conducted.

9.4. Statistical Analyses

The statistical analysis of this study will be the responsibility of the sponsor or its designee.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to unblinding. It will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

Efficacy analyses will be conducted on the Intent-to-Treat (ITT) Population. Selected efficacy analysis may also be conducted using the Per Protocol Set. Safety analyses will be conducted on the Safety Population.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Treatment comparisons of dichotomous efficacy variables between baricitinib 4-mg QD + background therapy and placebo + background therapy will be made using a logistic regression analysis with baseline stratification factors and treatment group in the model. The percentages,

difference in percentages, and 95% confidence interval (CI) of the difference in percentages will be reported. When logistic regression sample size requirements are not met (<5 responders in any category for any factor), the p-value from Fisher's exact test is produced instead of the odds ratio and CI.

Treatment comparisons for ordinal efficacy variables between baricitinib 4-mg QD + background therapy and placebo + background therapy will be made using proportional odds model with baseline stratification factors and treatment group in the model.

Treatment comparisons of continuous efficacy and health outcome variables will be made using analysis of covariance (ANCOVA) with baseline randomization factors and treatment group in the model, if the method is appropriate. Type III tests for least squares (LS) means will be used for statistical comparisons between treatment groups. The LS mean difference, standard error, p-value, and 95% CI may also be reported. The method used to handle missing data is described briefly in Section 9.4.1.3 and will be described in more detail in the SAP.

Treatment comparisons of ventilation-free days will be made using Wilcoxon rank sum test and will be described in more detail in the SAP.

When evaluating continuous measures over time, a restricted maximum likelihood-based mixed model for repeated measures (MMRM) may also be used. The model will include treatment, baseline randomization factors, visit, and treatment-by-visit-interaction as fixed categorical effects, and baseline score and baseline score-by-visit-interaction score (for endpoints other than baseline disease severity) as fixed continuous effects for endpoints other than baseline disease severity. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, other structures will be tested. The Kenward-Roger method will be used to estimate the degrees of freedom. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported. Contrasts will be set up within the model to test treatment groups at specific time points of interest. Further details on the use of MMRM will be described in the SAP.

Log-rank test will be used as the primary analysis method for evaluating treatment effect in time-to-event endpoints. Kaplan-Meier curves and median survival will be estimated for each treatment group. Hazard ratio with 95% CI will be calculated using a Cox proportional hazards model with treatment as covariate and adjusted for baseline stratification factors. Diagnostic tests for checking the validity of the proportional hazards assumption may be performed. If the assumption of proportional hazards is not justified, a statistical model capable of handling nonproportional hazard will be explored to assess treatment effect, such as a max-Combo test (Lee 1996), restricted mean survival time model (Royston and Parmar et al 2013), and win ratio analysis (Pocock et al. 2012). An additional analysis may be performed to treat death as a competing event. The competing risk survival model, such as Fine-Gray model (Fine and Gray 1999) and cause-specific hazard model, will be considered. Further details on these methods will be described in the SAP.

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: geographic region, duration of symptoms prior to enrollment, age, sex and comorbidities (if applicable). Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

Fisher's exact test will be used for TEAEs, discontinuation, and other categorical safety data for between-treatment group comparisons. Continuous vital signs, body weight, and other continuous safety variables, including laboratory variables, will be analyzed by an analysis of covariance (ANCOVA) with treatment and baseline value in the model. Shift tables for categorical safety analyses (for example, 'high' or 'low' laboratory results) will also be produced.

Adjustment for Multiple Comparisons

Multiplicity controlled analyses will be performed on the primary and key secondary endpoints to control the overall family-wise Type I error rate at a 2-sided α level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2011) will be used. The graphical approach is a closed testing procedure; hence it strongly controls the family-wise error rate (FWER) across all endpoints (Alosh et al. 2014). Details of the specific graphical testing scheme (including testing order, interrelationships, Type I error allocation, and the associated propagation) will be prespecified in the SAP.

The primary and key secondary endpoints to be tested are listed in Section 9.4.2 and Section 9.4.3, respectively.

9.4.1.1. Participant Disposition

A description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as the number and percentage of participants completing the study (participants who receive at least 1 dose of study drug and have at least 1 postbaseline assessment), or discontinuing (overall and by reason for discontinuation). All patients who discontinue from the study or from the study treatment will be listed and along with their reason for discontinuation. Patients who stop taking study drug because they are discharged from hospital are not considered as having discontinued study treatment (see Section 4.1 and Section 7). Reasons for discontinuation from the study will be summarized by treatment group and compared between groups with Fisher's exact test.

A summary of important protocol deviations will be provided.

9.4.1.2. Participant Characteristics

Baseline demographic data and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be summarized descriptively by treatment group. Descriptive statistics including number of patients, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures. No formal statistical comparisons will be made among treatment groups unless otherwise stated in the SAP. Other participant baseline characteristics will be summarized by group as deemed appropriate.

9.4.1.3. Missing Data Imputation

Efforts to minimize loss-to-follow-up will be considered. However, small amounts of missing data may occur. Missing data will be handled within the context of intercurrent events.

Analysis of ordinal, continuous and categorical endpoints will be performed on all available data. Additionally, these endpoints may be assumed missing from the time the intercurrent event occurs and will be imputed through modified last observation carried forward (mLOCF).

Additional sensitivity analyses for the primary and key secondary endpoints, such as tipping point analyses and reference-based multiple imputation method, may be done. Missing data imputation and handling of intercurrent events will be specified in more detail in the SAP.

9.4.2. Primary Endpoint

The primary comparison of interest is the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28. Patients on non-invasive ventilation/high-flow oxygen at baseline will be counted toward this endpoint if they progressed to invasive mechanical ventilation. Treatment comparisons between baricitinib 4-mg QD + background therapy and placebo + background therapy will be made using logistic regression with baseline stratification factors and treatment group in the model.

9.4.3. Secondary Endpoints

Secondary comparisons of interest (key secondaries) are:

- proportion of patients with at least 1-point improvement on the NIAID-OS or live discharge from the hospital at Day 4, Day 7, Day 10, Day 14
- number of ventilator-free days (Day 1 to Day 28)
- time to recovery (NIAID-OS) (Day 1 to Day 28)
- overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, Day 14
- duration of hospitalization (Day 1 to Day 28)
- proportion of patients with a change in oxygen saturation from <94% to ≥94% from baseline to Day 4, Day 7, Day 10, Day 14, and
- all-cause mortality (Day 1 to Day 28).

Analyses for these endpoints are described in Section 9.4.1.

9.4.4. Safety Analyses

Safety analyses will include adverse events, SAEs, AESIs, vital signs, and laboratory analytes, using the Safety Population data descriptively summarized by treatment group. Continuous safety measures will be summarized as mean change by visit and analyzed using ANCOVA with treatment and baseline value in the model. Fisher's exact test will be used to perform comparisons between the baricitinib 4-mg QD + background therapy group and the placebo + background therapy group. Further analyses may be performed and will be planned in the SAP.

Exposure to study intervention will be calculated for each participant and summarized by treatment group.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, severity, and relationship to the study intervention. A treatment-emergent adverse event (TEAE) is defined as an event that

either first occurred or worsened in severity after the first dose of study treatment and on or prior to the last visit date during the analysis period. The analysis period is defined as the treatment period plus up to 30 days off-drug follow-up time. The treatment period will be used as the postbaseline period for the analysis. Safety analyses will be conducted separately for the double-blind treatment period and the post-treatment follow-up period defined as up to 28 days off-drug follow-up time. For events that are gender-specific, the denominator and computation of the percentage will include only participants from the given gender.

Treatment-related TEAEs (TEAEs related to study intervention) are defined as events that the investigator indicates are related to treatment on the eCRF.

Adverse events of special interest will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA preferred term listing. The number and percentage of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an adverse event, incidence of abnormal values, and AESIs will be summarized. Treatment-emergent adverse events (all, by maximum severity), SAEs including deaths, and adverse events that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class and preferred term.

All clinical laboratory results will be descriptively summarized by treatment group. Individual results that are outside of normal reference ranges will be flagged in data listings. Shift tables will be presented for selected measures.

Post-Treatment Follow-up

Safety analyses for the post-treatment follow-up period will be conducted on the follow-up population. Follow-up emergent adverse events, SAEs including deaths, and adverse events that lead to study discontinuation will be summarized. All adverse events, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

9.4.5. Pharmacokinetic Analysis

If available, the concentration-time data for baricitinib will be evaluated via graphical comparison to known PK profiles at 4-mg QD dosing that have been characterized for other populations such as healthy subjects, patients with RA, etc. The PK data may also be analyzed using a population modeling approach via a nonlinear mixed-effects modeling (NONMEM) program, if deemed necessary. The SAP will describe the planned PK analyses in greater detail.

9.5. Interim Analyses

The analysis for the primary database lock will be conducted when all participants have either completed the double-blind treatment period or have discontinued.

Interim analyses at other time points, including time points prior to the primary database lock, will be conducted using safety and/or efficacy data. These interim analyses will be used for stopping for excess mortality, futility, to implement unexpected recommendations from the DMC or to support planning activities associated with the development program.

Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

Assessments of unblinded interim data will be conducted by an external data monitor committee (DMC). The DMC will be authorized to evaluate unblinded interim efficacy and safety analyses, including evaluation of excess mortality. See also Section 9.6.

The SAP will describe the planned interim analyses in greater detail. To minimize bias, the SAP will be finalized and approved before any unblinding. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Study sites will receive information about interim analysis results only if the investigators need to know for the safety of their participants.

9.6. Data Monitoring Committee (DMC)

An independent, external data monitoring committee (DMC) will oversee this study. The DMC will consist of members external to Lilly. This DMC will follow the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. The DMC may recommend stopping the study for futility. DMC membership will include, at a minimum, a specialist with expertise in statistics and other appropriate specialties. Details of the DMC will be documented in a DMC charter. See also Appendix 10.1, Section 10.1.5.

Access to the unblinded data will be limited to the DMC and statisticians providing the data. These statisticians will be independent from the study team. The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded interim analyses. The study sites will receive information about interim results ONLY if they need to know for the safety of their patients. The DMC may request to review efficacy data to evaluate the benefit/risk relationship in the context of safety observations for ongoing patients in the study. In addition to the DMC members, a limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the final database lock, in order to initiate the population PK/PD model development processes. These analyses will not be considered interim analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and
- Applicable laws and regulations.

The protocol, protocol amendments and addenda, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 United States Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each principal investigator will sign the separate protocol signature page and send a copy of the signed page to a Lilly representative.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The sponsor or its representatives must approve the ICFs, including any changes made by the ERBs, before the ICFs are used at the investigative sites.

Due to strict respiratory isolation policies, limited access to COVID-19 patient rooms, and SARS-CoV-2 transmissibility via droplet-contaminated paper, verbal consent and alternative methods of obtaining consent (for example, by phone) will be allowed if approved by the IRB. In addition, if a signed paper copy of the ICF is allowed by hospital policy, how it will be obtained and stored will need to be determined. Any variation from the standard the consent process due to isolation and infection control should be sent to the IRB for approval prior to enrollment. The site should document the process in their regulatory files and demonstrate that the process has IRB concurrence or approval.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study. The statement must include the date on which the written consent was obtained. The authorized person obtaining the informed consent and, if applicable, the individual designated to witness a verbal consent, must also sign the ICFs.

Participants must be re-consented to the most current version of the ICF during their participation in the study.

A copy of the ICFs must be provided to the participant or the participant's legally authorized representative and must be kept on file.

10.1.4. Data Protection

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

The participant must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his or her data to be used as described in the informed consent.

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

The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plans for appropriate and timely response in the event of a data security breach.

10.1.5. Committee Structure

Data Monitoring Committee (DMC)

The DMC is described in Section 9.6. Details about the DMC membership, purpose, responsibilities, and operation will be described in a DMC charter, which will be approved prior to the first unblinding.

Clinical Event Committee

A blinded Clinical Event Committee will adjudicate VTEs and deaths.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic (PK) or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www. vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data).

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. This documentation might include laboratory and diagnostic test reports, medical records, and clinical notes.

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

Data monitoring and management

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring),

methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

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

In the event that on-site monitoring activities cannot occur, alternative measures (for example, use of technology for off-site monitoring, providing or showing pseudonymized copies of source documents to the monitor electronically, etc.) will be used, as allowed by local regulations. The remote source data verification will be focused on critical efficacy data and important safety data.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Additionally, clinical outcome assessment (COA) data will be collected by the investigative site personnel, via a paper source document and will be transcribed by the investigative site personnel into the EDC system.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor's data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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

The definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study is open for recruitment of participants.

The sponsor or designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the sponsor.

Site Closure

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided a reasonable cause exists and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to, these:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator, and
- Discontinuation of further study intervention development.

Premature Termination or Suspension of the Study

Pending the evaluation by the Data Monitoring Committee and discussion with the sponsor, enrollment and/or further dosing may be stopped, or the dose and/or other study parameters may be modified (Section 9.5 and Section 10.1.5).

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Physicians with expertise in the care of patients with COVID-19 infection may participate as investigators. This includes physicians with a specialty in infectious disease, acute or critical care, pulmonary disease, immunology, or other appropriate specialties when justified.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable responses that may not be observed until later in the development of baricitinib or after it becomes commercially available for the studied indication.

The following table lists the maximum retention period for sample types.

The retention period begins after the last participant visit for the study.

The maximum retention times may be shorter, if specified in local regulations and/or if ERBs/IRBs impose shorter time limits, or by decision by the sponsor.

Any samples remaining after the specified retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics (PK)	Sponsor or designee	1 year
Long-term storage samples	Sponsor or designee	up to 15 years

10.2. Appendix 2: Clinical Laboratory Tests

10.2.1. Clinical Laboratory Tests

The clinical laboratory tests listed in the table below will be performed by a central laboratory or by a local laboratory as specified in the table.

Additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.

Protocol-specific requirements for the inclusion or exclusion of participants are specified in Section 5 of the protocol.

Pregnancy testing is described in the SoA, in Section 8.2.5.1, and in the table below.

Investigators must document their review of the laboratory safety report as described in Section 8.2.5.

Laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

	Notes
Hematology	Performed locally.
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells [RBC])	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (white blood cells [WBC])	
Absolute count of:	
Neutrophils, segmented (absolute)	
Neutrophils, juvenile (bands)	
Lymphocytes (absolute)	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	

	Notes
Clinical Chemistry	Performed locally
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Creatine kinase (CK)	
Lactate dehydrogenase (LDH)	

	Notes
Hormones (females)	Performed locally
Serum pregnancy	To be performed only on women of childbearing potential.

	Notes
Biomarkers	Performed locally
Erythrocyte sedimentation rate (ESR)	
C-reactive protein (CRP)	High-sensitivity (hs-CRP) is preferred if available.
Ferritin	
D-dimer	
Procalcitonin	
Cardiac troponin	

	Notes
Viral Testing	Performed locally
SARS-CoV-2 viral infection confirmation	Utilizing nasopharyngeal swabs

	Notes
Pharmacokinetics (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Baricitinib	

	Notes
Long-Term Stored Samples: Exploratory Biomarker Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory biomarker samples:	
Nasopharyngeal swab	
Serum	
Whole blood RNA	
Whole blood EDTA (epigenetics)	
Whole blood for cellular phenotyping (EDTA plus smart reagent)	To be collected by sites with the logistic or technical ability

10.2.2. Clinical Laboratory Calculations

eGFR (Modification of Diet in Renal Disease [MDRD])

- For creatinine results reported in conventional units (mg/dL):

  GFR (mL/min/1.73 m²) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

- For creatinine results reported in SI units (pmol/L):

  GFR (mL/min/1.73 m²) = $175 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
– Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). – Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or in intensity of the condition. – New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. – Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. – Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent; report such overdoses regardless of sequelae. – "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
– Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. – The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

– Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. – Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). – Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. The term does not refer to an event which hypothetically might have caused death if the event were more severe.
c. Prolongation of existing hospitalization or readmission after discharge but before discontinuation from study – In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. – Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity – The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. – This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: – Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may

require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

– Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF/eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities.

Note: An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF/eCRF.

The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper CRF

Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in in site training documents.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, consider additional evaluation.

Woman NOT of Childbearing Potential (not WOCBP)

Female patients of non–child-bearing potential are defined as

- Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation)
- Postmenopausal, defined as a woman meeting one of the following criteria:
  - woman at least 50 years of age with an intact uterus, not on hormone therapy, who has either
    - –At least 6 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) of ≥40 mIU/mL, or
    - – Women aged 55 years or older who are not on hormone therapy, and who have had at least 6 months of spontaneous amenorrhea.
  - Women aged 55 years or older who have a diagnosis of menopause.

10.4.2. Contraception

Females

Women of childbearing potential

Female patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex.

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

Otherwise, female patients of childbearing potential must agree to use 1 highly effective form of contraception for the entirety of the study and for at least 1 week following the last dose of investigational product.

The following contraception methods are considered acceptable; the patient should choose one that is highly effective, defined as less than 1% failure rate per year when used consistently and correctly:

Highly effective birth control methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
- Progestogen-only containing hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
- Intrauterine device (IUD)/intrauterine hormone-releasing system (IUS)
- Vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

Effective birth control methods

- Male or female condom with spermicide
  Diaphragm with spermicide
  Cervical sponge
  Cervical cap with spermicide

  It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

Women not of childbearing potential (not WOCBP)

Women who are not WOCBP may participate in the study if they meet all study entry criteria. For such women, there are no conception requirements.

Males

For men, there are no conception requirements.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. 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.

While pregnancy itself is not considered to be an adverse event (AE) or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5. Appendix 5: Abbreviations

Term	Definition
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AVPU	Alert Voice Pain Unresponsive
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BiPAP	bilevel positive airway pressure
blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CPAP	continuous positive airway pressure
CFR	United States Code of Federal Regulations
CI	confidence interval
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
COVID-19	coronavirus disease 2019
CRP	C reactive protein
DNA	deoxyribonucleic acid
DNI	Do Not Intubate
DNR	Do Not Resuscitate
DVT	deep vein thrombosis
EBP	extracorporeal blood purification
eCRF/CRF	electronic case report form/case report form
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate

enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board (see IRB)
ETV	early termination (discontinuation) visit
GCP	good clinical practice
HBV	hepatitis B virus
HCV	hepatitis C virus
hs-CRP	C reactive protein, high-sensitivity
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee (see IRB)
Ig	immunoglobulin
IL	interleukin
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IR	incidence rate
IRB	Institutional Review Board (IRB), also called Independent Ethics Committee (IEC) or Ethical Review Board (ERB)
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system

LDH	lactate dehydrogenase
MDRD	Modification of Diet in Renal Disease
MERS	Middle East respiratory syndrome
NAKs	numb-associated kinases
NEWS	National Early Warning Score
NIAID	National Institute of Allergy and Infectious Diseases
NIAID-OS	NIAID ordinal scale
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
NONMEM	nonlinear mixed effects modeling
NRI	non-responder imputation
NSAID	nonsteroidal anti-inflammatory drug
PA	posterior–anterior
participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term "subject," meaning an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control. In this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials. The term "patient" is also used to indicate an individual who participates in this clinical trial.
PD	pharmacodynamics
PE	pulmonary embolism
PK	pharmacokinetics
PK	pharmacokinetics
QD	once daily
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	novel SARS coronavirus 2
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SI	international system of units
SoA	Schedule of Activities

study drug	See "study intervention"
study intervention	Any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol
TB	tuberculosis
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TNFi	tumor necrosis factor inhibitor
ULN	upper limit of normal
VTE	venous thromboembolism
WBC	white blood cell
WOCBP	women of childbearing potential

10.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment A (27 May 2020):

Amendment A occurred before any study participant was consented or dosed at any study site.

Overall Rationale for Amendment A:

The main purpose of this protocol amendment was to address regulatory comments regarding the primary endpoint and regarding the role of an internal assessment committee in the review of unblinded data.

Sections # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design 9.1 Statistical Hypotheses 9.4.2 Primary Endpoint	Changed primary endpoint. Changed wording of primary objective.	Response to FDA feedback. The new primary endpoint is proportion of patients requiring non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 28. A related secondary endpoint ["Proportion of patients requiring mechanical ventilation (Day 1 to Day 28)"] has been removed; this secondary objective is unnecessary given the new primary endpoint. The primary objective wording was changed (from "on clinical improvement of patients" to "on disease progression in patients") to align with the primary endpoint.
1.1 Synopsis 3 Objectives and Endpoints 9.4.3 Secondary Endpoints	Added a secondary endpoint.	Response to FDA feedback. The new secondary endpoint is overall improvement in NIAID ordinal scale evaluated at Day 10. It has been incorporated into the existing key secondary endpoint of "Overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, Day 14."
1.2 Schema	Removed timepoint indicator for the primary endpoint.	Changed to maintain consistency with changed primary endpoint described above.
2.2 Background	Replaced "creatinine kinase" with "creatine kinase."	Changed to fix typographical error.
4.1 Overall Design	Removed a statement about use of oxygen therapy at time of study entry.	Changed to prevent misreading.

Sections # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	Provided rationale for the new primary endpoint.	New information is included for consistency with the new primary endpoint.
8.1.1 COVID-19 Clinical Status Assessment	Added two paragraphs defining terms relevant to the primary endpoint.	Changed for consistency with other listed changes and to improve clarity.
8.1.3 Other Efficacy Assessment	Added "high-flow oxygen" to the endpoint cell for non-invasive ventilation.	Changed for consistency with other listed changes and to improve clarity.
8.2.4 Chest Imaging Studies	Added "or appropriate physician" to the list of personnel who may assess the chest imaging scans.	Changed to provide flexibility to sites.
8.2.5 Laboratory Tests 10.2.1 Clinical Laboratory Tests	Changed the requirements for documentation of reviews of laboratory reports.	Changed to decrease site burden, allowing flexibility on how the review is documented.
9.2 Sample Size Determination	Modified rationale for sample size.	Changed to align with response to FDA feedback, and to use more recently available data as part of the justification of sample size.
9.4.1 General Considerations	Added Wilcoxon rank sum test for treatment comparison of ventilation-free days.	Changed for consistency with changes in other sections.
9.4.2 Primary Endpoint	Revised primary endpoint. Added statement about how patients on non-invasive ventilation at baseline will be counted in the new endpoint.	Changed as a result of response to FDA feedback.
9.4.3 Secondary Endpoints	Removed secondary endpoints, as previously described.	See above.
9.5 Interim Analyses 9.6 Data Monitoring Committee 10.1.5 Committee Structure 10.1.9 Study and Site Start and Closure	Removed all references to Internal Assessment Committee (IAC). Clarified the use of interim analyses.	Response to FDA feedback. Unblinded data reviews will be carried out by the external Data Monitoring Committee (DMC), not an IAC.
10.5 Appendix 5: Abbreviations	Added and removed abbreviations.	Editorial. Changed for consistency with other changed sections.
11 References	Added and removed references.	Editorial. Changed for consistency with other changed sections.

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