Statistical Analysis Plan I4V-MC-KHAB

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

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Title Page

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

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Version history

This Statistical Analysis Plan (SAP) for Study I4V-MC-KHAB is based on the protocol dated 05 May 2021.

Table 1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	14-Oct-2021	Not Applicable	Original version
2		Added language to remove staggered enrollment across age groups.	Changed in accordance to Addendum 2 of Protocol KHAB

The main changes incorporated in SAP Version 2 are as follows:

Change	Section	Summary of Changes
Study Design	Section 1.2	Removed requirement for staggered entry based on age in accordance with Protocol KHAB, Addendum 2.
Schema of Study I4V-MC-KHAB	Figure 1	Modified language for PK analysis in accordance with Protocol KHAB, Addendum 2 and added dose based on eGFR in Notes.
Main Analytical Approach	Section 4.3.1	Added language to change the PK analysis plan in accordance with Protocol KHAB, Addendum 2.
Interim Analyses	Section 4.8	Removed requirement of enrolling older participants and added an upper limit on the number of participants to trigger PK DMC.

1. Introduction

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

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 progress to noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28 • Proportion of patients who die or progress to 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)

Objectives	Endpoints
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; Cmax = 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

The primary endpoint of interest is PK parameters, including AUC and C_{max} of baricitinib administered to pediatric participants with COVID-19 for 14 days. As the treatment duration is quite short for this study, intercurrent events such as treatment discontinuation will be considered irrelevant in defining the treatment effect. The population of interest is pediatric participants with COVID-19.

Secondary estimand(s)

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 are 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 the treatment duration is quite short for this 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.

1.2. Study 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, with the Addendum 2 exception noted below:

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

Addendum 2, approved on 02 February 2022, removes the staggered enrollment (requirements to enroll Cohort 1 prior to Cohort 2) for countries to which this addendum is submitted.

Analyses of the PK and safety profile from at least [redacted] participants in the older cohort will confirm or, if necessary and time permits, 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

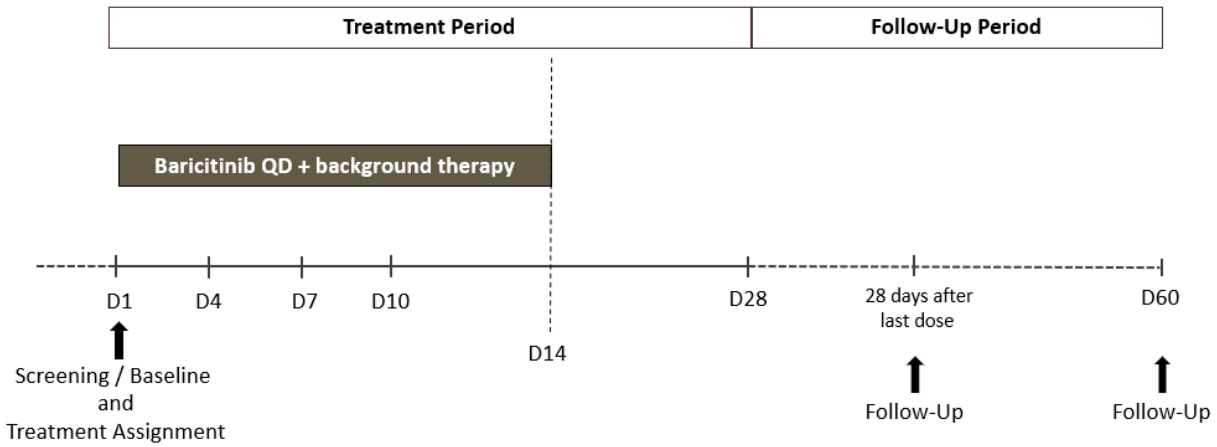
Follow-up: Period starting after treatment period, with a follow-up visit approximately 28 days after last dose of study drug and another follow-up visit at approximately Day 60.

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 and renal function. 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.



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

Notes: Baricitinib dose levels are assigned according to the participant's age and renal function. To allow for a safety review and dose confirmation for younger participants ([redacted] years), an early PK analysis will be conducted. For all participants, 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.

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

2. 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 provide summary data for pediatric participants with COVID-19 that can be used to assess similarity of response to adult participants with COVID-19 (from Study KHAA) as exploratory analyses. P-values will be provided for selected endpoints for pediatric patients treated with baricitinib versus adult placebo population as well as for pediatric patients treated with baricitinib versus adult patients treated with baricitinib. P-values are intended to assist with the interpretation of results rather than to be used for hypothesis testing.

2.1. Multiplicity Adjustment

Not applicable.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Intent-to-treat (ITT)	• All participants assigned to study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Pharmacokinetic (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.

The *ITT analysis set is used to analyze endpoints related to the efficacy objectives, the PK population analysis set is used to analyze endpoints related to PK, the safety analysis set is used to analyze the endpoints and assessments related to safety, and the follow-up analysis set is used to analyze data obtained in the follow-up period. When analyzing according to the treatment they actually received, participants will be analyzed according to a daily dose of baricitinib that produces an exposure equivalent to that produced by baricitinib 4 mg QD in adults and not the dose based on their age and eGFR values.*

4. Statistical Analyses

4.1. General Considerations

Descriptive summary statistics will be provided for the secondary endpoints. For continuous measures, descriptive statistics will include number of participants, mean, standard deviation, median, minimum, and maximum. For categorical measures, descriptive statistics will include frequency counts and percentages. Efficacy and safety analyses will be summarized overall, and by the following age groups

- [redacted] to less than 18 years of age
- [redacted] to less than [redacted] years of age
- [redacted] to less than [redacted] years of age, and
- [redacted] to less than [redacted] years of age.

4.2. Participant Dispositions

An overview of patient populations will be summarized. Frequency counts and percentages of patients excluded prior to randomization by primary reason for exclusion will be provided for patients who failed to meet study entry requirements during screening.

Patient disposition will be summarized using the ITT population. Frequency counts and percentages of patients will be summarized by the following dispositions:

- treatment disposition
  - ongoing treatment
  - discontinued treatment (reason will be summarized)
  - completed treatment
- study disposition
  - ongoing
  - discontinued (reason will be summarized), and
  - completed.

A listing of patient dispositions will be provided for all randomized patients, with the extent of their participation in the study, and the reason for discontinuation.

4.3. Primary Endpoint(s)/Estimand(s) Analysis

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. Details of the PK analysis will be described in a separate PK analysis plan.

4.3.1. Main Analytical Approach

Pharmacokinetic concentrations from samples taken from at least [redacted] patients in the CCI 18-year dose group along with supportive information such as dosing, weight, and laboratory measurements may be utilized to fit existing adult population PK models (with incorporated allometry) or pediatric population PK models. This initial derived interim population PK model will be used to verify or adjust the dosing for patients CCI years of age, if time permits. At the completion of the study, a final population model testing additional covariates as necessary will be developed to describe the exposure of pediatric COVID patients in the entire study. Further details may be found in the Population Pharmacokinetic Analysis Plan for KHAB.

4.4. Secondary Endpoint(s)/Estimands(s) Analysis

Secondary endpoints (key secondaries) are based upon KHAB only and 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).

Descriptive summary statistics will be provided for all secondary analyses. Unless otherwise mentioned, all of the secondary efficacy analysis will be performed on the ITT population. Consistent with a treatment policy strategy, all observed data will be used.

4.4.1. Definition of Endpoint(s)

Table 2. Description and Derivation of Secondary Analyses

Measure	Description	Variable	Derivation / Comment	Definition of Missing
NIAID-OS	Using data from the COVID-19 Clinical Status Assessment, results will be calculated for ordinal scales currently being used in other studies, and in this study, to measure clinical outcomes in patients treated for COVID-19, in particular the NIAID-OS. The NIAID-OS is as follows: 1. Not hospitalized, no limitations on activities 2. Not hospitalized, limitation on activities and/or requiring home oxygen 3. 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, and so forth).	Patients who progress to requiring ventilation	Proportion of patients who progress to ventilation. In order to be counted as having this event: • Patients who start at 5 must progress to at least OS 6. • Patients who start at OS 6 must progress to OS 7. • Patients who start at OS7 will not be included in the analysis. • Patients who are missing baseline and/or are missing all postbaseline observations will be excluded from the analysis.	Missing if NIAID-OS is missing and the variable status cannot be identified using remaining data.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
	4. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19–related or otherwise) 5. Hospitalized, requiring supplemental oxygen 6. Hospitalized, on noninvasive ventilation or high-flow oxygen devices 7. Hospitalized, on invasive mechanical ventilation or ECMO 8. Death.	Patients who die or progress to requiring ventilation	Proportion of patients who progress to ventilation or death. In order to be counted as having this event: • Patients who start at OS 5 must progress to at least OS 6. • Patients who start at OS 6 must progress to at least OS 7. • Patients who start at OS 7 must progress to at least OS 8 • Patients who are missing baseline and/or are missing all postbaseline observations will be excluded from the analysis.	Missing if NIAID-OS is missing and the variable status cannot be identified using remaining data.
		1-point improvement in OS (at Days 4, 7, 10, 14, and 28)	• Proportion of patients with baseline NIAID-OS minus NIAID-OS ≥1. • Patients who are missing baseline or are missing a postbaseline observation on the landmark day will be excluded from the corresponding analysis.	Missing if either baseline NIAID-OS is missing or if the observed NIAID-OS is missing on the day of assessment of 1-point improvement
		Ventilator-free days (days free of invasive mechanical ventilation)	• Total number of days patients are alive and have a NIAID-OS <7 by Day 28. • Patients who are missing baseline and/or are missing all postbaseline observations will be excluded from the analysis.	Missing if patient's NIAID-OS is missing for any day.
		Time to recovery	• Time to reach NIAID-OS 1, 2, or 3 for the first time. The date reached is the first full day that OS 1, 2, or 3 is the patient's maximum OS for the day. All deaths within 28 days will be considered censored at Day 28. • Patients who are missing baseline and/or are missing all postbaseline observations will be censored at baseline.	Missing if NIAID-OS is missing and time to event of interest cannot be identified using remaining data.
		Overall improvement (at days 4, 7, 10, 14, and 28)	• NIAID OS • Patients who are missing baseline or are missing a postbaseline observation on the landmark day will be excluded from the corresponding analysis.	Missing if observed NIAID-OS is missing.
		Duration of hospitalization	• Total number of days patients have a NIAID-OS of 4, 5, 6, or 7 by Day 28. If the patient died on or prior to Day 28, their duration of hospitalization is considered to be 28 days. On Day 1 the patient's worst ordinal scale between baseline and the rest of Day 1 will be used to define their hospitalization status. • Patients who are missing baseline and/or are missing all postbaseline observations will be excluded from the analysis.	Missing if patient's NIAID-OS is missing for any day.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
		All-cause mortality by Day 28	• Time to death by Day 28. Patients included: ITT population Start date: Baseline date Event date: date of death if death is within 28 days of their baseline date (ie, if baseline is Day 1, any deaths up to and including Day 28 are included). Censor date: Date of last non-missing OS or visit that is on or prior to Day 28. If there is other information that makes it clear that they were alive at Day 28, they will be censored at Day 28. Patients who are missing baseline and/or are missing all postbaseline observations will be censored at baseline.	Missing if the patient's maximum NIAID-OS is not 8 and patient's NIAID-OS is missing for all days after a particular day.
		All-cause mortality by Day 60	• Time to death by Day 60. Patients included: ITT population Start date: Baseline date Event date: date of death if death is within 60 days of their baseline date (ie, if baseline is Day 1, any deaths up to and including Day 60 are included). Censor date: Date of last nonmissing OS or visit that is on or prior to Day 60. If there is other information that makes it clear that they were alive at Day 60, they will be censored at Day 60. Patients who are missing baseline and/or are missing all postbaseline observations will be censored at baseline.	Missing if the patient's maximum NIAID-OS is not 8 and patient's NIAID-OS is missing for all days after a particular day.
Intensive Care Unit (ICU) stay	Duration of stay in the ICU	Total number of days spent in the ICU plus days from death up to and including Day 28.	• Missing if status of ICU stay is missing for any day for the patients and the patient is alive. • Patients who are missing baseline and/or are missing all postbaseline observations will be excluded from the analysis.	ICU stay.

Abbreviations: ECMO = extracorporeal membrane oxygenation; ITT = intent-to-treat; NIAID-OS = National Institute of Allergy and Infectious Diseases ordinal scale; OS = ordinal scale.

4.4.1.1. Main Analytical Approach

All analyses will be performed on the ITT population unless otherwise specified.

For ventilator-free days and days of hospitalization, NIAID-OS scores will be imputed using the last observation carried forward (LOCF) approach. For duration of stay in the intensive care unit, the status of ICU stay will be imputed using LOCF. Intermittent or terminally missing data will be filled in by carrying forward the last available measurement prior to the missing data. This methodology will only be utilized for patients who had both a baseline and a postbaseline measurement. Other descriptive analyses will be based on observed data.

For time to death and time to recovery analyses, Kaplan-Meier (KM) plots along with number of patients in the analysis population, number of events, number at risk, and median time to event with 95% confidence interval will be provided when available.

4.5. Exploratory Analysis

Exploratory analyses will compare baricitinib-treated pediatric participants in Study KHAB to baricitinib-treated adult participants from Trial KHAA and compare baricitinib-treated pediatric participants in Study KHAB to adult placebo participants from trial KHAA. These analyses are not based on a randomized comparison and therefore may be subject to bias to due to measured and/or unmeasured confounders. These analyses will only be used to provide additional contextual information in support of the PK-based extrapolation approach.

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.

The planned analyses are described in Table 3.

Table 3. Description of Exploratory Analyses

Measure	Variable	Population	Analysis Method	Time Point
NIAID-OS	Proportion of patients who progressed to non-invasive ventilation or high-flow oxygen (Progressed to OS 6 or 7)	ITT population with baseline OS <7	Fisher's exact test using LOCF	By Day 28
	Proportion of patients who died or progressed to non-invasive ventilation or high-flow oxygen (OS ≥6)	ITT	Fisher's exact test using LOCF	By Day 28
	Proportion of patients with 1-point improvement	ITT	Fisher's exact test using LOCF	Day 4, 7, 10, 14, 28
	Ventilator free days (VFD)	ITT	Wilcoxon rank-sum test using LOCF	By Day 28
	Time to recovery	ITT	Log-rank test	By Day 28
	Overall improvement	ITT	Proportional odds model using LOCF	Day 4, 7, 10, 14, 28
	Duration of hospitalization	ITT	Wilcoxon rank-sum test LOCF	By Day 28
	All-cause mortality	ITT	Log-rank test	By Day 28
				By Day 60
Intensive Care Unit (ICU) stay	Duration of stay in the intensive care unit (ICU)	ITT	Wilcoxon Rank Sum Test using LOCF	By Day 28

Abbreviations: ITT = intent-to-treat; LOCF = last observation carried forward; NIAID-OS = National Institute of Allergy and Infectious Diseases ordinal scale; VFD = ventilator-free days.

4.6. Safety Analyses

The planned safety analyses are consistent with compound level safety standards, which are based on various sources, including company standards, internal and external subject matter experts, and cross-industry initiatives (eg, white papers produced by a Pharmaceutical Users Software Exchange [PHUSE Computational Science Working Group (a collaboration with FDA and PHUSE)], published in the PHUSE Deliverables Catalog [PHUSE (WWW)]). Descriptions of the safety analyses are provided in this SAP; however, some details are in compound level safety standards.

A treatment-emergent adverse event (TEAE) during the analysis period is defined as an event that either first occurred or worsened in severity after the first dose of study treatment and on or prior to the end of the postbaseline period (defined as Day 28 for the primary outcome datalock).

A follow-up-emergent adverse event (FEAE) is defined as an event that either first occurred or worsened in severity after the treatment period and on or prior to the last visit date during the post-treatment follow-up period (up to the Day 60 visit) of the study.

Table 4. Baseline and Postbaseline Definitions

Analysis Type	Baseline	Postbaseline
1.1) Treatment-Emergent Adverse Events	The baseline period is defined as the start of screening and ends prior to the first dose of study treatment.	Starts after the first dose of study treatment and ends up to earliest of data cut date (for DMC interim analyses), up to Day 28 for the primary outcome datalock or study disposition.
1.2) Adverse Events including serious adverse events	NA	
1.3) Treatment-Emergent Abnormal Labs, Vital Signs, and shift summaries in labs	Baseline will be all scheduled and unscheduled measurements recorded during the baseline period as defined above (1.1).	Postbaseline will be defined as above (1.1). All scheduled and unscheduled measurements will be included.
1.4) Change from Baseline for Labs, Vital Signs	The last scheduled nonmissing assessment recorded prior to the date of first dose of study treatment during the baseline period defined above (1.1).	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The early termination visits (ETV) are considered scheduled visits.

Abbreviation: DMC = Data Monitoring Committee; NA = not applicable.

4.6.1. Extent of Exposure

Mean and median modal dose and total patient days of exposure will be reported. Descriptive statistics will be provided for subject days of exposure and the frequency of subjects falling into the following different exposure ranges will also be summarized:

- ≥4 days, ≥7days, and ≥10 days, and ≥14 days
- >0 to <4 days, ≥4 days to <7 days, ≥7 days to <10 days, ≥10 days to <14 days, and ≥14 days.

In addition, study duration will be analyzed in a similar fashion to what was planned for exposure duration but expanding ranges to 28 days.

4.6.2. Adverse Events

The planned summaries for AEs are provided in Table 5 and are described more fully in compound level safety standards and in the AE-related PHUSE white paper (Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents [PHUSE 2017]).

Table 5. Summary Tables Related to Adverse Events

Analysis	Population or Analysis Set
An overview table, with the number and percentage of subjects who experienced a TEAE, serious adverse event, death, discontinued from study treatment due to an adverse event	Safety population
An overview table, with the number and percentage of subjects who experienced an event, serious adverse event, death, discontinued from study due to an adverse event	Follow-up analysis set
The number and percentage of subjects with TEAEs using MedDRA Preferred Term nested within System Organ Class	Safety population
The number and percentage of subjects with FEAEs using MedDRA Preferred Term nested within System Organ Class	Follow-up analysis set
The number and percentage of subjects with TEAEs using MedDRA Preferred Term	Safety population
The number and percentage of subjects with TEAEs by maximum severity using MedDRA Preferred Term	Safety population
The number and percentage of subjects with TEAEs using MedDRA Preferred Term for the common TEAEs (occurred in ≥2% before rounding of treated subjects)	Safety population
The number and percentage of subjects who experienced a serious adverse event (including deaths and SAEs temporally associated or preceding deaths) using MedDRA Preferred Term nested within System Organ Class	Safety population
The number and percentage of subjects who experienced a serious adverse event (including deaths and SAEs temporally associated or preceding deaths) using MedDRA Preferred Term nested within System Organ Class	Follow-up analysis set
Listing of All SAEs	Safety population and follow-up set
The number and percentage of subjects who permanently discontinued from study treatment due to an adverse event (including adverse events that led to death) using MedDRA Preferred Term nested within System Organ Class	Safety population
The number and percentage of subjects who temporarily discontinued from study treatment due to an adverse event (including adverse events that led to death) using MedDRA Preferred Term nested within System Organ Class	Safety population
Listing of AEs which led to permanent discontinuation from the study treatment and from the study	Safety population
Listing of AEs which led to temporary discontinuation from the study treatment and from the study	Safety population

Abbreviations: AEs = adverse events; FEAE = follow-up-emergent adverse event; ITT = Intent-to-Treat; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4.6.3. Clinical Laboratory Evaluation

The planned summaries for clinical laboratory evaluations are provided in Table 6 and are described more fully in compound level safety standards and in the laboratory-related PHUSE white papers (Analyses and Displays Associated with Measures of Central Tendency – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents [PHUSE 2013] and Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs,

Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Summary Documents [PHUSE 2015]).

Table 6. Summary Tables Related to Clinical Laboratory Evaluations

Analysis	Population or Analysis Set
Box plots for observed and/or change from baseline values	Safety population
Common Terminology Criteria for Adverse Events (CTCAEs) shifts tables for labs	Safety population
Tables with the number and percentage of subjects who shift from normal/high to low (ie, treatment-emergent low) and the number and percentage of subjects who shift from normal/low to high (ie, treatment-emergent high) may be analyzed using appropriate and validated reference ranges	Safety population
Listing of abnormal findings for laboratory analyte measurements, including qualitative measures	Safety population

4.6.4. Vital Signs and Other Physical Findings

The planned summaries for vital signs (systolic blood pressure [BP], diastolic BP, pulse, weight, BMI, temperature) are provided in Table 7 and are described more fully in compound level safety standards and in the vitals-related PHUSE white papers (Analyses and Displays Associated with Measures of Central Tendency – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents [PHUSE 2013] and Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Summary Documents [PHUSE 2015]).

Table 7. Summary Tables Related to Vital Signs

Analysis	Population or Analysis Set
Box plots for observed and/or change from baseline values	Safety population
Tables with the number and percentage of subjects who shift from normal/high to low (ie, treatment-emergent low) and the number and percentage of subjects who shift from normal/low to high (ie, treatment-emergent high); the limits are defined in the compound level safety standards and are based on literature.	Safety population

4.6.5. Special Safety Topics

This section includes safety topics of interest, whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, safety topics of interest will be identified by 1 or more SMQs, by an Eli Lilly and Company (Lilly)-defined MedDRA Preferred Terms (PT) listing based upon the review of the most current MedDRA version, or by treatment-emergent relevant laboratory changes. The topics of interest may include, but may not be limited to:

- abnormal hepatic changes
- hematologic changes
- renal function effects
- elevations in creatinine phosphokinase

- serious infections, herpes zoster, and confirmed opportunistic infection,
- major adverse cardiovascular events and other cardiovascular events, and
- venous thromboembolic and arterial thromboembolic events.

Refer to the compound level safety standards for details of analyses of the special safety topics.

4.6.6. Subgroup Analyses

For selected endpoints, along with age group (as described in Section 4.1), the following subgroup analyses may be performed:

- baseline disease severity:
  - hospitalized requiring supplemental oxygen by prongs or mask (OS 5)
  - hospitalized requiring noninvasive ventilation or high-flow oxygen (OS 6)
  - hospitalized, requiring invasive mechanical ventilation or ECMO (OS 7)
- baseline steroid use: dexamethasone and/or other systemic corticosteroid used at baseline for primary study condition (Yes/No)

4.7. Other Analyses

Not applicable.

4.8. Interim Analyses

A review of PK and safety data is planned upon completion of at least CCI and no more than CCI participants to confirm the doses to be administered 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.

4.8.1. 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. The details of the DMC can be found in a separate DMC charter.*

5. 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 CCI participants in the age group of CCI to <18 years will achieve at least CCI 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 CCI for AUC. Given possible uncertainty in the PK in participants with COVID-19 (ie, possibly augmented renal clearance and/or different absorption and bioavailability), this estimated number was increased to at least CCI participants, which represents a 50% increase in the sample size in the CCI <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 CCI participants aged CCI years should be included.

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

- at least CCI participants from CCI years of age
- at least CCI participants from CCI years of age, and
- at least CCI participants from 1 CCI years of age.

6. Supporting Documentation

6.1. Appendix 1: Demographic

Patient demographics will be summarized using the ITT population. Frequency counts and percentages of patients will be summarized. The following demographic information will be included

- age
- gender (male, female)
- race (American Indian or Alaska Native, Asian, Black, or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- geographic region (US, Europe, Rest of World)
- country
- weight (kg)
- height (cm)
- body mass index (BMI) (kg/m^2)
- body mass index category (<25 kg/m^2, ≥ 25 to <30 kg/m^2, ≥ 30 kg/m^2), and
- baseline renal function status: impaired (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) or not impaired (eGFR ≥ 60 mL/min/1.73 m^2).

A listing of patient demographics will also be provided for the ITT population.

6.2. Appendix 2: Baseline Disease Characteristics

The below baseline disease information (although not inclusive) will be categorized and presented for baseline coronavirus disease 2019 (COVID-19) clinical characteristics, baseline health outcome measures, and other baseline demographic and disease characteristics as described above

- duration of symptoms prior to enrollment (≥ 7 days or <7 days)
- duration of hospitalization prior to enrollment
- World Health Organization (WHO) ordinal scale
- baseline disease severity:
    - hospitalized not requiring supplemental oxygen, requiring ongoing medical care
    - hospitalized requiring supplemental oxygen by prongs or mask
    - hospitalized requiring noninvasive ventilation or high-flow oxygen
    - hospitalized requiring noninvasive ventilation, including ECMO
- inflammatory biomarkers:
    - C-reactive protein, high-sensitivity (hs-CRP)
    - Lactate dehydrogenase (LDH)
- Prior therapy of interest: nonsteroidal anti-inflammatory drugs (NSAIDs), Antivirals, Antibiotics, Immunosuppressants (anti-malarials, corticosteroids and others)

- Symptom onset (<7 days, ≥7 days)
- Renal function status (impaired, no impaired)
- Preexisting comorbid conditions (None, Any; obesity; diabetes, chronic respiratory disease, hypertension)
- dexamethasone and/or other systemic corticosteroid used at baseline for primary study condition (Yes/No)
- remdesivir (Yes/No)

6.3. Appendix 3: Historical Illness and Preexisting Conditions

Historical illnesses are defined as those conditions recorded in the Preexisting Conditions and Medical History electronic case report form (eCRF) or from the Prespecified Medical History: Comorbidities eCRF with an end date prior to the informed consent date. The number and percentage of patients with selected historical diagnoses will be summarized using the ITT population. Historical diagnoses will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA; most current available version) algorithmic Standardized MedDRA Queries (SMQs) or similar pre-defined lists of PTs of interest.

Preexisting conditions are defined as those conditions recorded in the Pre-existing Conditions and Medical History eCRF, or the Prespecified Medical History: Comorbidities eCRF with a start date and time prior to the informed consent and with a stop date that is after the informed consent date or have no stop date (ongoing). Adverse events (AEs) are recorded in the eCRFs. For events recorded on the AE page, we considered it as a preexisting event if its onset date was before the first dose date. For events occurring on the day of the first dose of study treatment, the date and time of the onset of the event will both be used to determine if the event was preexisting. Conditions with a partial or missing start date (or time if needed) will be assumed to be 'not preexisting' unless there is evidence, through comparison of partial dates, to suggest otherwise. Preexisting conditions will be categorized using the SMQs or similar predefined lists of PTs of interest. Frequency counts and percentages of patients with selected preexisting conditions will be summarized using the ITT population.

The number and percentage of participants using preferred terms of prior medications will be presented.

The following historical illness and preexisting conditions will be presented

- preexisting comorbid conditions:
    - none, any
- preexisting comorbid conditions of interest
    - obesity
    - diabetes (Type I and Type II)
    - chronic respiratory disease
    - hypertension

6.4. Appendix 4: Treatment Compliance

As all study drug doses will be administered at the study site, treatment compliance will not be reported.

6.5. Appendix 5: Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the WHO drug dictionary. Medication start and stop dates will be compared to the date informed consent is obtained to allow medications to be classified as concomitant.

Prior medications are those medications that start and stop prior to the date of the first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment and continue into the treatment period. For all summary tables of concomitant medications, PTs of concomitant medication will be sorted by descending frequency in the LY total arm.

If dose-related corticosteroid analyses are conducted, the information in Section 6.8 will be used as reference for a conversion factors for each corticosteroid medication identified during the study, instructions for selecting corticosteroids, and the manual review process.

Table 8. Summary Tables Related to Concomitant Medications

Analysis	Details
Prior medications	Number and percentage of participants using Preferred Terms of prior medication • Ordered by decreasing frequency No inferential statistics
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication • Ordered by decreasing frequency No inferential statistics

6.6. Appendix 6: Protocol Deviations

Protocol deviations will be tracked by the clinical team and their importance will be assessed by key team members during protocol deviation review meetings.

Potential examples of deviations include patients who receive excluded concomitant therapy, significant noncompliance with study medication (<80% of assigned doses taken, failure to take study medication, and taking incorrect study medication), patients incorrectly enrolled in the study, and patients whose data are questionable due to significant site quality or compliance issues. Refer to a separate document for the important protocol deviations.

Trial Issue Management Plan includes the categories and subcategories of IPDs and whether or not these deviations will result in the exclusion of patients from per protocol set.

The number and percentage of patients having IPD(s) will be summarized within category and subcategory of deviation using the ITT population. Individual patient listings of IPDs will be provided.

6.7. Appendix 7: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include a summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized by treatment group and by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures (eg, clinical study report, manuscripts).

Similar methods will be used to satisfy the European Clinical Trials Database requirements.

6.8. Appendix 8: Dose Conversion for Corticosteroid

In case conversion of dosage of corticosteroids is needed, the following table should be used for converting nonprednisone medications to prednisone equivalent:

> Multiply the dose of the corticosteroid taken by the patient (in milligrams) in Column 1 by the conversion factor in Column 2 to get the equivalent dose of prednisone (in milligrams).
>
> *Example: Patient is taking 16 mg of methylprednisolone po daily. To convert to prednisone: 16 mg methylprednisolone × 1.25 = 20 mg prednisone. 16 mg of methylprednisolone po daily is equivalent to 20 mg of prednisone po daily.*

Column 1	Column 2
Corticosteroid Preferred Term	Conversion factor for converting to an equivalent prednisone dose
Prednisone	1
Prednisone acetate	1
Prednisolone	1
Prednisolone acetate	1
Prednisolone sodium phosphate	1
Methylprednisolone	1.25
Methylprednisolone acetate	1.25
Methylprednisolone sodium succinate	1.25
Triamcinolone	1.25
Triamcinolone acetonide	1.25
Triamcinolone hexacetonide	1.25
Cortisone	0.2
Cortisone acetate	0.2
Hydrocortisone	0.25
Hydrocortisone acetate	0.25
Hydrocortisone sodium succinate	0.25
Betamethasone	6.25
Betamethasone acetate	6.25
Betamethasone dipropionate	6.25
Betamethasone sodium phosphate	6.25
Dexamethasone	6.25
Dexamethasone acetate	6.25
Dexamethasone phosphate	6.25
Dexamethasone sodium phosphate	6.25
Paramethasone	2.5
Deflazacort	0.83
Celestona bifas	6.25
Depo-Medrol med lidocaine	1.25
Diprospan	6.25
Fluocortolone	1
Meprednisone	1.25

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