

Protocol I4V-MC-KHAB(a)

A Multicenter, Open-Label, Pharmacokinetic and Safety Study of Baricitinib in Pediatric Patients from 1 Year to Less Than 18 Years Old Hospitalized with COVID-19

NCT05074420

Approval Date: 08-Oct-2021

Title Page

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Protocol Title: A Multicenter, Open-Label, Pharmacokinetic and Safety Study of Baricitinib in Pediatric Patients from 1 Year to Less Than 18 Years Old Hospitalized with COVID-19

Protocol Number: I4V-MC-KHAB

Amendment Number: A

Compound: baricitinib (LY3009104)

Study Phase: 3

Acronym: COV-BARRIER-PEDS

Sponsor Name: Eli Lilly and Company

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Initial KHAB protocol	05-May-2021

Amendment A

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety of the study participants.

Overall Rationale for the Amendment:

The main purpose of this amendment is to

- address the regulatory feedback about dose adjustments for participants with renal impairment, and
- include the OS 7 participants in the study.

Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	eGFR calculation row: added a reference to Section 6.1.1	To align with changes in Section 6.1.1
Section 2.1, Study Rationale	Updated the sentence about the supplemental oxygen/OS criteria (“Baricitinib may be an effective treatment ...”)	Per revised inclusion criterion [4]
Section 2.2, Background	Added a sentence to support the inclusion of the OS 7 participants	Per revised inclusion criterion [4]
Section 4.1, Overall Design	Updated the “Screening” subsection	Per revised inclusion criterion [4]
Section 5.1, Inclusion Criteria	Revised inclusion criterion [4]	To include the OS 7 participants (that is, participants who require invasive mechanical ventilation, including ECMO)
Section 5.2, Exclusion Criteria	Marked exclusion criterion [10] as not applicable	Replaced with revised inclusion criterion [4]
Section 6.1, Study Interventions Administered	• Updated the terminology for initial versus actual doses administered • Updated the eGRF categories for which dose reductions are needed	For clarity and consistency with changes in Section 6.6.1

Section # and Name	Description of Change	Brief Rationale
Section 6.6, Dose Modification	Updated the beginning of the section	For clarity and accuracy
Section 6.6.1, Dose Adjustment Based on eGFR	Updated the section title and content	Per regulatory feedback, to provide dose adjustment for participants with eGFR ≥ 60 mL/min/1.73 m ² at baseline whose eGFR becomes < 60 mL/min/1.73 m ² and ≥ 30 mL/min/1.73 m ² during the study so that exposure in participants with moderate renal function would remain approximately the same level as before the eGFR changes.
Section 8.1.4, Secondary Endpoint Efficacy Assessments	Updated the definition of the following endpoint: proportion of patients who die or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28	Per revised inclusion criterion [4]
Section 8.1.5, Ordinal Scale	Added a sentence to define invasive mechanical ventilation	Per revised inclusion criterion [4]
Section 9.2.4, Secondary Endpoint(s)/Estimand(s)	Clarified that for the analysis of progression to ventilation, participants requiring invasive mechanical ventilation (including ECMO) at baseline would not be included	Per revised inclusion criterion [4]

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Open-Label, Pharmacokinetic and Safety Study of Baricitinib in Pediatric Patients from 1 Year to Less Than 18 Years Old Hospitalized with COVID-19

Rationale: Baricitinib, an approved therapy for the treatment of moderately to severely active RA and AD in adults, is proposed as a potential therapy for pediatric patients with COVID-19. The proposed mechanism of action in COVID-19 includes reduction of cytokine-mediated inflammation and the potential for antiviral activity. In this study, a small number of pediatric patients with COVID-19 will receive short-term administration of baricitinib (up to 14 days) for the purpose of characterizing the PK and safety profile of baricitinib in this population. Data from this study in pediatric patients will be used together with data from studies in hospitalized adults with COVID-19 (Study ACTT-2, which evaluated baricitinib in combination with remdesivir; and Study I4V-MC-KHAA [KHAA], which evaluated baricitinib in addition to standard of care) to extrapolate the effectiveness and safety of baricitinib for the treatment of COVID-19 in pediatric patients.

Objectives and Endpoints

This table describes primary and secondary objectives and endpoints for this study.

Objectives	Endpoints
Primary	
To characterize the pharmacokinetics (PK) of baricitinib* in pediatric patients with COVID-19	Pharmacokinetic parameters, including AUC and C _{max} of baricitinib, in pediatric patients with COVID-19
Secondary	
To describe the safety of baricitinib* in pediatric patients with COVID-19	Safety assessments, including AEs and laboratory abnormalities
To describe the effect of baricitinib* on COVID-19 progression in pediatric patients	Proportion of patients who require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28 Proportion of patients who die or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28
To describe clinical outcomes in pediatric patients with COVID-19 treated with baricitinib	• 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, and Day 28 • Number of ventilator-free days (Day 1 to Day 28) • Time to recovery on the NIAID-OS (Day 1 to Day 28) • Overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, Day 14, and Day 28 • Duration of hospitalization (Day 1 to Day 28) • All-cause mortality (Day 1 to Day 28 and Day 60) • Duration of stay in the intensive care unit (ICU) in days (Day 1 to Day 28)
Notes: *Baricitinib dose that produces an exposure equivalent to that produced by baricitinib 4 mg QD in adults. 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).	

Abbreviations: AE = adverse event; AUC = area under the concentration–time curve; C_{max} = maximum observed drug concentration; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; NIAID-OS = National Institute of Allergy and Infectious Diseases ordinal scale.

Overall Design

Study I4V-MC-KHAB (KHAB) is a multicenter, open-label, single-group Phase 3 study designed to characterize the PK and safety profile of baricitinib in pediatric patients (1 to <18 years of age) who are hospitalized with confirmed COVID-19. All participants will receive a daily dose of baricitinib that produces exposure equivalent to that produced by baricitinib 4 mg QD in adults.

The study will be opened to enrollment of participants in order by age:

- The first enrolled cohort will be participants aged [redacted] to <18 years.
- The second enrolled cohort will be participants aged 1 to [redacted] years.

Analyses of the PK and safety profile from at least [redacted] participants in the older cohort will confirm or, if necessary, adjust the planned dose for the younger cohort.

The study duration will be up to approximately 60 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, with a follow-up visit approximately 28 days after last dose of study drug and another follow-up visit at approximately Day 60.

Disclosure Statement: This is a single-group treatment study without blinding (open-label).

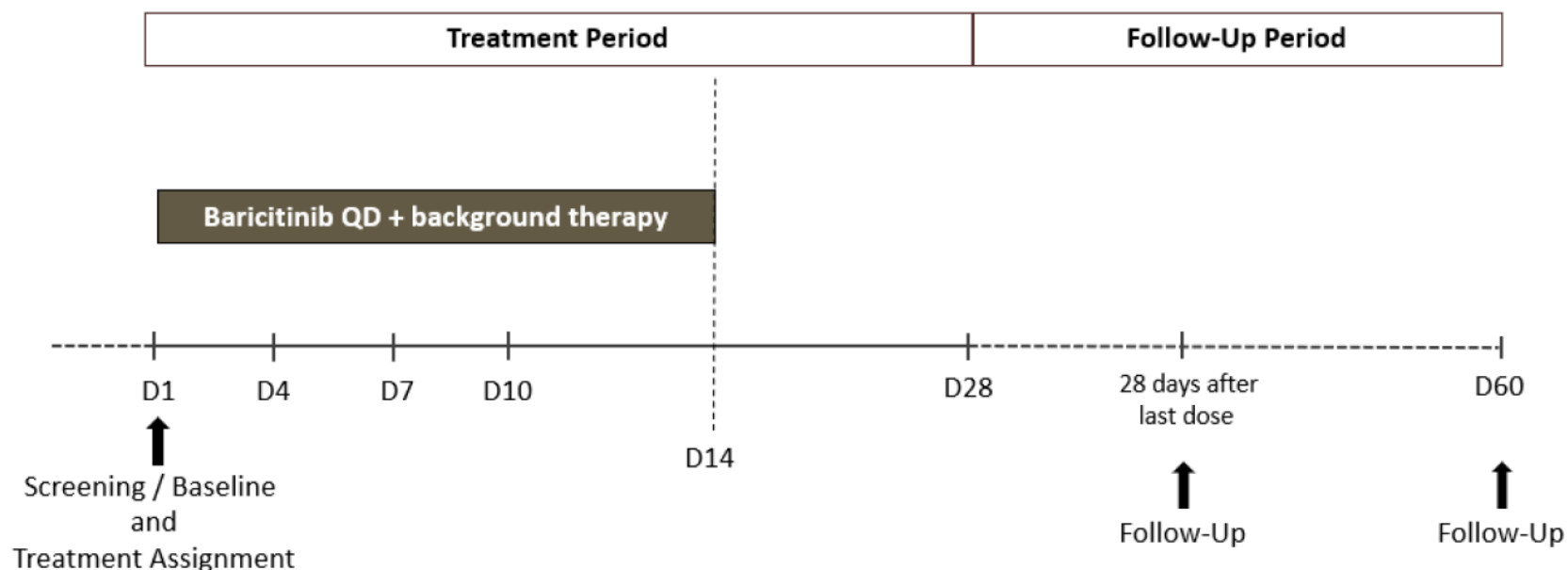
Number of Participants: A total of approximately 24 participants will be enrolled to achieve the planned minimum numbers of treated participants in these age groups:

- at least [redacted] participants from [redacted] to <18 years of age, including at least [redacted] participants from [redacted] years of age
- at least [redacted] participants from [redacted] years of age
- at least [redacted] participants from [redacted] years of age, and
- at least [redacted] participants from 1 [redacted] years of age.

Intervention Groups and Duration: At baseline, all enrolled participants will be assigned to baricitinib treatment at a dose level according to age. Baricitinib treatment is administered for up to 14 days, or up to the day of hospital discharge, whichever comes first. Participants will receive background therapy in keeping with local clinical practice for management of COVID-19 infection.

Data Monitoring Committee: Yes

1.2. Schema



Notes: Baricitinib dose levels are assigned according to the participant's age. To allow for optimization of the dose for younger participants (<18 years), enrollment will be conducted in age-based cohorts, beginning with older participants (<18 to <18 years). For all cohorts, dosing will occur from the day of treatment assignment up to Day 14, or until hospital discharge, whichever comes first. Baricitinib is 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-KHAB.

1.3. Schedule of Activities (SoA)

Adherence to study visit schedule

Study visits are expected to occur on the study days as shown in this SoA.

A participant should remain in the study and complete visits as specified in this SoA even if the participant

- is discharged from the hospital
- is transferred to another hospital or to another hospital unit that is not a study site, or
- is permanently discontinued early from study drug as described in Section 7.

Use of telephone visits

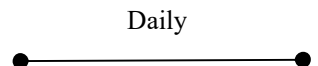
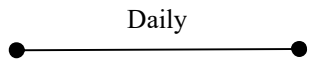
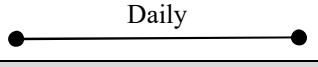
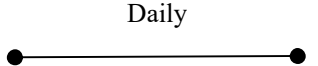
Site visits are preferred after hospital discharge through Day 28, but telephone visits are acceptable. Telephone visits are also acceptable for participants who transfer to another hospital or hospital unit that is not a study site.

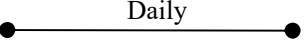
Telephone visits should include collection of concomitant medications, AEs, COVID-19 clinical symptoms, and Clinical Status Assessment. Failure to conduct activities that cannot be reasonably performed over the telephone will not be considered a protocol deviation.

Schedule of Activities

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	X	
Informed consent	X										Informed consent form must be signed before any protocol-specific tests or procedures are performed. Parent or legally authorized representative signs ICF as appropriate per local requirements. See Appendix 10.1, Section 10.1.3.

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	X	
Informed assent	X										Informed assent form must be signed before any protocol-specific tests or procedures are performed. Participant signs assent form as appropriate per local requirements. See Appendix 10.1, Section 10.1.3.
Inclusion and exclusion criteria, review and confirm	X										Inclusion and exclusion criteria should be confirmed on Day 1 before enrollment and administration of first dose of study drug.
Demographics	X										Includes ethnicity (United States only), age, gender, and race.
Do Not Intubate/Do Not Resuscitate Order (DNI/DNR)	X										Update throughout the study if orders change.
Prespecified medical history: COVID-19	X										Includes COVID-19 diagnosis date and onset of COVID-19 symptoms.
Prespecified medical history: comorbidities	X										Includes risk factors and comorbidities associated with COVID-19.
Preexisting conditions and medical history, including relevant surgical history	X										Includes other relevant comorbidities obtained from interview or available information, for example, medical records.
Prior treatments for indication within last 2 weeks	X										Includes NSAIDs, antivirals, antibiotics, antimalarials, corticosteroids, immunosuppressive medications, convalescent plasma, or any investigational treatments used as recommended or required by local COVID-19 treatment guidelines.
Prior non-COVID-19 vaccine treatments within the last 90 days	X										
Prior COVID-19 vaccine treatment	X										
Substance use (tobacco use)	X										Includes use of e-cigarettes, such as vaping.

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	X	
Concomitant medications							X	X	X	X	Assess daily and document during hospitalization and on study days after discharge. Includes medications of interest: background therapy, supportive care, sedating/paralytic drugs, VTE prophylaxis, if used.
Adverse events (AEs)							X	X	X	X	Assess daily and document during hospitalization and on study days after discharge. AE collection begins when ICF is signed. For infections and VTEs, additional data are collected (see Section 8.3.3).
COVID-19 clinical symptoms							X	X	X	X	Assess daily and document while hospitalized, and on study days after discharge.
Physical evaluation											
Height or length	X										Collect height or length as appropriate for participant age. Failure to obtain height or length if, in the opinion of the investigator, it is not safe and/or feasible to do so for a severely ill participant, will not be considered a protocol deviation.
Weight	X										
Vital signs											Assess and document daily while hospitalized. Includes respiratory rate and oxygen saturation, blood pressure, body temperature, and heart (pulse) rate. See Section 8.2.1.
Physical examination	X										The complete physical examination is performed if feasible (excludes pelvic, rectal, and breast exams). An assessment of risk factors for and signs and symptoms of TB is included (Section 8.2.2).
Symptom-directed physical examination		X	X	X	X	X	X				

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	X	
Chest imaging (CT scan or x-ray) (local)	X										Assessed by radiologist or pulmonologist or other appropriate physician (see Section 5.1, Section 5.2, and Section 8.2.3). Documentation of hospital-based imaging obtained up to 72 hours prior to study entry is acceptable.
Education of participant and parent or legally authorized representative											
Instructions for home monitoring of COVID-19 symptoms, physical activity, and oxygen use											At the time of hospital discharge, provide instructions to participant and parent or legally authorized representative.
Clinician-administered assessments											
Hospitalization							X		X	X	Assess daily and on study days after discharge. Record dates of hospitalization and any changes to hospital care (such as general ward, emergency room, and ICU).
Clinical Status Assessment							X		X	X	Assess daily and document during hospitalization, and on study days after discharge. Documentation from hospital records is acceptable at any time. Includes additional organ support (for example, ECMO, renal replacement), proning, supplemental oxygen, and any means of ventilatory support. After hospital discharge, assess and document whether home oxygen was needed and any limitations on physical activity.

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	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. See Appendix 10.2, Section 10.2.1 for prioritization of sample collection.
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.
eGFR calculation	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. Check most recently available eGFR result prior to dosing; for participants with eGFR <60 mL/min/1.73 m ² , see Section 6.6.1 for dose adjustment. If eGFR is <30 mL/min/1.73 m ² , hold until eGFR returns to ≥30 mL/min/1.73 m ² .
Serum pregnancy	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. Collect sample for females of childbearing potential (see Section 8.2.4.1 and Appendix 10.4, Section 10.4.2).

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	X	
C-reactive protein (CRP)	X	X	X	X	X	X	X	X			Performed locally. Blood sample not required if participant weighs <32 kg. Unscheduled collection, if clinically warranted, will be entered into the eCRF.
SARS-CoV-2 viral infection confirmation via NP swab	X										Performed locally. Test performed prior to study entry will be accepted for determination of eligibility requirements (see Section 5.1). If additional samples are collected per participant clinical care during study participation, record results in the eCRF.
Pharmacokinetic (PK) sample	X	X					X	X			Performed by central laboratory. A minimum of 6 samples per participant will be collected during the study: - Day 1 at approximately 15 minutes, 30 minutes, and between 2 to 4 hours postdose - Day 4 at predose (that is, approximately 24 hours after previous day's dose), 1 hour postdose, and between 6 to 10 hours postdose. If participant is discharged from hospital prior to Day 4, PK samples should be collected predose, 1 hour postdose, and between 6 to 10 hours postdose on the day of discharge. Additional PK sampling may be needed, for example, for samples evaluating concordance, or if an error in dosing or sampling occurs. See Section 8.5.

Study day	1	4	7	10	14	28	ETV	UV	Follow-Up 28 Days after Last Dose	Follow-Up Study Day 60	Comments
Interval tolerance (days)	≤3	—	—	—	—	—	—		±4	+7	Day 1 procedures may be conducted over up to 3 days, unless otherwise specified.
Site visit	X	X	X	X	X	X	X	X			
Telephone visit							X	X	X	X	
Stored samples											For stored sample collections, the timing can be +1 day or -1 day from the designated day, unless otherwise specified.
Exploratory biomarker sample: NP or MT swab	X	X		X			X	X			Obtained and sent to the Lilly-designated laboratory. Methods include NP (preferred) or MT. For an individual participant, the same sampling method should be used for each sample. See Section 8.8.
Exploratory biomarker sample	X	X	X	X			X				Obtained and sent to the Lilly-designated laboratory. Blood sample is not required if participant weighs <15 kg. If sample is not collected because of volume limits, this will not be considered a protocol deviation. See Appendix 10.2, Section 10.2.1. for prioritization of sample collection. See Section 8.8.
Treatment assignment and dosing											
Study drug assignment via IWRS	X										Process Day 1 in IWRS.
Administer study drug to participant											Dosing is daily from treatment assignment on Day 1 through Day 14, or until participant is discharged from hospital, whichever comes first. Collect and record date, time, CCI for each dose administered during hospitalization. Check the most recently available laboratory results prior to dosing to confirm whether any criteria for study drug discontinuation (Section 7.1.1) or for study drug interruption (Section 7.1.2) have been met.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; ETV = early termination visit; ICF = informed consent form; ICU = intensive care unit; IWRS = interactive web-response system; MT = mid-turbinate; NP = nasopharyngeal; NSAIDs = nonsteroidal anti-inflammatory drugs; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; UV = unscheduled visit; VTE = venous thromboembolism.

2. Introduction

2.1. Study Rationale

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

Mechanism of action of baricitinib

Baricitinib is a selective inhibitor of the JAK family of protein tyrosine kinases. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate STATs, which modulate intracellular activity including gene expression. Baricitinib modulates the signaling pathway at the point of JAKs, preventing the activation of STATs.

Mechanism of action of baricitinib in relation to COVID-19

Patients diagnosed with COVID-19 are at an elevated risk of excess morbidity and mortality due to the underlying SARS-CoV-2 infection and subsequent cytokine activation. Respiratory failure from ARDS is the leading cause of mortality. The cause of respiratory failure in COVID-19 is a hyperinflammatory state characterized by upregulation of multiple cytokines. In Wuhan, China, COVID-19-infected patients admitted to the ICU exhibited increased plasma concentrations of the following cytokines compared with the non-ICU patients:

- IL-2
- IL-7
- IL-10
- GM-CSF
- IP-10
- MCP-1
- macrophage inflammatory protein 1 alpha, and
- tumor necrosis factor-alpha.

Elevated interleukin-6 (IL-6) and hyperferritinemia were predictors of death in these patients with COVID-19 (Huang et al. 2020; Ruan et al. 2020; Zhou et al. 2020).

Baricitinib may be a viable treatment option in patients with COVID-19 because of its anti-inflammatory activity and ability to reverse dysregulated inflammatory markers in patients with COVID-19 (McInnes et al. 2019; Sims et al. 2021). The potent anti-inflammatory effects of baricitinib have 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). Furthermore, dose-dependent decreases in IFN biomarkers confirmed an in vivo effect of baricitinib on type-1 IFN signaling in pediatric patients suffering from CANDLE and SAVI (Kim et al. 2018). Relevant to COVID-19 and the potential role played by IL-6, it is notable that treatment with baricitinib 4 mg resulted in reduced plasma levels of IL-6 in hospitalized patients with COVID-19, a finding that was replicated after being observed in patients with RA (Bronte et al. 2020; Sims et al. 2021; Stebbing et al. 2020).

The biochemical inhibitory effects of baricitinib on human NAK members responsible for SARS-CoV-2 viral propagation were recently confirmed by measuring its nanomolar affinities for adaptor-associated protein kinase (AAK1), bone morphogenic protein (BMP)-inducible kinase (BIKE), and cyclin G-associated kinase (GAK) (Stebbing et al. 2020). Inhibiting NAK proteins that activate the adaptor-related protein 2 (AP-2) scaffolding protein vital to viral entry and propagation could be one therapeutic approach to managing COVID-19. In addition, some plasma markers that were dysregulated in moderate to severe hospitalized patients with COVID-19, that represent myeloid dysregulation, endothelial and cardiovascular inflammation, along with reduced antigen presenting plasmacytoid dendritic cells, were normalized over time with baricitinib treatment (Sims et al. 2021). The impact of antiviral host activity in patients with COVID-19 is being evaluated in NP swab, serum, and whole blood samples collected in a study of baricitinib versus placebo in adults with COVID-19 (Study I4V-MC-KHAA [KHAA], NCT04421027).

The efficacy of baricitinib for the treatment of COVID-19 in hospitalized patients requiring supplemental oxygen has been demonstrated by the results of 2 randomized, double-blind, placebo-controlled, Phase 3 studies, Study ACTT-2 (baricitinib in combination with remdesivir) (Kalil et al. 2021), and Study KHAA (baricitinib plus standard of care) (data on file). Together, these studies demonstrated a consistent, clinically meaningful effect of baricitinib on reducing mortality, as well as time to recovery, progression to ventilation or death, and overall improvement of clinical status (measured on the NIAID-OS), although not all endpoints demonstrated statistically significant improvements in the baricitinib groups versus placebo. No new safety signals were identified; the safety data from these clinical trials in adult patients with COVID-19 are consistent with the known safety profile for baricitinib (Section 2.2).

Baricitinib may be an effective treatment for hospitalized children with COVID-19, including those who require supplemental oxygen, including noninvasive ventilation or high-flow oxygen, or invasive mechanical ventilation, including ECMO (OS 5, OS 6, and OS 7) because of its potential antiviral host activity and mitigation of the hyperinflammatory state and cytokine storm associated with SARS-CoV-2 infection.

The safety profile, along with the known mechanism of action of baricitinib, provides rationale to evaluate the PK of baricitinib in pediatric patients with COVID-19 in a clinical trial setting.

2.1.1. Planned Extrapolation to Specific Pediatric Populations

In this study, a small number of pediatric patients with COVID-19 will receive short-term administration of baricitinib (up to 14 days) for the purpose of characterizing the PK and safety profile of baricitinib in this population.

Rationale for study design with extrapolation of effectiveness

The sponsor plans to extrapolate the effectiveness of baricitinib for the treatment of COVID-19 in pediatric patients using data from Study KHAB and from

- Study ACTT-2, which evaluated baricitinib in combination with remdesivir as a treatment for hospitalized adults with COVID-19, and
- Study KHAA, which evaluated baricitinib + SOC as a treatment for hospitalized adults with COVID-19.

This approach aligns with the 2021 FDA Guidance for Industry entitled, *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*, which encourages sponsors to consider extrapolation by leveraging existing data in adults and other pediatric populations to support effectiveness and safety in pediatric patients with COVID-19. The extrapolation plan is also based on the

- common clinical classification and measures of COVID-19 progression, as well as the comparable pathophysiology of SARS-CoV-2 infection in adults and pediatric patients, including the common initial stages of COVID-19 in adult and pediatric patients when viral infection and replication occurs (Siddiqi and Mehra 2020; Zimmermann and Curtis 2020)
- similar (although usually less severe) clinical course of SARS-CoV-2 infections in pediatric patients as compared to adults (Hoang et al. 2020), and
- consistent predicted and observed drug exposure (PK) in adults and pediatric patients with other inflammatory conditions, which support an assumption that appropriate pediatric doses can be established across the pediatric age range through achieving a similar exposure in pediatric patients as in adults.

Rationale for study design with extrapolation of safety

The sponsor plans to extrapolate the safety of baricitinib for the treatment of COVID-19 in pediatric patients using data from Study KHAB and from

- Study ACTT-2 and Study KHAA in adult patients with COVID-19
- ongoing studies in pediatric patient populations, including those with JIA, AD, and interferonopathies, and
- a substantial safety database for baricitinib available from adult populations across multiple indications.

2.2. Background

COVID-19 is a severe viral respiratory disease, caused by SARS-CoV-2 infection, that generally affects the lower respiratory tract. The predominant symptoms of COVID-19 reported to date include fever, cough, and nasal congestion. Less common symptoms include headache, fatigue, and gastrointestinal issues (Hoang et al. 2020).

The pathogenesis of COVID-19 is thought to be similar in adult and pediatric patients and involves inhaled SARS-CoV-2 binding to epithelial cells in the nasal cavity and starting to replicate. The virus propagates and migrates down the respiratory tract, and a stronger innate immune response is triggered (Mason 2020; Hoffmann et al. 2020; Siddiqi and Mehra 2020). Some patients with COVID-19 develop a cytokine storm that manifests clinically as a hyperinflammatory state (persistent fever, elevated inflammatory markers, and multiple organ dysfunction) with pulmonary involvement. Severe cases can progress to pulmonary failure, ARDS, and death.

Compared to adults, most infected children appear to have a milder disease course, including asymptomatic infections and better outcomes overall (Hoang et al. 2020). Although the percentages of ICU admissions for hospitalized patients are similar for adults (32.0%) and

children (33.2%) as reported to COVID-19-Associated Hospitalization Surveillance Network, invasive mechanical ventilation is required less frequently in children (5.8%) than in adults (18.6%) (Kim et al. 2020a, 2020b), and hospitalizations (0.6% to 6.9% of all pediatric cases) and deaths (0% to 0.15% of all pediatric cases) occur less often in children than in adults (AAP/CHA 2020). Typically, the disease is milder in young children, with a less severe phenotype and lower fatality rate, whereas in adolescents the later stages of the disease appear to be similar to and continuous with that of young adults (Liao et al. 2020).

Similar to adults, outcomes in pediatric patients are generally worse in the presence of comorbid conditions, such as immune suppression, malignancy, chronic lung disease, and other medical complexities (Shekerdemian et al. 2020). Such groups are more likely to be hospitalized and require ICU admission (Zachariah et al. 2020).

Currently, there are no approved vaccines for the prevention of COVID-19 in pediatric patients <16 years of age. Remdesivir is approved by the FDA and the EMA to treat COVID-19 in adults and pediatric patients ≥12 years of age. In addition, dexamethasone is approved by the EMA to treat COVID-19 in adults and pediatric patients ≥12 years of age. While COVID-19 is generally less severe in a pediatric population compared to adults, the risk for hospitalization and serious complications, including death, remains, and additional treatment options are needed.

Safety data from studies in pediatric patient populations

Safety data are available for 91 patients (range: 6 to 17 years) with JIA in the ongoing Study JAHV, and 27 patients (range: 6 to <18 years) with AD in the ongoing Study JAIP to date. In Study JAHV, 36 patients completed the open-label lead-in period and received baricitinib for 12 weeks. There were no deaths, discontinuations due to AEs, venous thromboembolic events, major adverse cardiovascular events, TB, or serious herpes zoster cases in the JIA and AD pediatric populations.

For the pediatric population with type I interferonopathies, the safety evaluation of observed AEs is compatible both with the safety profile of baricitinib and with that expected for patients with such serious disease states (CANDLE, CANDLE-like syndromes, juvenile dermatomyositis [JDM], SAVI, and Aicardi-Goutières syndrome [AGS]). Adverse events were reported in 94% of patients, and SAEs were reported in 52% of patients. Three patients were permanently discontinued due to AEs. Three fatal cases occurred while patients were being treated, two of which were considered not related to treatment and one was possibly related. This specific patient population is under a **CCl** of baricitinib (mean 6 mg per day) and varying doses of corticosteroids as background therapy due to the inherent difficulties to control the baseline disease and its complications.

No new safety signals have been identified in ongoing reviews of these pediatric studies.

Safety data from studies in adult patient populations

Baricitinib is a JAK inhibitor approved for the treatment of adult patients with RA and AD and has a well-established safety profile, based on clinical trial data and postmarketing data in patients with RA (Olumiant package insert 2020; Olumiant summary of product characteristics).

Baricitinib is currently under development in other autoimmune conditions in adults and children, including adult alopecia areata, adult systemic lupus erythematosus, pediatric AD, and JIA.

Baricitinib has an established safety profile with a positive benefit/risk profile in adults with RA. An integrated analysis of adult patients with active RA exposed to baricitinib with 3770 patients and 13,148 patient-years for a maximum exposure of 8.4 years (as of 1 September 2019) was recently published (Genovese et al. 2020). Incidence rates for safety topics of interest remained consistent over time, including serious infection (2.7); TB (0.15); herpes zoster (3.0); MACE (0.50); DVT (0.31); PE (0.24); DVT/PE (0.45); and malignancies 0.90).

Regarding VTEs, including DVT and PE, during the 16-week, placebo-controlled period of RA studies, the incidence rates (IRs) per 100 patient-years for VTE 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.

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).

Baricitinib has demonstrated a positive benefit/risk profile in adults with AD. In a pooled safety analysis, 2531 patients received baricitinib for 2247 patient-years (median duration 310 days) (Bieber et al. 2021). The frequency of serious infections was low in baricitinib-treated patients, and similar to placebo. No events of malignancy, positively adjudicated MACE, or TB were reported in the placebo-controlled period in baricitinib-treated patients. In an analysis of all patients with AD who received at least one dose of baricitinib, there were 2 positively adjudicated MACE (2-mg group), and 2 VTE events (4-mg group).

The ACTT-2 study demonstrated that baricitinib + remdesivir was superior to placebo + remdesivir for the treatment of hospitalized adult patients with COVID-19. In this study, 507 patients received baricitinib + remdesivir and 509 received placebo + remdesivir. SAEs and serious infections were reported less frequently in the baricitinib + remdesivir group compared with the placebo + remdesivir group. Serious and non-serious VTE AEs were reported by patients treated with baricitinib + remdesivir (4%) and by those treated with placebo + remdesivir (3%).

In Study KHAA, 750 patients received baricitinib plus standard of care, and 752 patients received placebo plus standard of care. SAEs and serious infections were reported less frequently in the baricitinib plus standard-of-care group (14.7% and 8.5%, respectively) compared with the placebo plus standard-of-care group (18.0% and 9.8%, respectively). Positively adjudicated VTEs were reported in 2.7% of patients treated with baricitinib plus standard of care, and 2.5% of patients treated with placebo plus standard of care. Overall, the safety profile of baricitinib in adult patients with COVID-19 is consistent with the established safety profile in patients with RA and AD. From an addendum to Study KHAA, in a separate cohort of 101 participants on invasive mechanical ventilation or ECMO at randomization, overall mortality was reduced with baricitinib plus standard compared to placebo plus standard of care with a safety profile similar to the main study population.

Vaccine response with baricitinib

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). Three out of the 4 patients with bilateral COVID-19 pneumonia, while treated with baricitinib, achieved sero-conversion, as evidenced by the appearance of immunoglobulin antibodies with neutralizing activity against SARS-CoV-2 (Stebbing et al. 2020).

2.3. Benefit/Risk Assessment

Potential benefits

COVID-19 is a severe viral respiratory disease caused by SARS-CoV-2 infection, with respiratory presentation in pediatric patients similar to that in adult patients. Of hospitalized adult patients with COVID-19 infection in Wuhan, China, 26% were transferred to the ICU, and of those patients in the ICU, complications included ARDS (61.1%), arrhythmia (44.4%), and shock (30.6%) (Wang et al. 2020a). In addition, patients with COVID-19 will inherently be at higher risk for VTE due to immobilization and the hyperinflammatory state (Klok et al. 2020; Huang et al. 2020). The disease is typically milder in pediatric patients, but some pediatric patients have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Hoang et al. 2020; Liao et al. 2020; Kim et al. 2020a, 2020b).

As stated in the study rationale, the cytokine storm which may be responsible for the significant complications of COVID-19 may potentially be ameliorated by immunomodulators such as the use of baricitinib. In addition, the clinical efficacy of baricitinib for the treatment of COVID-19 in hospitalized adult patients requiring supplemental oxygen was demonstrated in 2 randomized, controlled trials. The potential benefit of baricitinib in the treatment of COVID-19 infection is described further in the study rationale (Section 2.1).

Risks and mitigations

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 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.

VTE has been classified as an important potential risk for baricitinib and is also an adverse drug reaction. In this protocol, 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), and the limited treatment period (up to 14 days). To manage the risk of VTE, investigators should consider the use of prophylaxis (Section 6.5.2).

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 (Section 6.5.2) and criteria for permanent discontinuation of study drug if the patient is diagnosed with active TB, hepatitis B, or hepatitis C (Section 7.1). Permanent discontinuation of study drug will also occur if a participant develops a SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug (Section 7.1).

Baricitinib has an established safety profile for RA, with approximately 18,422 patients, including 123 patients ≤ 18 years of age, having received baricitinib in all clinical trials and approximately 232,500 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 cytochrome P450 [CYP] inhibitory activity) so it can be given concomitantly with background therapies. In addition, data are available from 2 completed randomized, controlled trials in hospitalized adult patients with COVID-19. In ACTT-2 and Study KHAA, a total of 1257 patients received baricitinib (1442 total patient-weeks of exposure); the safety data are consistent with the established safety profile for baricitinib.

More detailed information about the known risks and reasonably expected AEs of baricitinib may be found in the IB.

Benefit/risk summary

There are limited therapeutic options available for the treatment of COVID-19, and an unmet medical need remains for approved, novel therapies with an acceptable benefit/risk profile in hospitalized pediatric patients with COVID-19. Given the cumulative knowledge of the baricitinib safety profile and the risk mitigations included in this protocol, the potential to mitigate the hyperinflammatory state and cytokine storm associated with SARS-CoV-2, the clinical efficacy demonstrated in adult patients with COVID-19, and the unmet need for COVID-19 treatments to slow the progression of the disease, the benefit/risk balance for this study in pediatric patients is assessed to be favorable.

3. Objectives, Endpoints, and Estimands

This table describes objectives and endpoints for this study.

Objectives	Endpoints
Primary	
To characterize the pharmacokinetics (PK) of baricitinib* in pediatric patients with COVID-19	Pharmacokinetic parameters, including AUC and C _{max} of baricitinib, in pediatric patients with COVID-19
Secondary	
To describe the safety of baricitinib* in pediatric patients with COVID-19	Safety assessments, including AEs and laboratory abnormalities
To describe the effect of baricitinib* on COVID-19 progression in pediatric patients	Proportion of patients who require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28 Proportion of patients who die or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28
To describe clinical outcomes in pediatric patients with COVID-19 treated with baricitinib	• 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, and Day 28 • Number of ventilator-free days (Day 1 to Day 28) • Time to recovery on the NIAID-OS (Day 1 to Day 28) • Overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, Day 14, and Day 28 • Duration of hospitalization (Day 1 to Day 28) • All-cause mortality (Day 1 to Day 28 and Day 60) • Duration of stay in the intensive care unit (ICU) in days (Day 1 to Day 28)
Exploratory	
Exploratory objectives and endpoints include cytokines and other inflammatory markers implicated in COVID-19 such as interleukins and chemokines.	
Notes: *Baricitinib dose that produces an exposure equivalent to that produced by baricitinib 4 mg QD in adults. 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).	

Abbreviations: AE = adverse event; AUC = area under the concentration–time curve; C_{max} = maximum observed drug concentration; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; NIAID-OS = National Institute of Allergy and Infectious Diseases ordinal scale.

Primary estimand/coprimary estimand

The primary endpoint of interest is PK parameters, including AUC and $C_{\max}$ of baricitinib. The population of interest is pediatric participants with COVID 19.

Secondary estimands

A treatment policy strategy estimand will be implemented for the secondary estimands. All of the listed secondary efficacy endpoints are endpoints of interest for this study. Pediatric participants from 1 year to <18 years of age who are hospitalized with COVID-19 is the population of interest. The summary measure for binary variables will be proportion, and the summary measure for continuous variables will be the average. As this is expected to be a short study, intercurrent events such as treatment discontinuation will be considered irrelevant in defining the treatment effect. The value for the variable of interest is used, regardless of whether or not the intercurrent event occurs. Additionally, as death is an endpoint for this study, it will not be considered as an intercurrent event.

4. Study Design

4.1. Overall Design

Study KHAB is a multicenter, open-label, single-group Phase 3 study designed to characterize the PK and safety profile of baricitinib in pediatric patients (1 to <18 years of age) who are hospitalized with confirmed COVID-19. The study schema is presented in Section 1.2.

Enrollment by age cohorts and analyses for dose determination

The study will be opened to enrollment of participants in order by age:

- The first enrolled cohort will be participants aged [CCI] to <18 years.
- The second enrolled cohort will be participants aged 1 to [CCI] years.

Notably, baricitinib is dosed according to age ([CCI] to <18, [CCI], and 1 to [CCI] years), as described in Section 6.1. Additionally, a minimum number of participants will be enrolled to ensure participation across the age range for this pediatric population, as described in Section 9.4.

All participants will receive a daily dose of baricitinib that produces exposure equivalent to that produced by baricitinib 4 mg QD in adults (Section 4.3). Participants aged [CCI] to <18 years will receive baricitinib 4 mg. For younger participants, the planned doses are 2 mg for participants aged [CCI] years, and [CCI] mg for participants aged 1 to [CCI] years (Section 6.1).

After at least [CCI] enrolled members of the first cohort (older, aged [CCI] to <18 years) have completed the PK and safety assessment (up to 14 days of treatment), an analysis will be conducted to examine the PK and safety profile of the drug and to confirm, or if necessary adjust, the planned doses for the younger age groups (aged [CCI], and 1 to [CCI] years). Following confirmation of the dosing, the enrollment will be opened to the second cohort (younger, aged 1 to [CCI] years).

Study duration and periods

The study duration will be up to approximately 60 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, with a follow-up visit approximately 28 days after last dose of study drug and another follow-up visit at approximately Day 60.

Screening

Patients will be enrolled if they are hospitalized with coronavirus (SARS-CoV-2) infection and meet other study entry criteria, including requiring oxygen supplementation.

Treatment period

While hospitalized, enrolled participants will receive baricitinib until Day 14 or until the day of hospital discharge, whichever comes first. Baricitinib will not be provided to participants for use after hospital discharge. Site visits are preferred for the duration of the Treatment Period through Day 28, including after hospital discharge, but telephone visits are acceptable.

Follow-up

A follow-up visit approximately 28 days after last dose is required for all enrolled participants, including those discharged from hospital before Day 14. Another follow-up visit occurs at approximately Day 60. These follow-up visits will be conducted as telephone visits.

Hospital discharge

Discharge from the hospital prior to Day 14 is **not** considered early discontinuation from study drug or from the study.

After hospital discharge, participants should be encouraged to remain in the study for study assessments specified in the SoA (Section 1.3; Section 7.1).

Early discontinuation from study

Either before or after hospital discharge, participants who meet criteria for early discontinuation from the study (Section 7.2) should have an ETV and follow-up visits, if possible, as shown in the SoA (Section 1.3).

Allowed and prohibited concomitant medications

Participants may remain on stable background therapy per local guidelines, as described in Section 6.5.2. Certain concomitant medications are not permitted (Section 6.5.3).

4.2. Scientific Rationale for Study Design

Design elements

The open-label design of this study with a single treatment group (baricitinib) means that no participant enrolled in this study will receive placebo. Furthermore, a design focusing on confirmation of PK and safety, with a plan to extrapolate effectiveness and safety, minimizes the number of pediatric patients to be exposed to the investigational intervention.

A treatment period lasting 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. Data have been 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).

The posttreatment follow-up period allows for continued safety and efficacy monitoring after the last dose.

Primary endpoint

The primary endpoint of the study will be to characterize the PK of baricitinib in pediatric patients with COVID-19. A primary objective of proving efficacy is not planned for this study, and pediatric efficacy will be extrapolated from the adult pivotal trials (see Section 2.1.1).

This study includes patients 1 to <18 years of age, with a primary objective to characterize the PK of baricitinib in pediatric patients. Data for PK analysis will be collected in patients **CC1** to <18 years of age, to inform the PK modeling and confirm appropriate dosing in patients **CC1** years of age.

Plan for extrapolation of safety and efficacy

The justification for a proposed clinical trial design, focused on confirming PK with extrapolation of safety and efficacy, is primarily driven by the similar disease pathophysiology in adult and pediatric patients (see Section 2.2).

Substantial safety data are available from ongoing and completed studies of baricitinib in other adult and pediatric populations to support extrapolation (see Section 2.2).

Secondary endpoints

A secondary endpoint of this study is the proportion of patients who die and/or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28. Progression to requiring noninvasive or invasive mechanical ventilation is an indicator of critical disease and can occur at any time point 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). A secondary endpoint capturing progression to death or noninvasive 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.

A secondary endpoint of this study is improvement on an ordinal scale. The ordinal scale to be used in this study (NIAID-OS) was used in the NIAID ACTT-1 study (Beigel et al. 2020), the ACTT-2 study (Kalil et al. 2021), and Study KHAA in adult patients with COVID-19 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 et al. 2020b) and was an endpoint recommended by the WHO R&D Blueprint expert group (WHO R&D).

Exclusion of participants aged <1 year

While COVID-19-related hospitalization among children <1 year of age has been reported, publications vary regarding COVID-19 severity and the impact of comorbidities in this age group (Castagnoli et al. 2020; Ding et al. 2020; Dong et al. 2020; Kim et al. 2020b; Zachariah et al. 2020). Based on the limited information available on the clinical presentation and disease characteristics in children <1 year of age, it is difficult to evaluate the benefit/risk for use of baricitinib in this patient population.

4.2.1. Rationale for Collection of Race and Ethnicity

In this study, collection of demographic information includes ethnicity (in the United States only) and race (in all countries). The scientific rationale is based on the possible need to describe 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.

4.2.2. Rationale for Collection of Full Date of Birth

See Appendix 10.1, Section 10.1.4.1.

4.3. Justification for Dose

Given the generally comparable pathophysiology of COVID-19, and the available safety data on the use of baricitinib in pediatric patients with other inflammatory conditions, extrapolation of efficacy and safety data from adult patients with COVID-19 will support the indication in patients 1 to <18 years of age. Therefore, dose selection for this study is based on the objective to match the 4 mg QD exposure in adults.

To date, baricitinib has been studied for long-term use in the setting of chronic autoimmune conditions. The selection 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 (Stebbing et al. 2020). 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, AD, and alopecia areata. In addition, 2 studies (ACTT-2 and KHAA) demonstrated efficacy of baricitinib 4 mg for the treatment of COVID-19 in hospitalized adult patients requiring supplemental oxygen.

The proposed duration of treatment with baricitinib 4 mg in the setting of COVID-19 infection is brief (up to 14 days or hospital discharge, whichever comes first).

Thus, 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 adults in the setting of a clinical trial in a hospital setting.

Further, the elimination mechanism of baricitinib is well understood based on the PK in adults (patients with RA and AD, healthy subjects, and patients with various degrees of renal impairment) has been thoroughly characterized. It is well established that weight is the main physiological factor that may lead to different PK in patients ^{CCI} to <18 years of age compared to adults, since maturation in drug-elimination organs has fully completed. However, the difference in weight between patients ^{CCI} to <18 years of age and adults does not cause appreciable differences in the PK of baricitinib based on PK modeling.

In this study in a hospitalized pediatric patient population with COVID-19, the 4 mg QD, 2 mg QD, and ^{CCI} mg QD doses for patients aged ^{CCI} to <18 years, ^{CCI} years, and 1 to ^{CCI} years, respectively, are the doses expected to produce an exposure equivalent to that produced by baricitinib 4 mg QD in adults. The doses were selected based on observed and PBPK model-predicted PK and safety data from other pediatric patient populations treated with baricitinib. The observed concentration–time profiles of baricitinib in patients with JIA ^{CCI} years and ^{CCI} to <18 years of age receiving 4 mg QD, and ^{CCI} years receiving 2 mg QD, were within the expected efficacious exposure range in adult patients with RA receiving baricitinib 4 mg QD in Study JAHV that involves patients with JIA. Similarly, the observed concentration profile of baricitinib in patients with AD aged ^{CCI} to <18 years receiving 4 mg QD and ^{CCI} years receiving 2 mg QD was consistent with the anticipated efficacious exposure range in adult patients with AD receiving baricitinib 4 mg QD (Study JAIP). The observed data are consistent with predictions based on PBPK modeling. Therefore, a dose of 4 mg QD is planned for patients with COVID-19 aged ^{CCI} to <18 years.

For patients aged CCI years and 1 to CCI years of age, the planned doses are 2 mg QD and CCI mg QD, respectively (Section 6.1). This is supported by PBPK predictions and observed data from Study JAGA (NCT01724580) in pediatric patients with type I interferonopathy as young as 6 months.

To further optimize the baricitinib doses for younger patients with COVID-19 (that is, 1 to CCI and CCI years of age), a PK and safety analysis is planned upon data being available from at least CCI patients in the older age group (CCI to <18 years). The PK data will be used to inform the model for predicting the PK and selecting optimal doses prior to dosing in the younger age cohorts (1 to CCI and CCI years of age). See Section 4.1 for more information.

4.4. End of Study Definition

A participant is considered to have completed the study if the participant 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. For screen failures and rescreening activities within the screening period, see Section 5.4.

Note: Due to the criticality of participant health and the setting of this research study, verbal interview of either the potential participant or the participant's legally authorized representative may be the source for preexisting conditions and prespecified medical history, unless otherwise specified within the eligibility criteria.

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] The investigator, or a person designated by the investigator, will obtain written informed consent from the participant's legally authorized representative. The legally authorized representative must be able to read, understand, and give documented informed consent in order for a child to participate in this study. **In addition**, before any study-specific activity is performed, the participant may be required to give documented consent/assent, if the participant is capable and if required by local ethics board(s). The consent/assent indicates intent to comply with the requirements of this study as described in this protocol and in the informed consent/assent documents (Appendix 10.1, Section 10.1.1 and Section 10.1.3).

Participant characteristics

- [2] Are male or female patients from 1 to <18 years of age (inclusive) at the time of enrollment (Day 1).

Notes: Full date of birth will be collected except in countries in which it is not allowed (see Appendix 10.1, Section 10.1.4.1).

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. See Appendix 10.4 for contraception requirements.

COVID-19 diagnosis and pulmonary infection-related inclusion criteria

- [3] Hospitalized with coronavirus (SARS-CoV-2) infection, confirmed by NAAT such as real-time reverse-transcription polymerase chain reaction (rt-PCR) tests or immunodiagnostic tests detecting viral structural protein antigens such as nucleocapsid protein antigen spike (S) or other structural protein antigens. All SARS-CoV-2 virus NAAT or immunodiagnostic tests must be certified for diagnostic testing in compliance with local and national regulation, with a positive result in a sample collected no more than 14 days prior to treatment assignment.

- [4] Require supplemental oxygen, or noninvasive or invasive mechanical ventilation (including ECMO), and have chest imaging findings to confirm respiratory disease due to COVID-19 within 72 hours of study entry and enrollment.

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 below:

Prior or concomitant therapy

- [5] Are receiving biologic treatments (such as TNF inhibitors, interleukin inhibitors, T-cell- or B-cell-targeted therapies, interferons, or JAK inhibitors) for any indication at study entry; or are receiving other immunosuppressants such that, in the opinion of the investigator, participating in the study would put the participant at an unacceptable risk of immunosuppression.

Note: A washout period is required prior to screening:

- B-cell-targeted therapies: 24 weeks or 5 half-lives (whichever is longer)
- TNF inhibitors: 2 weeks or 5 half-lives (whichever is longer)
- JAK inhibitors: 1 week or 5 half-lives (whichever is longer), and
- Other biologic therapy (including interleukin inhibitors, T-cell-targeted therapies, and interferons): 4 weeks or 5 half-lives, whichever is longer, prior to screening.

See Section 6.5 for requirements.

- [6] Are receiving strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry. See Section 6.5 for requirements.

Current or historical infections

Acceptable documentation includes medical records or documentation from verbal interview with the participant's legally authorized representative.

- [7] Have diagnosis of current active TB or, if known, latent TB treated for <4 weeks with appropriate anti-TB therapy per local guidelines (by history only; no screening tests required).
- [8] 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

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

Note: Use of non-live (inactivated) vaccinations is allowed for all participants (see Section 6.5.2.1).

Other medical conditions or history

- [10] Not applicable (replaced with revised inclusion criterion [4]).
- [11] Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product.
- [12] Have any history of VTE (DVT and/or PE) or are considered at high risk of VTE (DVT/PE) by the investigator.
- [13] 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

- [14] Have neutropenia (absolute neutrophil count <1000 cells/ μL) ($<1.00 \times 10^3/\mu\text{L}$ or <1.00 GI/L).
- [15] Have lymphopenia (absolute lymphocyte count <200 cells/ μL) ($<0.20 \times 10^3/\mu\text{L}$ or <0.20 GI/L).
- [16] Have ALT or AST >5 times AAULN.
- [17] Estimated glomerular filtration rate (eGFR) <40 mL/min/ 1.73 m^2 .

Note: For each aforementioned diagnostic assessment (criteria [14], [15], [16], and [17]), one 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 (see Section 5.4.1). 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

- [18] 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 (started) in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 28.

Other exclusions

- [19] Have a known hypersensitivity to baricitinib or any of its excipients.
- [20] Are pregnant, or intend to become pregnant or breastfeed during the study.
- [21] Are, in the opinion of the investigator or sponsor, at risk of immunosuppression or otherwise unsuitable for inclusion in the study.
- [22] 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[®].

[23] 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 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 SAE.

5.4.1. Allowed Retesting of Screening Investigations

Repeating the screening labs associated with criteria [14], [15], [16], and [17] during the screening period does not constitute rescreening (see Section 5.2).

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 the individual is expected to meet study requirements per investigator assessment. It is not necessary to repeat all screening requirements. The individual will not be required to re consent due to rescreening.

Rescreened individuals will 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/used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This study involves open-label once-daily (QD) oral administration of baricitinib as shown in this table.

Treatment Name	Baricitinib	CCI
Dose Levels by Age Group	Dose	CCI
CCI to <18 years	4 mg	
CCI years	2 mg*	
1 to CCI years	CCI mg*	

*Planned dose regimen; pending a data review after at least CCI participants aged CCI to <18 years complete the PK and safety assessments, the actual dose may be adjusted, if necessary, for participants aged 1 to CCI years.

The intent of the dosing regimen for each age group is to match the exposure in adults receiving baricitinib 4 mg (see Section 4.1). The justification for the dose is provided in Section 4.3.

Participants aged CCI to <18 years will receive baricitinib 4 mg (CCI QD). After at least CCI participants in the older age groups (CCI to <18 years) have completed the safety and PK assessment, an analysis will be conducted to evaluate the PK and confirm baricitinib exposure and dosing prior to enrollment of participants in the younger age groups (CCI and 1 to CCI years). The planned baricitinib dose is 2 mg CCI for participants aged CCI years, and CCI mg CCI for participants 1 to CCI years of age; however, the dose may be adjusted (pending confirmation of the PK in participants aged CCI to <18 years with COVID-19) to a dose that will produce exposure comparable to the exposure at 4-mg QD in adults.

Package assignment will be managed using an IWRS. The IWRS will be used to assign a bottle containing baricitinib CCI to each participant. The system will notify the site personnel of the appropriate initial dose of CCI to administer based on the participant's age and eGFR at baseline. The site will contact the IWRS before the participant's first dose of baricitinib and will record the actual dose administered on the applicable eCRF.

Participants with renal impairment or renal immaturity (defined as eGFR ≥ 40 and < 60 mL/min/1.73 m²) at baseline or ≥ 30 and < 60 mL/min/1.73 m² at any time during the study will have their dose reduced (see Section 6.6.1).

Due to the possibility of participants being intubated, alternate administration via nasogastric (NG) tubing may be necessary and is allowed.

Location of study drug administration

Baricitinib will be administered to the participant at the study site.

Baricitinib will **not** be provided to participants for use after hospital discharge.

Packaging and labeling

Study interventions (baricitinib) will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. All investigational product 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 storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, 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 study personnel.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

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.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator and/or appropriate designee at the study site.

Note: To ensure that a participant receives an accurate dose according to the participant's age (Section 6.1) and eGFR status (Section 6.6.1), a second person should verify the dose as indicated by the IWRS before the first administration.

The date, time, CCI of each dose administered will be recorded in the source documents and recorded in the 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 be discontinued from following medications before enrolling in the study:

- 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)
- JAK inhibitors: a washout period of 1 week or 5 half-lives (whichever is longer), and
- Other biologic therapy, including interleukin inhibitors, T-cell-targeted therapies, and interferons, must be discontinued 4 weeks or 5 half-lives, whichever is longer, prior to screening.

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

6.5.2. Permitted Concomitant Therapy

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

- Prophylaxis for VTE for participants at high risk per the investigator's judgment.

The following will be permitted as background therapy for COVID-19, in keeping with local treatment guidelines, during the study:

- Antibiotics
- Antiviral (for example, remdesivir)
- Dexamethasone and/or other systemic corticosteroids
- Neutralizing antibodies, such as bamlanivimab, etesevimab, casirivimab, and imdevimab for COVID-19
- Convalescent plasma for COVID-19, and
- Intravenous immunoglobulin (IVIg).

6.5.2.1. Permitted Vaccines

Non-live (inactivated) seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed during the study.

Non-live vaccines (that is, RNA vaccines, vaccines with inactive viral elements, and/or non-replicating viral vectors) for COVID-19 are also allowed during the study. Live vaccines are not permitted during the study (Section 6.5.3).

6.5.3. Prohibited Concomitant Therapy

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

- Biologic therapy (such as TNF inhibitors, interleukin inhibitors, T-cell- or B-cell-targeted therapies, interferons, JAK inhibitors [other than baricitinib as study treatment]) for any indication
- Strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry
- Live vaccines, including herpes zoster vaccination (see Section 6.5.2.1 for permitted non-live vaccines), and
- 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

During this study, baricitinib doses will be adjusted as follows, if needed:

- Based on the PK analyses: for the second cohort (aged 1 to CC years) based on the first cohort (aged CC to <18 years); see Section 4.1, and
- Based on eGFR: see Section 6.6.1.

See Section 7.1.2 for temporary interruption of study drug.

6.6.1. Dose Adjustment Based on eGFR

Participants with eGFR <40 mL/min/1.73 m² at baseline are excluded from the study; see Section 5.2.

Participants with eGFR ≥ 40 and < 60 mL/min/1.73 m² **at baseline or ≥ 30 and < 60 mL/min/1.73 m² at any time during the study** will have their dose reduced by approximately 50% to avoid exposures that exceed that of the baricitinib 4-mg QD dose in participants with eGFR ≥ 60 mL/min/1.73 m². This table shows planned dose adjustments for participants with eGFR ≥ 40 and < 60 mL/min/1.73 m² **at baseline or ≥ 30 and < 60 mL/min/1.73 m² at any time during the study**:

Age	Dose of Baricitinib
to < 18 years	2 mg
1 to < 18 years	1 mg*
1 to < 18 years	0.5 mg*

*Planned dose regimen; pending a data review after at least participants aged to < 18 years complete the PK and safety assessments, the actual dose may be adjusted, if necessary, for participants aged 1 to years. For the youngest age group, is slightly lower than 50% of the typical dose due to limitation of the .

Based on the data entered into IWRS, a dose will be indicated for participants with eGFR ≥ 40 and < 60 mL/min/1.73 m² **at baseline** according to the table above, and these participants will remain on that indicated dose during the study.

Dose adjustment is not required for participants whose eGFR is ≥ 60 mL/min/1.73 m² **at baseline** and remains ≥ 60 mL/min/1.73 m² during the study. However, for participants with eGFR ≥ 60 mL/min/1.73 m² **at baseline**, if eGFR decreases to < 60 mL/min/1.73 m² and ≥ 30 mL/min/1.73 m² at any time **after baseline**, the participant should be administered a dose that is approximately 50% of the dose indicated by IWRS **at baseline** until eGFR returns to ≥ 60 mL/min/1.73 m².

Baricitinib is not recommended for use in patients with eGFR of < 30 mL/min/1.73 m². For temporary interruption of dosing in participants whose eGFR becomes < 30 mL/min/1.73 m² during the study, see Section 7.1.2.

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 intervention or discontinue from the study.

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 study as a whole is 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. Study visits are expected to occur on the study days as shown in the SoA (Section 1.3), including after a participant is discharged from the hospital.

7.1. Discontinuation of Study Intervention

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 participant permanently discontinues study drug early (that is, prior to hospital discharge or Day 14, whichever comes first), the participant 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 and/or their legally authorized representatives should be educated on the continued scientific importance of continued collection of participant study data even if the participant does not continue to receive study drug.

Unless consent is withdrawn or the participant meets other criteria listed in Section 7.2, a participant who discontinues the study drug early will remain in the study. The reason for a participant's discontinuation of study drug should be documented in the CRF.

If a participant not receiving study drug is unwilling or unable to continue the scheduled study assessments, or if the participant's legally authorized representative is unwilling to have the participant continue the scheduled study assessments (withdraws consent [Section 7.2]), the study personnel should attempt to collect as much follow-up information as possible, including, at minimum, information specified for an ETV **and** information for the follow-up visits.

Criteria for permanent discontinuation of study drug

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

Decision of participant or participant's legally authorized representative

- The participant or participant's legally authorized representative requests discontinuation of 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.

Transfer to another hospital

- Participant, for any reason, needs to be transferred to another hospital or to another hospital unit which is not a study site.

Safety considerations

- 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 for T-SPOT.TB assay)
 - active hepatitis B (HBV DNA) or hepatitis C (HCV RNA), and
 - 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/ μ L
 - Absolute neutrophil count (ANC) <500 cells/ μ L
 - Absolute lymphocyte count (ALC) <200 cells/ μ L
- The participant has an AE or SAE 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

- The study drug should be interrupted or discontinued if one or more of these conditions occur. Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified:

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/discontinuation decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/discontinuation decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Other reasons

- Throughout the trial, investigators should continue to assess the benefit/risk for each individual participant to remain on study drug and should consider discontinuing a participant from study drug if sufficient clinical benefit for that participant is not observed within the protocol-allowed concomitant medications.

7.1.2. Criteria for Temporary Discontinuation of Study Drug

This table describes when study drug should be interrupted and resumed.

Interrupt study drug for...	when...	Resume study drug when, at the discretion of the investigator...
any participant	ANC <500 cells/ μ L	this criterion no longer applies
any participant	ALC <200 cells/ μ L	this criterion no longer applies
any participant	ALT >5 times AAULN	this criterion no longer applies
any participant	AST >5 times AAULN	this criterion no longer applies
any participant	eGFR <30 mL/min/1.73 m ²	eGFR $\geq$ 30 mL/min/1.73 m ²

Note: Baricitinib is not recommended for use in patients with eGFR of <30 mL/min/1.73 m².

Abbreviations: AAULN = age-adjusted upper limit of normal; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate.

Check the most recently available laboratory results prior to dosing and interrupt study drug (within at least 48 hours of sample collection) if temporary discontinuation criteria are met. The timing and frequency of laboratory retesting to determine resumption of study drug are at the investigator's discretion.

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 the participant's own request, or at the request of the participant's legally authorized representative
- 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 enrolls in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of COVID-19. 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 visits 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/assent for disclosure

If the participant's legally authorized representative withdraws consent or the participant withdraws assent for disclosure of future information, the sponsor may retain and continue to use

any data collected before such a withdrawal of consent/assent. If a participant withdraws from the study, the participant or the participant's legally authorized representative may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

Participants are expected to be followed throughout the duration of the study (Day 60), including after hospital discharge, transfer to another hospital or unit, or early discontinuation of study drug (unless the participant withdraws from study participation as described in Section 7.2). Therefore, a participant's being lost to follow-up is expected to be rare. A participant will be considered lost to follow-up if the participant 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).

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1. Efficacy Assessments

The primary endpoint of this study is PK; see Section 8.5.

Clinical status assessment and information regarding hospitalization and death will be used for evaluation of secondary efficacy endpoints. These elements are required to derive the ordinal scale scores used in this study (Section 8.1.5).

8.1.1. Hospitalization Form and Death Disposition Form

Information regarding hospitalization and death will be recorded in the eCRF, as specified in the SoA (Section 1.3). Such information includes, but is not limited to, use of general ward, emergency room, or ICU; and cause, date, and time of death.

8.1.2. Clinical Status Assessment

During hospitalization

During hospitalization, the Clinical Status Assessment will collect information regarding whether a participant required additional organ support (for example, ECMO, renal replacement), proning, supplemental oxygen, and any means of ventilatory support. In addition, the reason for discontinuation of invasive mechanical ventilation will be collected, if applicable.

The assessment will be completed for each day during hospitalization (that is, midnight to midnight; 00:00 – 23:59 [24-hour clock]).

At screening/baseline, the participant's status will be reported.

On Day 1, the status will be reported for the period from treatment assignment to midnight on Day 1.

Thereafter, the participant's clinical status will be captured daily up to Day 28 or until hospital discharge, whichever comes first.

A clinical status assessment will be conducted via telephone visit for Follow-Up Day 60 to collect whether home oxygen use was required, and whether there were any limitations to the participant's physical activities within the past 24 hours.

After hospital discharge

On each study day after hospital discharge, this assessment will collect whether home oxygen use was required, and whether there were any limitations to the participant's physical activities within the past 24 hours. After hospital discharge, in-person site visits are preferred for each remaining study day; however, telephone visits are acceptable to complete this assessment.

8.1.3. COVID-19 Clinical Symptoms

As specified in the SoA (Section 1.3), each of the following COVID-19 clinical symptoms will be assessed as either present or not present:

- dry cough
- diarrhea, and
- vomiting.

These COVID-19 clinical symptoms will be assessed daily during hospitalization.

On each study day after hospital discharge, and on follow up days, COVID-19 clinical symptoms within the past 24 hours will be assessed. After hospital discharge, in-person site visits are preferred for each remaining study day; however, telephone visits are acceptable to complete this assessment.

8.1.4. Secondary Endpoint Efficacy Assessments

This table defines secondary endpoints and describes how they are measured.

Endpoint	Defined as	Measured by
Proportion of patients who require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28	Participants who require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) on at least 1 day after baseline. For participants on noninvasive ventilation/high-flow oxygen at baseline, the participant needs to worsen by at least 1 point on the NIAID-OS	Derived score on NIAID-OS
Proportion of patients who die or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28	Participants who require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) at any time after baseline or who die. For participants on noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) at baseline, the participant needs to worsen by at least 1 point on the NIAID-OS	Derived score on NIAID-OS, and death disposition status
Ventilator-free days	Participant breathing without mechanical ventilation assistance, if the period of unassisted breathing lasts at least 24 consecutive hours and the participant is alive	Derived score on NIAID-OS, and death disposition status
Recovery	Participant satisfies 1 of the following 3 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

Endpoint	Defined as	Measured by
Duration of hospitalization	Period of time the participant is hospitalized	Date of admission to date of discharge
All-cause mortality	28-day all-cause mortality	Derived score on NIAID-OS
Duration of stay in the ICU	Date of admission to ICU to date of discharge from ICU	Date of admission to date of discharge reported on hospitalization form
Clinical improvement	Overall (baseline minus observed ordinal scale score) and 1-point (one category decrease on the ordinal scale) improvement of participant clinical status	Derived score on NIAID-OS
Safety assessments, including AEs and laboratory abnormalities	Treatment-emergent adverse events, abnormal labs and vital signs; change from baseline in labs and vitals	Adverse events and laboratory results after the first dose of baricitinib up to the end of the treatment period or study discontinuation, whichever occurs first

Abbreviations: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; NIAID-OS = National Institute of Allergy and Infectious Diseases ordinal scale.

8.1.5. Ordinal Scale

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

Supplemental oxygen includes patients requiring oxygen via mask or nasal prongs (cannula), or oxygen tent, as appropriate per participant age and local practice. Noninvasive 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). Invasive mechanical ventilation includes any ventilatory support given through endotracheal or tracheostomy tube.

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 noninvasive ventilation or high-flow oxygen devices
Hospitalized, on invasive mechanical ventilation or ECMO
Death

Abbreviations: ECMO = extracorporeal membrane oxygenation; COVID-19 = coronavirus disease 2019.

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.

8.2. 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) AE collection, and finally
- 3) sample collection for PK, clinical laboratory, and biomarker testing.

Data collection and reporting

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

Safety monitoring

The principal 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 AEs and SAEs, discontinuations, medical history, concomitant medications, vital signs, and clinical laboratory results by means of periodic 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.

8.2.1. Vital Signs

Vitals signs (body temperature, blood pressure, heart [pulse] rate, respiration rate, and oxygen saturation) will be assessed and documented daily during hospitalization.

The minimum and maximum value should be entered into the eCRF as specified in the SoA (Section 1.3) and as clinically indicated.

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 screening if feasible. The screening examination excludes pelvic, rectal, and breast examinations unless clinically indicated. The screening examination includes an assessment of signs of TB. The investigator should also assess risk factors and symptoms of TB.

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

Height or length 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. Chest Imaging Studies

A chest x-ray or CT scan will be obtained and assessed by a radiologist, pulmonologist, or appropriate physician, as specified in the SoA (Section 1.3 and Section 5.1). The result should be recorded in the eCRF.

A report on imaging (that is, documentation of hospital-based test result) available prior to study entry is acceptable for the Day 1 imaging; imaging obtained up to 72 hours prior to study entry is acceptable.

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB, including chest imaging.

8.2.4. Clinical Safety Laboratory Assessments

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 SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator and/or appropriate designee (for example, SAE or AE or dose modification), then report the information as an AE.

Recommendations for prioritization of sampling for clinical laboratory tests are provided in Appendix 10.2, Section 10.2.1.

Reviewing and recording test results

The investigator and/or appropriate designee must review the laboratory results and record any clinically relevant changes occurring during the study as an AE.

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

The laboratory results must be retained with 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. 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.

Sample retention

Unless otherwise specified 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.

8.2.4.1. Pregnancy Testing

Pregnancy testing is to be performed

- only on females of childbearing potential (WOCBP) (Appendix 10.4) and
- only at screening, as shown in the SoA (Section 1.3).

Participants who are pregnant will be not dosed; they will be permanently discontinued from study drug (Section 7.1.1).

8.2.5. Hepatic Safety Monitoring*Close hepatic monitoring**

Laboratory tests (Appendix 10.5), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert’s syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert’s syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

***All ULN values should be age adjusted (AAULN)**

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example,

heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of at least 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels. Special care should be taken to minimize the volume of blood taken during hepatic monitoring.

*Comprehensive hepatic evaluation**

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST $\geq 3x$ ULN with hepatic signs/symptoms**, or ALT or AST $\geq 5x$ ULN
ALP <1.5x ULN	ALP $\geq 3x$ ULN
TBL <1.5x ULN	TBL $\geq 2x$ ULN (except for participants with Gilbert's syndrome)
ALT or AST $\geq 1.5x$ ULN	ALT or AST $\geq 2x$ baseline with hepatic signs/symptoms**, or ALT or AST $\geq 3x$ baseline
ALP $\geq 1.5x$ ULN	ALP $\geq 2x$ baseline
TBL $\geq 1.5x$ ULN	TBL $\geq 2x$ baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

***All ULN values should be age adjusted (AAULN).**

****Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.**

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR and direct bilirubin, if total bilirubin was elevated.

Based on the participant's age, medical history, and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for viral hepatitis A, B, C, E; autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, MRI, or CT scan). Consider additional tests, based on the medical history and clinical picture, including tests for HDV, CMV, EBV, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Special care should be taken to prioritize more pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a pediatric hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP),

endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

8.2.5.1. Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Tests during the Study

Additional hepatic safety data collection in the hepatic safety eCRF should be performed in study participants who meet 1 or more of the following 5 conditions*:

1. Elevation of serum ALT to ≥ 5 times AAULN on 2 or more consecutive blood tests (if baseline ALT < 1.5 times AAULN)
 - In participants with baseline ALT ≥ 1.5 times AAULN, the threshold is ALT ≥ 3 times baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2 times AAULN (if baseline TBL < 1.5 times AAULN) (except for cases of known Gilbert's syndrome)
 - In participants with baseline TBL ≥ 1.5 times AAULN, the threshold should be TBL ≥ 2 times baseline
3. Elevation of serum ALP to ≥ 2 times AAULN on 2 or more consecutive blood tests (if baseline ALP < 1.5 times ULN)
 - In participants with baseline ALP ≥ 1.5 times AAULN, the threshold is ALP ≥ 2 times baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be a SAE
5. Discontinuation of study drug due to a hepatic event

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

***All ULN values should be age-adjusted (AAULN).**

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 10.3:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

These 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 these definitions and remain responsible for following up 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 (see Section 7).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest, as defined in Section 8.3.3, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3. For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.3.

Serious adverse events caused by COVID-19 disease progression, including death, should not be reported on the SAE form unless the investigator deems them to be possibly related to study treatment (Appendix 10.3).

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the ICF/assent form	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	Signing of the ICF/assent form	Start of intervention	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE* – after participant’s study participation has ended and the investigator becomes aware	After participant’s study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	See Section 8.3.2.	Within 24 hours of learning of the pregnancy	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event

* These SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. 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, and ectopic pregnancy) are considered SAEs as stated in Appendix 10.3, Section 10.3.2.

8.3.3. Adverse Events of Special Interest: 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 AE or SAE. All suspected VTE events will be independently adjudicated by a Clinical Event Committee.

Infections

Completion of the Infection Follow-Up eCRF page is required for each infection reported as an AE 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.

8.4. Treatment of Overdose

For this study, an overdose of baricitinib is considered any dose higher than the dose assigned to the participant. In case of an overdose, the participant should be monitored for signs and symptoms of adverse reactions. Participants 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

Visits and times of sample collection

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.

Microsampling may be used for participants in the younger age groups (that is, **CC** years) to ensure the blood sample volume limit is not exceeded. Participants in the older age group will provide samples to assess concordance between venous blood samples and microsamples.

Concentrations of baricitinib in human plasma will be determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.

The timing of blood sample collection will be as follows:

- On Day 1, the participant will receive the baricitinib dose, and PK samples will be collected at the following timepoints:
 - 15 minutes postdose
 - 30 minutes postdose, and
 - any time between 2 to 4 hours postdose.
- On Day 4, a predose PK sample will be collected BEFORE the participant receives the baricitinib dose (that is, 24 hours postdose on previous day). Immediately after collection of the predose PK sample, the participant will receive the dose. Then, additional PK samples will be collected at the following timepoints:

- 1 hour postdose (includes a microsample and venous blood sample for participants in the CCI to <18 years group), and
- any time between 6 to 10 hours postdose.

The actual date and exact timing (24-hour clock) of sample collection, and the actual date, time, CCI of dose of study drug administration, must be accurately recorded.

The PK sampling schedule in the SoA (Section 1.3) should be followed as closely as possible. However, if an error in dosing or PK sampling occurs, PK samples should be collected on a subsequent dosing day at the specified timepoints, and this will not be considered a protocol deviation.

For participants who have study drug temporarily interrupted on Day 4 (no dose administered), the 3 PK samples planned to be collected on Day 4 should be collected on a subsequent dosing day, if possible. For participants who are discharged from the hospital prior to Day 4, the 3 PK samples planned to be collected on Day 4 should be collected on the day of discharge. For participants who permanently discontinue study drug prior to Day 4, the 3 PK samples planned to be collected on Day 4 should be collected on the day of discontinuation, if possible. Additional participants may be enrolled to ensure that at least 24 participants provide evaluable samples for the PK analysis.

Provision of PK results

The PK results will not be provided to investigative sites.

Instructions for collection and handling of PK samples

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Sample analysis and retention

Samples will be analyzed at a laboratory approved by the sponsor. The purpose of retention, the maximum duration of retention, and facility for storage of samples are 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

Serum and NP or MT swabs to assess viral load and other characterizations for exploratory nonpharmacogenetic biomarker research will be collected on days specified in the SoA (Section 1.3), where local regulations allow.

Use of either the NP (preferred) or MT swabs for the exploratory sample collection is permitted at the investigator's discretion, but for each individual participant, the same sampling method should be used consistently throughout the study.

The blood samples for biomarker research are not required if the blood sample volume is limited because of the participant's weight; if blood samples are not collected because of the sample volume limits, this will not be considered protocol deviation.

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.

C-reactive protein has been identified as a relevant marker in hospitalized pediatric patients with COVID-19 and will be evaluated in this study. In addition, cytokines and other inflammatory markers, such as interleukins and chemokines, will be explored to augment understanding of the similarities of COVID-19 in adult and pediatric patients. 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. The NP and/or MT samples may be used for additional exploratory studies to better understand baricitinib and the disease, which may include sequencing and/or culture of the virus for future studies.

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 are 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

The SAP will be finalized prior to first participant first visit, and 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.

9.1. Statistical Hypotheses

The primary objective of this study is to characterize the PK of baricitinib in pediatric participants with COVID-19, as assessed by PK parameters such as AUC and $C_{\max}$ of baricitinib in pediatric patients with COVID-19.

This study will compare summary data between pediatric participants and adult participants (from Study KHAA) with COVID-19 that have been treated with baricitinib. Hypothesis testing will be performed to compare selected comparable endpoints for pediatric patients treated with baricitinib and adult placebo population.

Additional details will be described in the SAP.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. 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 SAP and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to first patient visit. 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 secondary endpoints.

9.2.1. Populations for Analyses

This table defines the analysis populations for this study:

Population	Description
Entered	All participants with signed informed consent/assent forms.
Intent-to-treat (ITT)	All participants assigned to study intervention. Participants will be analyzed according to the intervention to which they were assigned.
PK population	Participants who receive at least 1 dose of study intervention and have evaluable PK samples.
Safety	All participants 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.
Follow-up	All participants who received at least 1 dose of investigational product and have entered the posttreatment follow-up period. Participants will be analyzed according to the intervention which they received in the treatment period.

9.2.2. General Considerations

Efficacy analyses will be conducted on the ITT Population. Safety analyses will be conducted on the Safety Population. PK analyses will be conducted on the PK population.

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

Descriptive summary statistics will be displayed side by side with data from the adult trial KHAA whenever available. Descriptive statistics including number of participants, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures.

For comparable endpoints, p-values for the comparison between adult placebo participants and pediatric baricitinib participants may be provided. The p-values, when provided, will be calculated based on simple tests of hypothesis without controlling for covariates. For categorical endpoints, the p-values will be generated using Fisher’s exact test. For continuous endpoints, p-values will be produced using the Wilcoxon Rank-Sum test without continuity correction. For assessing overall improvement, a proportional odds model with only the treatment group in the covariates will be used to generate p-values. An unstratified log-rank test will be utilized for obtaining p-values for time-to-event analysis.

9.2.3. Primary Endpoint(s)/Estimand(s)

The primary endpoint of this study is PK parameters, such as AUC and C_{max} of baricitinib in pediatric participants with COVID-19. The primary analysis will be performed on the PK population.

9.2.4. Secondary Endpoint(s)/Estimand(s)

Secondary comparisons of interest (key secondaries) are

- Safety assessments, including AEs and laboratory abnormalities

- Proportion of patients who require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28
- Proportion of patients who die or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28
- 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, and Day 28
- 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, Day 28,
- Duration of hospitalization (Day 1 to Day 28)
- All-cause mortality (Day 1 to Day 28 and Day 60), and
- Duration of stay in the ICU in days (Day 1 to Day 28).

Analyses for these endpoints are described in Section 9.2.2. Unless otherwise mentioned, all the secondary efficacy analysis will be performed in the ITT population. For the analysis of progression to ventilation, participants requiring invasive mechanical ventilation (including ECMO) at baseline would not be included. Consistent with a treatment policy strategy, all observed data will be used. Any other missing data imputation, if implemented, will be described in detail in the SAP.

9.2.5. Exploratory Endpoints

Exploratory objectives and endpoints include cytokines and other inflammatory markers implicated in COVID-19, such as interleukins and chemokines.

9.2.6. Pharmacokinetic Analysis

Plasma baricitinib concentration–time data will be pooled and evaluated using PopPK methods. A covariate screen of participant and study-specific factors will be included in the analyses based on factors investigated in previous PK analyses and on their relevance to the target population. Exploratory and/or model-based analyses examining the relationships between baricitinib exposure and efficacy and response endpoints may be conducted. Other analyses of efficacy and safety outcome measures may also be assessed as scientifically appropriate and warranted by available data. Details about the analyses to be conducted will be contained in the PopPK analysis plan.

9.3. Interim Analysis

A review of PK and safety data is planned upon completion of at least █ participants in the █ to <18 age group to confirm the doses to be administer in the younger age groups; however, this will not be considered a formal interim analysis in this open-label study. A detailed description of the analyses to be conducted will be contained in the PopPK analysis plan. The SAP will describe the planned safety data review in greater detail.

9.3.1. Data Monitoring Committee

An independent, external DMC will oversee this study. The DMC will be authorized to evaluate PK, safety, and efficacy analyses, including evaluation of excess mortality. The study sites will receive information about the DMC's findings only if the sites need to know for the safety of their study participants. In addition, in this open-label clinical trial involving hospitalized pediatric participants, study team members will have access to the data prior to the final database lock. See Appendix 10.1, Section 10.1.5 for more information.

9.4. Sample Size Determination

The sample size for Study KHAB was estimated based on the method proposed by Wang et al. (Wang et al. 2012). It estimated that a total of [REDACTED] participants in the age group of [REDACTED] to <18 years will achieve at least [REDACTED] power to be able to estimate the 95% CI within 60% and 140% of the geometric mean estimates of the PK parameters of interest, using the variability estimates of [REDACTED] for AUC. Given possible uncertainty in the PK in participants with COVID-19 (that is, possibly augmented renal clearance and/or different absorption and bioavailability), this estimated number was increased to at least [REDACTED] participants, which represents a 50% increase in the sample size in the [REDACTED] <18 years of age group. In addition, to ensure adequate coverage of the low end of the age range, it is further specified that at least [REDACTED] participants aged [REDACTED] years should be included.

Because severe respiratory disease in patients with COVID-19 is rare in children [REDACTED] years of age, enrollment is likely to be challenging in this age group. Therefore, the plan is to include

- at least [REDACTED] participants from [REDACTED] years of age
- at least [REDACTED] participants from [REDACTED] years of age, and
- at least [REDACTED] participants from 1 [REDACTED] years of age.

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 ICH 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 or IEC by the investigator and reviewed and approved by the IRB or IEC before the study is initiated.

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation, 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
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Reporting cases of suspected child abuse and/or neglect according to local regulations and local medical association (for example, American Academy of Pediatrics [AAP], EU Academy of Pediatrics [EAP]) or health department guidelines.

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 CTA.

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 and Assent Process

The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant and the participant's legally authorized representative, and answer all questions regarding the study. The participant's legally authorized representative(s) should be fully informed, and participants should be informed, to the fullest extent possible about the study in language and terms they are able to understand. Participants must be informed that their participation is voluntary. As appropriate, participants may be given the opportunity to meet privately with a member of site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legally authorized representative, unless required by local law.

Participants or their legally acceptable representative (parent/legal guardian) will be required to sign a written statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center. Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate. Assent forms should be written in language appropriate to the child's development and functional status. The sponsor or its representatives must approve the ICFs/assent forms, including any changes made by the ERBs, before the ICFs/assent forms are used at the investigative sites.

The original copy of each participant's signed consent/assent document must be kept on file. However, 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/assent is allowed by hospital policy, how it will be obtained and stored will need to be determined. Any variation from the standard the consent/assent 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 the participant's legally acceptable representative (parent/legal guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally acceptable representative (parent/legal guardian). The acceptable person obtaining the informed consent must also sign the ICF.

Participants and their legally acceptable representative (parent[s]/legal guardian) must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.

Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating. Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if the legally authorized representative wants the participant to continue.

A copy of the ICF(s) must be provided to the participant or to the participant's legally acceptable representative (parent/legal guardian).

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.

10.1.4.1. Rationale for Collection of Full Date of Birth

This study includes patients from 1 to <18 years of age (Section 5.1). Within this age range, participants' height/length and weight, as well as normal ranges for laboratory tests, vary by age and sex. Therefore, it is necessary to collect a participant's full date of birth (day, month, year) to appropriately analyze and interpret changes in laboratory parameters.

In countries where local regulations do not permit collection of the full date of birth, providing the supporting regulatory/ethics documentation is available, the month and year of birth, at a minimum, must be collected on the eCRF.

10.1.5. Committees Structure

Clinical Event Committee

A Clinical Event Committee will adjudicate VTEs and deaths.

Data Monitoring Committee (DMC)

A DMC will oversee the conduct of this study, as described in Section 9.3.1. The DMC will consist of members external to Lilly. The 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 safety reasons. The DMC membership will include, at a minimum, specialists with expertise in pediatrics, statistics, and other appropriate specialties. Details about the DMC membership, purpose, responsibilities, and operation will be described in a DMC charter.

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 PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and 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, SAP, clinical study report, blank or annotated CRFs, 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 CRF. 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/assents, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the 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 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 CRF.

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 or access 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/electronic transfers will be provided to the investigator for review and retention, if applicable. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global PC 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 designee reserves the right to close the study site or 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 there is reasonable cause 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:

For study termination

- Discontinuation of further study intervention development

For site closure

- 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 (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

Premature termination or suspension of the study

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 should 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 pediatrics, infectious disease, acute or critical care, pulmonary disease, immunology, or other appropriate specialties when justified.

10.1.12. 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 of 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
PK	Sponsor or designee	1 year
Exploratory biomarkers	Sponsor or designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

Use of central or local laboratories

The tests detailed in the tables below (Section 10.2.2) will be performed by a central laboratory or by a local laboratory as specified in this appendix.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing, the local laboratory must be qualified in accordance with applicable local regulations.

Laboratory tests for inclusion/exclusion of potential study participants

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

Pregnancy testing

Pregnancy testing is described in the SoA, in Section 8.2.4.1, and in Section 10.2.2.

Allowance for additional testing

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

Investigator responsibilities

Investigators must document their review of the laboratory safety results as described in Section 8.2.4.

10.2.1. Laboratory Test Prioritization to Minimize Blood Sampling

Care should be taken to safeguard study participants with regard to the amount of blood drawn for study procedures.

Efforts have been made to minimize the blood sampling required by this protocol. However, the following guidance is provided to assist sites in further minimization when deemed necessary by investigator discretion or according to local requirements.

Sites should follow local IRB guidelines, where applicable.

Weight range (kg)	Guidance	Requested prioritization of sample collection (with 1 being the highest priority)
≥ 32	All samples should be collected unless difficulties arise during collection. If difficulties arise, follow requirements outlined in the “Requested prioritization of sample collection” column.	1. PK 2. Chemistry and hematology 3. Serum exploratory biomarker sample 4. CRP
<32 and ≥ 15	Reduced blood volume collection will be required. In the situation where blood volume is limited and all samples cannot be collected, follow requirements outlined in the “Requested prioritization of sample collection” column.	1. PK 2. Chemistry and hematology 3. Serum exploratory biomarker sample <i>Note: CRP samples are not required for these participants.</i>
<15	Reduced blood volume collection and the exclusion of some tests will be required. In the situation where blood volume is limited and all samples cannot be collected, follow requirements outlined in the “Requested prioritization of sample collection” column.	1. PK 2. Chemistry and hematology <i>Note: CRP and serum exploratory biomarker samples are not required for these participants.</i>

Abbreviations: CRP = C-reactive protein; PK = pharmacokinetics.

Please reference the laboratory manual for reduced volumes of central laboratory samples for participants <32 kg and >15 kg and <15 kg, as appropriate.

10.2.2. Tables of Clinical Laboratory Tests

	Notes
Hematology	Performed locally. Enter results obtained during hospitalization in EDC.
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells [RBC])	
Leukocytes (white blood cells [WBC])	
Platelets	
<i>Absolute count of:</i>	
Neutrophils, segmented (mature) + bands (juvenile); absolute neutrophil count (ANC)	Request ANC from local laboratory with each hematology sample.
Lymphocytes (absolute)	

	Notes
Clinical chemistry	Performed locally. Enter results obtained during hospitalization in EDC.
Sodium	
Potassium	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Blood urea nitrogen (BUN)	
Creatinine	
Total protein	
Albumin	
Calcium	
Glucose	
Creatine kinase (CK)	
Lactate dehydrogenase (LDH)	

	Notes
Hormones (females)	Performed locally.
Serum pregnancy	Females of childbearing potential only (Appendix 10.4, Section 10.4.1).

	Notes
Biomarkers	Performed locally.
C-reactive protein (CRP)	

	Notes
Viral testing	Performed locally. Enter results obtained during hospitalization in EDC. See Section 1.3 (Comments column) for additional information.
SARS-CoV-2 viral infection confirmation	Utilizing NP swab.

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

	Notes
Long-term stored samples: exploratory biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
NP or MT swab	
Serum	

Abbreviations: EDC = electronic data capture system; MT = mid-turbinate; NP = nasopharyngeal; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

10.2.3. Clinical Laboratory Formula

Obtain quantitative eGFR results using appropriate formula for pediatric patients per local laboratory.

10.3. Appendix 3: Adverse Events and Serious 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, electrocardiogram, radiological scans, and 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 preexisting condition, including either an increase in frequency and/or 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. Such overdoses should be reported 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 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 that 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one of more of the criteria listed:

a. Results in death**b. Is life-threatening**

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. 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 or emergency ward (usually involving at least an overnight stay) 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 preexisting 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

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

f. Other situations:

Medical or scientific judgment should be exercised by the investigator 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. Definition of Product Complaints**Product Complaint**

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- Deficiencies in labeling information, and
- Use errors for device or drug–device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording
When an AE/SAE/PC 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/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate eCRF page, and PC information is reported on the PC form. Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE. 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 eCRF page for AE/SAE and the PC form for PCs. 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 1 of the following categories: Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. 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 one 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. The investigator will use clinical judgment to determine the relationship.

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.

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 in his or her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he or 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 or 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.

10.3.5. Reporting of SAEs**SAE Reporting via an Electronic Data Collection Tool**

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or by telephone.

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

SAE Reporting via Paper Form (back-up method)

Facsimile transmission of the SAE paper form 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 site training documents.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward 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, IRB/IEC, 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.

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

10.4.1. Definitions

Females of childbearing potential

A female is considered fertile (a woman of childbearing potential [WOCBP]) if she has had at least 1 cycle of menses. Any amount of spotting should be considered menarche. 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.

Females not of childbearing potential

A female in one of these categories is considered not of childbearing potential:

- Premenarchal
- Have a congenital anomaly such as Müllerian agenesis,
- Are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, and tubal ligation).

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, androgen insensitivity), investigator discretion should be applied to determining study entry. Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.4.2. Contraception Guidance

Males

For males, there are no contraception requirements.

Females not of childbearing potential

For females not of childbearing potential, there are no contraception requirements.

Females of childbearing potential

Study participants will be hospitalized while they are receiving baricitinib in this study.

No birth control methods should be initiated during hospitalization. The prescriber may choose to interrupt oral contraception during hospitalization due to the severity of the disease state and risks associated with such medications.

A pregnancy serum test will be performed prior to study drug initiation, as specified in the SoA (Section 1.3) and in Section 8.2.4.1.

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 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 also 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 gestational age, 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 gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an 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 poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. 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 be discontinued from the study intervention. If the participant is discontinued from the study intervention, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing

See Section 8.2.5 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	Clinical Chemistry
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	Other Chemistry
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	Urine Chemistry
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	Other Serology
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) ^a
HBV DNA ^d	Anti-actin antibody ^b

table continues

table continued

Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA ^d	EBV DNA ^d
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA ^d
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA ^d	HSV (Type 1 and 2) DNA ^d
Microbiology^c	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviations: INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

- a Not required if anti-actin antibody is tested.
- b Not required if anti-smooth muscle antibody (ASMA) is tested.
- c Assayed ONLY by investigator-designated local laboratory; no central testing available.
- d Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.6. Appendix 6: Abbreviations and Definitions

Term	Definition
AAP	American Academy of Pediatrics
AAULN	age-adjusted upper limit of normal
ACTT-1	Adaptive COVID-19 Treatment Trial 1
ACTT-2	Adaptive COVID-19 Treatment Trial 2
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
assent	agreement from a minor or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in research
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
BiPAP	bilevel positive airway pressure
CANDLE	chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
caregiver	Person responsible for ensuring the participant communicates with or visits the site according to the SoA and is consistently being available to provide information on the participant after hospital discharge when, for example, study-site personnel are performing follow-up. The caregiver may be the participant’s legally authorized representative, or another appropriate person, as delegated by participant’s legally authorized representative.
CI	confidence interval
C_{max}	maximum observed drug concentration
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
CFR	Code of Federal Regulations

Term	Definition
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CRF	case report form
CT	computerized tomography
CTA	clinical trial agreement
DMC	data monitoring committee
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture system
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
enroll/enrollment	Treatment assignment; 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	A participant entered into a study is one who signs the informed consent form directly or else through a legally acceptable representative (parent/legal guardian). See “legally authorized representative.”
ERB	Ethics (or ethical) review board. An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human participants involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial participants.
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials, European clinical trials database
FDA	United States Food and Drug Administration
GCP	good clinical practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
IB	investigator’s brochure
ICF	informed consent form

Term	Definition
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee (IEC); see “ERB”
IFN	interferon
IFN- γ	interferon gamma
IL	interleukin
IND	Investigational New Drug application
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.
interim analysis	An analysis of clinical trial data by treatment group that is conducted before the primary outcome database lock.
investigational product	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.
IP-10	interferon gamma-inducible protein-10
IR	incidence rate
IRB	institutional review board (IRB); see “ERB”
ITT	intent-to-treat
IWRS	interactive web-response system
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
legally acceptable representative	See “legally authorized representative”
legally authorized representative	The participant’s parent(s), preferably all parents, if available, or one parent (if one parent is allowed by national and local law and regulations), who provide(s) consent on behalf of a minor; OR The participant’s legally appointed guardian(s) or legally acceptable representative(s), as defined by national and local laws and regulations, who provide(s) consent on behalf of a minor.

Term	Definition
legal guardian	See “legally authorized representative”
MACE	major adverse cardiovascular events
MCP-1	monocyte chemoattractant protein-1
MT	mid-turbinate
NAAT	nucleic acid amplification tests
NAK	numb-associated kinase
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
OAT3	organic anion transporter 3
OS	ordinal scale
parent	See “legally authorized representative” and “caregiver”
participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PBPK	physiologically based pharmacokinetic
PC	product complaint
PD	pharmacodynamic(s)
PE	pulmonary embolism
PK	pharmacokinetic(s)
PopPK	population PK
QD	once daily
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAVI	STING (stimulator of interferon genes)-associated vasculopathy with onset in infancy

Term	Definition
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.
SoA	schedule of activities
STAT	signal transducer and activator of transcription
TB	tuberculosis
TNF	tumor necrosis factor
VTE	venous thromboembolism
WHO	World Health Organization

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