J2W-MC-PYAB Addendum (2.2)

# A Randomized, Double-blind, Placebo-Controlled, Phase 2/3 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness

NCT04427501

Approval Date: 12-Mar-2021

# Title Page



**Protocol Title:**

A Randomized, Double-blind, Placebo-Controlled, Phase 2/3 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness

**Protocol Number: J2W-MC-PYAB**

**Addendum Number: 2.2**

**Addendum Statement:** This addendum is to be performed in addition to all procedures required by protocol J2W-MC-PYAB or any subsequent amendments to that protocol. Participants enrolled in this addendum will follow the specified sections in this addendum in place of the corresponding sections in the main PYAB protocol.

**Compound(s):** LY3819253, LY3832479

**Sponsor Name:** Eli Lilly and Company
**Legal Registered Address:** Indianapolis, Indiana USA 46285

**Regulatory Agency Identifier Number(s)**
IND: 150440

**Approval Date:** Protocol Addendum (2.2) Electronically Signed and Approved by Lilly on date provided below.

# Protocol Addendum Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Revision 2.1 | 9-February-2021 |
| Original Protocol Addendum | 19-January-2021 |

## Revision 2.2

### Overall Rationale for the Changes:

The purpose of this addendum revision is to incorporate regulatory agency feedback and provide clarifications for operational efficiency.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page; 2. Protocol Additions | Added statement that sections in the addendum are to be used in place of corresponding sections in parent protocol. | Clarification |
| Throughout | Changed addendum arm from 15 to 22 | Operational/administrative |
| 2.0 Protocol Additions | Added statement that participants enrolled in this addendum will follow the specified sections in this addendum in place of the main PYAB protocol | clarification |
| 2.1 Schema | Updated schema to include all treatment arms included in the parent protocol and addenda.<br>Updated notes to figure. | Updated to reflect current study design |
| 2.2. Schedule of Activities<br>2.2.1 Treatment arm 22 | Hematology:<br>Removed instructions for hospitalized patients | Instructions not needed for pediatric participants |
| 2.3 Objectives and Endpoints | Removed windows from secondary endpoints | Not needed for these analyses |
| 2.3 Objectives and Endpoints | Exploratory:<br>Added emergence of viral resistance and<br>Added safety endpoint of MIS-C | Added new objectives to addendum |
| 2.4.1 Design Outline | Removed reference to arms outside of addendum | Arms not applicable to addendum |
| 2.6 Justification for Dose | Updated doses of LY3819253 and LY3832479 | Regulatory feedback |
| 2.7. Study Population | Added information pertaining to the eligibility criteria | To match what is stated in the main protocol |
| 2.7.1 Inclusion Criteria and<br>2.7.2 Exclusion Criteria | Included full list of inclusion and exclusion criteria from main PYAB protocol and identified if criteria from the main protocol are not applicable to this addendum. | Operational/administrative |
| 2.7.1 Inclusion Criteria | Criterion 3 – removed criterion | Created new criterion 35 with |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | | symptoms for pediatric participants |
| 2.7.1 Inclusion Criteria | Criterion 5 – updated to indicate that these are agreements and "requirements" in Section 10.4, Appendix 4. | Clarification |
| 2.7.1 Inclusion Criteria | Criterion 30 – Added clarification that this is a list of risk factors<br>Added "are pregnant" to list<br>Added examples of neurodevelopmental disorders | Clarifications |
| 2.7.1 Inclusion Crite | Criterion 35 added | Updated symptoms for pediatric participants |
| 2.7.2 Exclusion Criteria | Criteria 9 and 10 - Added 'due to COVID-19' | Clarification |
| 2.7.2 Exclusion Criteria | Criterion 24- specified this applies to mothers who are breast feeding | Clarification that this does not include infants who are breastfeeding |
| 2.9.2 Sample Size Determination | Updated sample size and minimum enrollment numbers for particular age groups | Updated to reflect study addendum strategy and regulatory feedback |
| 2.9.4.1 General Considerations | Updated analyses age groups to match changes for minimum sample size enrollment | For consistency |
| 2.9.5 Interim Analyses | Broadened language of when interim analysis may occur | Operational/administrative |
| 2.13 Section 10.10. Appendix 10: Blood Collection Restrictions and Guidance | Added pediatric guidance and restrictions for blood collection | Added to provide clarification and guidance for sites |
| 3 References | Added 2 new references | editorial |
| Throughout | Minor editorial and formatting changes | Minor, therefore not detailed |

**Table of Contents**

# 1. Rationale for Addendum

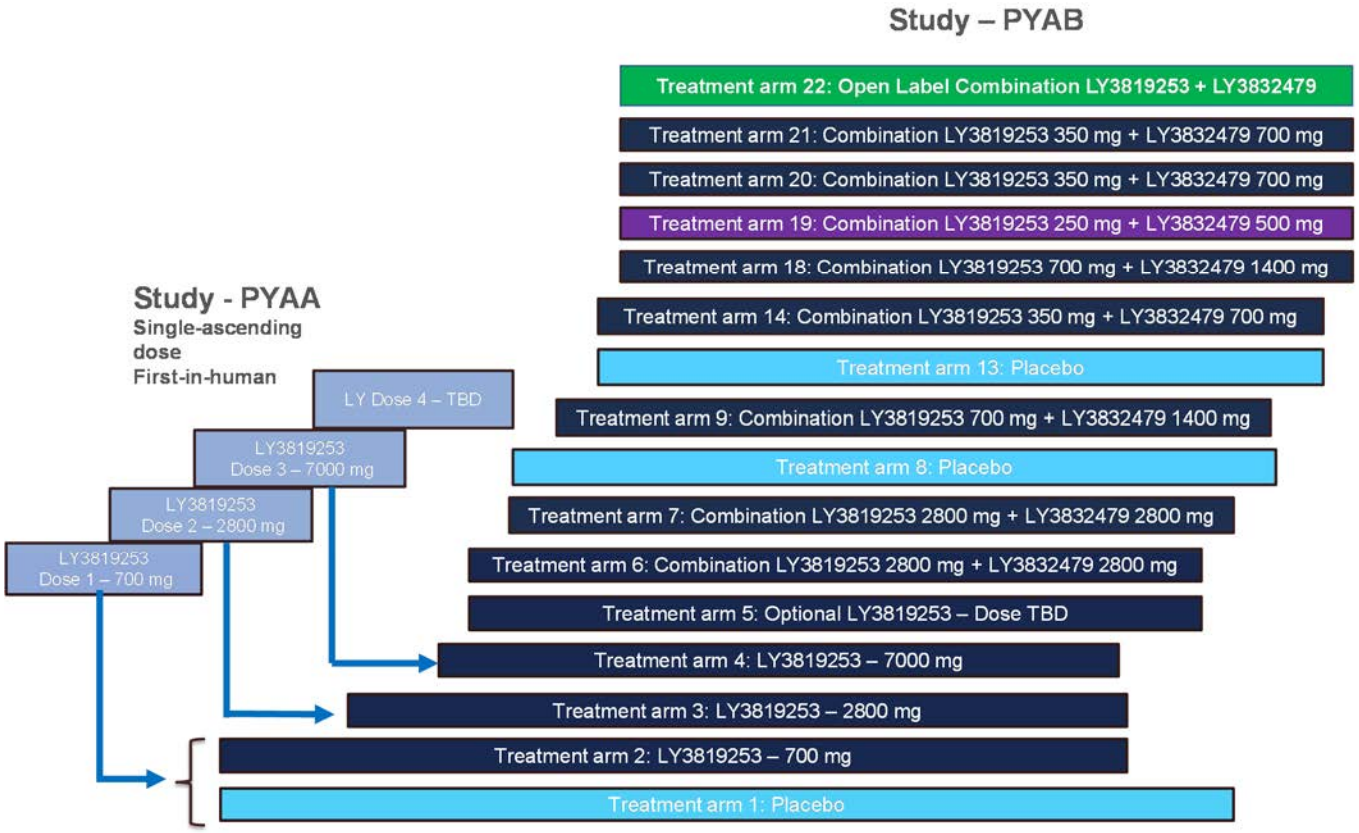
The rationale for this addendum is to allow pediatric participants ≤17 years old in the study, in a new open-label treatment arm 22.

## 2. Protocol Additions

Participants enrolled in this addendum will follow the specified sections in this addendum in place of the corresponding sections in the main PYAB protocol.

### 2.1. Section 1.2. Schema

Participants enrolled into this addendum will enter treatment arm 22.




Abbreviations: LY = Lilly study intervention; PYAA = J2W-MC-PYAA; PYAB = J2W-MC-PYAB; TBD = to be determined.

Note: Treatment arm 22 dose levels are weight dependent.
Addendum 3 contains information for treatment arms 20 and 21.
The main PYAB protocol contains information for treatment arms 1-19.

**Figure 1. Study J2W-MC-PYAB schema**

## 2.2. Section 1.3. Schedule of Activities

### 2.2.1. Section 1.3.3. Treatment arm 22

This SoA is for participants in treatment arm 22. Please see Section 2.13, Appendix 10 for pediatric blood collection restrictions and guidance.

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day. *=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | |
| Informed Assent for pediatric participants | X | | | | | | | | | | | | | | | Parent or legal guardian signs informed consent form and participant signs assent form, as appropriate per local requirements. |
| Inclusion and exclusion criteria review | X | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | Including age, gender, race, ethnicity |
| Preexisting conditions and medical history | X | | | | | | | | | | | | | | | Obtained from interview or available information. Includes: risk factors and comorbidities associated with severe COVID-19 illness. |
| Prespecified medical history for COVID-19 | X | | | | | | | | | | | | | | | Includes COVID-19 diagnosis date and onset of COVID-19 symptoms. |
| Prior treatments of special interest within the last 30 days | X | | | | | | | | | | | | | | | NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or any investigational treatments. |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day. *=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Prior non-COVID vaccine treatments within the last 90 days | X | | | | | | | | | | | | | | | |
| Substance use (Tobacco) | X | | | | | | | | | | | | | | | Includes use of e-cigarettes, such as vaping |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse events (AEs) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. Additional details regarding reporting frequency and method of detecting AEs and SAEs can be found in Section 8.3. |
| **Physical Evaluation or Clinical Assessments** | | | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | | | |
| Symptom-directed physical exam | | | | X | | | | | | | X | X | | | | As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations. |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day.<br>*=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Vital Signs and Oxygen Support<br>Includes: body temperature, pulse rate, BP, respiratory rate, SpO2, and supplemental oxygen flow rate, FiO2 if known, method of delivery, if applicable, and oxygen support procedures. | X | X | | X | | X | | X | X | | X | X | X | X | X | Documentation of hospital-based exam is acceptable.<br>Record SpO2 while participant is at rest.<br>**Screening visit only**: SpO2 while breathing room air. Data not collected on CRF.<br>**Day 1 timing:**<br>• immediately before administration<br>• every 15 minutes during the infusion, as possible and applicable<br>• if infusion is <15 minutes, immediately following completion of infusion<br>• every 30 minutes for 1 hour after the administration.<br>Only record temperature, pulse rate, BP and SpO2. Automation may be used. See Section 8.2.2 for data collected on CRF.<br>**All other study days:** once daily. |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day.<br>*=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Height | | X | | | | | | | | | | | | | | For participants ≥2 years of age |
| Length | | X | | | | | | | | | | | | | | Only for participants <2 years of age |
| Weight | | X | | | | | | | | | | | | | | |
| Hospitalization events | | | Daily | | | | | | | X | X | X | X | X | X | Record if the following events occur or occurred since prior visit:<br>• Emergency room visits<br>• hospitalized<br>• ICU admittance, and<br>• Discharge |
| Clinical status and concomitant procedures if participant is hospitalized | | | Daily if hospitalized | | | | | | | X | X | X | X | | | Documentation from hospital records is acceptable if hospitalized at any time.<br>Includes:<br>• NEWS 2 Consciousness (ACVPU)<br>• Additional organ support (e.g. ECMO, pressors, renal replacement)<br>• Supplemental oxygen and any means of ventilatory support, and<br>• Vital signs. |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day.<br>*=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| **Laboratory Tests and Sample Collection** | | | | | | | | | | | | | | | | |
| Hematology | | X | | X | | | | | X | | X | X | | | | Day 1: before treatment administration<br>All other days: sample may occur at any time during the day<br>Lilly-designated central laboratory<br>Local laboratory acceptable for participants <4.4 kg. |
| Clinical Chemistry | | X | | X | | | | | X | | X | X | | | | Day 1: before treatment administration<br>All other days: sample may occur at any time during the day.<br>If participant is hospitalized and if sample is available, collect sample, otherwise sample is not required during hospitalization.<br>Lilly-designated central laboratory<br>Local laboratory acceptable for participants <4.4 kg. |
| Documentation of positive SARS-CoV-2 viral infection | X | | | | | | | | | | | | | | | Sample for first positive test must be collected within 3 days prior to start of infusion.<br>Local laboratory and/or Point-of-Care testing. |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day.<br>*=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Urine or serum pregnancy | X | | | | | | | | | | | | | X | X | Pregnancy tests prior to the first dose of investigational product for females if<br>• aged ≥10 years<br>• <10 years at investigator's discretion<br>• menarche is reached or<br>• there is reason to believe that the patient is sexually active.<br>Local laboratory |
| Pharmacokinetic (PK) sample | | X | | | | | | | X | | X | X | | X | X | Day 1: immediately after end of infusion.<br>All other scheduled samples may occur at any time during the day.<br>Pharmacokinetic samples for participants <12 kg may be collected using alternative techniques.<br>If participant is hospitalized and if sample is available, collect sample.<br>Lilly-designated central laboratory |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day.<br>*=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Immunogenicity (ADA) sample | | X | | | | | | | X | | X | X | | X | X | Day 1: collect before treatment administration.<br>All other scheduled and unscheduled immunogenicity samples should be collected with a time-matched PK sample.<br>No samples needed if participant is hospitalized or <12 kg.<br>Lilly-designated central laboratory |
| Pharmacodynamic (PD) swab | | X | | X | | X | | X | X | | X | X | | | | Swab is taken from both nostrils.<br>Day 1: swab before treatment administration.<br>Methods include nasopharyngeal (preferred) or mid-turbinate.<br>The same method of sample collection must be used per participant for the duration of the study. Switching methods is not allowed.<br>Lilly-designated central laboratory |
| **Treatment Assignment and Dosing** | | | | | | | | | | | | | | | | |
| Treatment assignment | | X | | | | | | | | | | | | | | |

| Schedule of Activities for Treatment Arm 22 – Pediatric Participants | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study J2W-MC-PYAB** | **Screen** | **Double-blind treatment and assessments** | | | | | | | | | | ED | Follow-up if hospital inpatient on Day 29 | **Post-treatment follow-up** | | **Comments** |
| **Study Day** | | **1** | **2*** | **3** | **4*** | **5** | **6*** | **7** | **11** | **22*** | **29** | ED | Every 7 days until discharge or Day 60 | **60** | **85** | Screening and Day 1 procedures may occur on the same day.<br>*=telephone visit(s) |
| **Visit window (number of days)** | | -- | -- | +1 | -- | +1 | -- | +1 | -2/+3 | ±3 | ±3 | ±2 | ±2 | ±4 | ±4 | Visits may not be combined. |
| **Procedures** | | | | | | | | | | | | | | | | |
| Administer study intervention | | X | | | | | | | | | | | | | | Study intervention must be administered within 3 days from the time of first positive SARS-CoV-2 test sample collection.<br>For participants that receive dialysis on the same day as administration of study intervention, complete dialysis first followed by the study treatment.<br>Participants will be monitored for at least 1 hour after completion of treatment administration. |
| **Participant Symptom Assessment** | | | | | | | | | | | | | | | | |
| COVID-19 Symptoms | | Daily on Days 1-11 for outpatients only | | | | | | | | X | X | X | | X | X | Day 1: assess prior to dosing<br>The presence of absence of symptoms are collected from the participants or their parents/legal guardian. |

Abbreviations: ACVPU = alert, consciousness, verbal, pain, unresponsive scale; ADA = anti-drug antibody; AEs = adverse events; BP = blood pressure; CRF = case report form; ECMO = Extracorporeal membrane oxygenation; ED = early discontinuation visit; FiO2 = fraction of inspired oxygen in the air; ICU = intensive care unit; NP = nasopharyngeal; NSAIDS = non-steroidal anti-inflammatory drugs; SAEs = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen.

## 2.3. Section 3.0. Objective and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| Characterize the pharmacokinetics of LY3819253 in combination with LY3832479 after intravenous infusion | Area under the concentration-time curve (AUC) from 0 to infinity for both LY3819253 and LY3832479 |
| **Secondary** | |
| Characterize the effect of LY3819253 in combination with LY3832479 after intravenous infusion on… | |
| • Safety | • Safety assessments such as AEs and SAEs |
| • overall participant clinical status | • Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29 |
| • the reduction of SARS-CoV-2 viral load | • Change from baseline to Day 7 |
| • persistently high SARS-CoV-2 viral load | • Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 |
| • overall participant clinical status | • Proportion (percentage) of participants who experience these events by Day 29<br>o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or<br>o a COVID-19 related emergency room visit, or<br>o death from any cause |
| • SARS-CoV-2 viral load reduction | • Change from baseline to<br>o Day 3<br>o Day 5<br>• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7 |
| • SARS-CoV-2 viral clearance | • Time to SARS-CoV-2 clearance |
| • symptoms and resolution | • Presence or absence of a symptom<br>• Absence of all symptoms<br>• Time to absence of all symptoms<br>• Time to sustained absence of all symptoms<br>• Proportion of participants demonstrating absence of symptoms on Days 2-11 |

| **Exploratory** | |
|---|---|
| • overall participant clinical status | • Proportion (percentage) of participants who experience these events by Days 22, 60 and 85<br>o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or<br>o death from any cause |
| • Characterize emergence of viral resistance to LY3819253 in combination with LY3832479 | • Comparison from baseline to the last evaluable time point up to Day 29 |
| • safety | • Proportion (percentage) of participants who experience MIS-C |

Abbreviations: AE = adverse event; SAE =serious adverse event; MIS-C = multisystem inflammatory syndrome in children; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 2.4. Section 4.0. Study Design

This addendum adds a single, open-label treatment arm 22 to evaluate the combination of LY3819253 and LY3832479 administered as an intravenous infusion to pediatric participants.

### 2.4.1. Section 4.1.1. Design Outline

This table describes the visit types for treatment arm 22.

| **Study Day** | **Activity** | **Visit Type** |
|---|---|---|
| 1 | Follow SoA | Site |
| 2, 4, 6 and 22 | Follow SoA | Telephone visits |
| 3, 5, 7, 11, and 29 | Follow SoA | May be conducted as outpatient clinic or home visits |
| 8, 9, and 10 | Collect symptom assessment | Telephone visits |
| Early discontinuation and follow-up | Follow SoA | May be conducted as outpatient clinic or home visits |

## 2.5. Section 4.2. Scientific Rationale for Study Design

COVID-19 is a severe viral respiratory infection caused by SARS-CoV-2 that affects all age groups (Hoang et al. 2020).

**SARS-CoV-2 Incidence in the Pediatric Population**

Children of all ages may be infected with SARS-CoV-2, but there is a bimodal pattern to infections, with higher incidence in adolescents, neonates, infants, and young children (AAP 2020; DeBiasi et al. 2020). For reasons that are unknown, school age children (roughly 4 to 12 years of age) appear least likely to be infected and have the least severe outcomes of any age group, pediatric or adult (DeBiasi et al. 2020; Woolf et al. 2020).

**Severity of Disease**

While the disease is generally less severe in the pediatric population than in adults, there are still individual pediatric patients who are infected with SARS-CoV-2 that become symptomatic, and

in some cases die (AAP 2020). There are also concerns about potential later term sequela that may result in pediatric patients from SARS-CoV-2 infections (Hertting et al. 2021). This includes Multisystem Inflammatory Syndrome in Children (MIS-C) which occurs 2 to 4 weeks after infection, is uncommon (2 in 100,000 persons <21 years of age, approximately 1/161 the infection rate), and is sometimes fatal but may include less severe cases (Levin 2020).

As in adults, outcomes in pediatric patients of all ages are generally worse in the presence of a number of comorbid conditions, such as medical complexity requiring long-term technological support, immune suppression or malignancy, obesity, diabetes, seizures, congenital heart disease, or chronic lung disease (Shekerdemian et al. 2020). Such groups are more likely to be hospitalized and require intensive care unit (ICU) admission (Zachariah et al. 2020).

**Unmet Need for Treatment**

Currently, there are no FDA-approved therapies for the treatment of COVID-19 in non-hospitalized pediatric patients, which necessitates the urgent need to have access to experimental therapies, especially for patients under 12 years of age.

## 2.6. Section 4.3. Justification for Dose

In treatment arm 22, participants will receive weight category-based doses that are predicted to match exposure in adults of 700 mg LY3819253 and 1400 mg LY3832479 administered together. These adult doses were selected based on PK/PD modeling, interim PK, viral load, symptoms, and clinical outcome and safety data from Study J2X-MC-PYAH (BLAZE-4).

This table describes the weight categories and dose levels.

| Pediatric Weight Category (kg) | LY3819253 and LY3832479 Dose |
|---|---|
| ≥40 | 700 mg and 1400 mg |
| >20 to <40 | 350 mg and 700 mg |
| >12 to 20 | 175 mg and 350 mg |
| 1.5 to 12 | 15 mg/kg and 30 mg/kg |

## 2.7. Section 5.0. Study Population

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

Due to the criticality of participant health, verbal interview of the potential participant, or their legal representative or family member, may be the source for disease characteristics and medical history, unless otherwise specified within the eligibility criteria.

### 2.7.1. Section 5.1. Inclusion Criteria

Participants are eligible to be included in this addendum only if all of the following criteria apply:

1. This criterion is not applicable to participants in this addendum
2. This criterion is not applicable to participants in this addendum

3. This criterion is not applicable to participants in this addendum
4. Must have sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion
5. Are males or females, including pregnant females
   Reproductive and Contraceptive requirements are provided in the main PYAB protocol, Section 10.4, Appendix 4. Contraceptive use by males or females should be consistent with local regulations for those participating in clinical studies.
6. Understand and agree to comply with planned study procedures
7. Agree to the collection of nasopharyngeal swabs and venous blood
8. The participant or legally authorized representative give signed informed consent and/or assent as described in the main PYAB protocol, Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

27. This criterion is not applicable for participants in this addendum
28. This criterion is not applicable for participants in this addendum
30. Are 0 (≥ 32 weeks gestational age AND ≥ 1.5 kg) to 17 years of age (inclusive) AND satisfy at least one of the following risk factors at the time of screening
    - Are pregnant
    - Have a BMI ≥85$^{th}$ percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
    - Have sickle cell disease
    - Have congenital or acquired heart disease
    - Have neurodevelopmental disorders, for example, cerebral palsy, autism, or Down syndrome (FAIR Health 2020; Spreat et al. 2020)
    - Have a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
    - Have asthma, cystic fibrosis, reactive airways disease or other chronic respiratory disease that requires daily medication for control
    - Have type 1 or type 2 diabetes
    - Have chronic kidney disease
    - Have immunosuppressive disease, or
    - Are currently receiving immunosuppressive treatment, or
    - Are <1 year of age.

35. Have one or more COVID-19 symptoms (CDC December 2020, FDA February 2021)
    - shortness of breath or difficulty breathing
    - fever
    - sore throat
    - nausea
    - diarrhea
    - tiredness
    - headache
    - new loss of taste
    - nasal congestion or runny nose
    - chills
    - stomachache
    - vomiting
    - cough
    - muscle or body aches and pain
    - new loss of smell, or
    - poor appetite or poor feeding (in babies).

## 2.7.2. Section 5.2. Exclusion Criteria

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

9. Have SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute due to COVID-19 (FDA February 2021)
10. Require mechanical ventilation or anticipated impending need for mechanical ventilation due to COVID-19
11. Have known allergies to any of the components used in the formulation of the interventions
12. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
13. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
14. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
15. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.

**Other Exclusions**

16. Have a history of a positive SARS-CoV-2 serology test
17. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
18. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
19. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
20. Have received convalescent COVID-19 plasma treatment

21. Exclusion criterion [21] removed
22. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
23. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
24. Mothers who are breast feeding
25. Are investigator site personnel directly affiliated with this study
29. This criterion is not applicable for participants in this addendum
31. Have a diagnosis of MIS-C in the opinion of the investigator
32. This criterion is not applicable for participants in this addendum
33. This criterion is not applicable for participants in this addendum, and
34. Are currently hospitalized for treatment of COVID-19. Other reasons for hospitalization are acceptable.

## 2.8. Section 8.1. Efficacy Assessments

### 2.8.1. Section 8.1.2. Symptom Assessment for Pediatric Participants

The presence or absence of symptoms associated with COVID-19, within the past 24 hours, will be collected from participants or their parents/legal guardian.

Signs and symptoms associated with COVID-19 should not be captured as AEs, unless more severe than expected.

Symptoms include

- shortness of breath or difficulty breathing
- nasal congestion or runny nose
- fever
- chills
- sore throat
- stomachache
- nausea
- vomiting
- diarrhea
- cough
- tiredness
- muscle or body aches and pain
- headache
- new loss of smell
- new loss of taste, and
- poor appetite or poor feeding, especially in babies under 1 year old.

Source: Centers for Disease Control (CDC) resource page; COVID-19 in Children and Teens, 2020.

## 2.9. Section 9.0. Statistical Considerations

### 2.9.1. Section 9.1. Statistical Hypotheses

This is an open-label addendum with a primary objective of assessing PK and secondary objective of safety and tolerability. No hypothesis testing is planned.

### 2.9.2. Section 9.2. Sample Size Determination

The planned sample size is approximately 85 participants with a minimum of 5 participants in each of these age groups

- 0 to <2
- 2 to <6, and
- 6 to <12 years.

Participant PK profiles were simulated using the current PK model with established allometric relationships (Betts et al. 2018) for a typical monoclonal antibody to enable a Monte Carlo assessment to achieve adequate power of the trial to estimate population PK model in pediatrics across the weight range.

### 2.9.3. Section 9.3. Populations for Analyses

The pediatric populations for analysis include the adolescent participants from Study PYAB and the participants in this addendum who are ≤17 years old at the time of screening. This table defines the pediatric populations for analysis.

| **Pediatric Population for Analysis** | **Description** |
|---|---|
| Pharmacokinetic | All pediatric participants who received study intervention and have evaluable PK sample. |
| Safety | All pediatric participants who received study intervention. Participants will be analyzed according to the intervention they actually received. |
| Efficacy | All pediatric participants who received study intervention and provided at least one post-baseline measure for the relevant endpoint. Participants will be analyzed according to the intervention to which they were randomized or assigned. |

## 2.9.4. Section 9.4. Statistical Analyses

### 2.9.4.1. Section 9.4.1. General Considerations

Statistical analysis of this addendum will be the responsibility of the sponsor or its designee.

Unless otherwise specified, all endpoints will be summarized descriptively. Descriptive summaries will include

- number of participants
- mean, standard deviation, median, minimum and maximum for continuous measures, and
- frequency counts and percentages for categorical measures.

Analyses will be performed overall and separately by age group. The age groups are defined as

- 0 to <2
- 2 to <6
- 6 to <12 years, and
- 12 to ≤17 years.

For endpoints that are common between Study PYAB Arms 7-9, 13-14, and the PYAB Addendum, analyses will also be performed by treatment arm.

Additional details may be provided in the statistical analysis plan (SAP).

### 2.9.4.2. Section 9.4.2. Primary Endpoint

**Treatment Arm 22**

The primary objective is to assess PK in the pediatric pharmacokinetic population. The primary parameter for analysis is the area under the concentration-time curve (AUC) from 0 to infinity. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

### 2.9.4.3. Section 9.4.3. Secondary Endpoints

The secondary objective is to assess safety and tolerability. The pediatric safety population is described in Section 2.9.3. Safety analyses will be conducted as stated in Section 2.9.4 and as stated in the main PYAB protocol.

### 2.9.4.4. Section 9.4.3.4. Pharmacokinetic and Pharmacodynamic Analyses

LY3819253 and LY3832479 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. In addition, the effects of participant factors, such as weight, age and gender on PK parameters may be evaluated. If antidrug antibody is detected from immunogenicity testing, its impact on LY3819253 and LY3832479 PK may also be evaluated.

Pharmacodynamic endpoints will be summarized using descriptive methodology. The SARS-CoV-2 viral dynamics will include evaluation of

- change from baseline in SARS-CoV-2 viral load (Days 3, 5 and 7)
- AUC, and
- time to SARS-CoV-2 clearance.

Additional PK/PD concentration-response analysis may be performed.

### 2.9.5. Section 9.5. Interim Analyses

An interim analysis may occur to evaluate safety or efficacy in support of regulatory interactions. This interim may include all pediatric data available at that time and relevant analyses.

Early review of PK data may be planned but is not considered a formal interim analysis.

The approximate timing, decision criteria, and statistical methods associated with each possible modification to this addendum will be fully described in the SAP.

## 2.10. Section 10.1.11. Investigator Information

Physicians with specialties, including, but not limited to pediatrics, infectious disease, acute or critical care, pulmonary disease, immunology, or other appropriate specialties may participate as investigators for this addendum.

An investigator or sub-investigator must also confirm that they have clinical experience to adequately manage participants in a particular age range in order for the site to enroll participants in that respective age range. The age ranges are

- less than 1 year of age
- 1 to 11 years of age, and
- 12 to 17 years of age.

This addendum will be conducted at a diverse group of sites that may include academic and community affiliated outpatient clinics and emergency departments, as well as other locations where children may be seen for outpatient care. Clinicians providing care in such settings may include pediatricians, neonatologists, family practitioners, emergency room specialists, and other physicians. The investigator requirements are written to reflect this reality of pediatric patient care in outpatient settings during the pandemic.

## 2.11. Section 10.6. Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events

### Clinical Lab Tests for Hypersensitivity Events

| **Hypersensitivity Tests** | **Notes**<br>Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. |
|---|---|
| LY3819253 and LY3832479 anti-drug antibodies (immunogenicity/ADA) | Assayed by Lilly-designated laboratory*.<br>Results will not be provided to the investigative sites. |
| LY3819253 and LY3832479 concentrations (PK) | Assayed by Lilly-designated laboratory*.<br>Results will not be provided to the investigative sites. |
| Tryptase | Assayed by Lilly-designated laboratory or local laboratory*.<br>Results will not be provided to the investigative sites.<br>Urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Collect a follow-up urine sample after approximately 4 weeks.<br>**Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, collect a urine sample for N-methylhistamine testing. |
| N-methylhistamine | Assayed by Lilly-designated laboratory or local laboratory*.<br>Results will not be provided to the investigative sites. |
| Drug-specific IgE | Will be performed if a validated assay is available.<br>Assayed by Lilly-designated laboratory*.<br>Results will not be provided to the investigative sites. |
| Basophil activation test | Will be performed if a validated assay is available.<br>Assayed by Lilly-designated laboratory*.<br>Results will not be provided to the investigative sites.<br>**NOTE:** The basophil activation test is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE but is not specific for IgE. |
| Complement (C3, C3a and C5a) | Assayed by Lilly-designated laboratory or local laboratory*.<br>Results will not be provided to the investigative sites. |
| Cytokine panel | Assayed by Lilly-designated laboratory or local laboratory*.<br>Results will not be provided to the investigative sites. |

Abbreviations: ADA = anti-drug antibody; IgE = immunoglobulin E; PK = pharmacokinetic.

* The priority of testing and use of a Lilly-designated laboratory or local laboratory, is determined based on the participants age, weight, in consultation with the investigator and the medical monitor.

## 2.12. Section 10.7. Appendix 7: Liver Safety Suggested Actions and Follow-up Assessments

**Close Hepatic Monitoring**

This table describes when close hepatic monitoring should 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.
Notes: All ULN values should be age adjusted (AAULN).

The laboratory tests listed in Appendix 2, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the Lilly designated medical monitor.

At a minimum, this evaluation should include a 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 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 laboratory 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 ≥3x ULN with hepatic signs/symptoms*, or<br>ALT or AST ≥5x ULN |
| ALP <1.5x ULN | ALP ≥3x 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 with hepatic signs/symptoms*, or<br>ALT or AST ≥3x baseline |
| ALP ≥1.5x ULN | ALP ≥2x baseline |
| TBL ≥1.5x ULN | TBL ≥2x baseline (except for participants with Gilbert's syndrome) |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin.

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

Notes: All ULN values should be age adjusted (AAULN).

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 and weight, 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 hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (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.

**Hepatic Evaluation Testing**

Please refer to main protocol for the complete list of tests for evaluation.

For participants ≥ 4.4 kg, assays will use a Lilly-designated laboratory or local laboratory.

For participants <4.4 kg assays will use only a local laboratory.

The microbiology blood and urine assay must use a local laboratory.

**Additional hepatic data collection in study participants who have abnormal liver tests**

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants if one or more of these conditions occur during the study:

| If a participant with baseline results of... | develops the following elevations… |
|---|---|
| ALT <1.5x ULN | Serum ALT to ≥5x ULN on 2 or more consecutive blood tests |
| ALT ≥1.5x ULN | Serum ALT to ≥3x ULN on 2 or more consecutive blood tests |
| TBL <1.5x ULN | TBL to ≥2x ULN (except for participants with Gilbert's syndrome) |
| TBL ≥1.5x ULN | TBL to ≥2x baseline |
| ALP <1.5x ULN | Serum ALP to ≥2x ULN on 2 or more consecutive blood tests |
| ALP ≥1.5x ULN | Serum ALP ≥2x baseline on 2 or more consecutive blood tests |
| | Or |
| If a hepatic event is considered a serious adverse event, or | |
| If discontinuation of intervention is due to a hepatic event. | |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; TBL = total bilirubin.
Notes: All ULN values should be age adjusted (AAULN).
The interval between the 2 consecutive blood tests should be at least 2 days.

## 2.13. Section 10.10. Appendix 10: Blood Collection Restrictions and Guidance for Pediatric Participants

**Sampling Restrictions**

Blood draws are not allowed from dialysis shunts or catheters, apheresis catheters or arterial catheters.

**No ADA samples for participants <12 kg**

Due to blood volume restrictions participants <12 kg will not have immunogenicity (ADA) samples taken.

**Minimizing the number of blood draws and venipunctures**

Blood draws should be consolidated, and the number of attempts should be kept to the minimum number required and in keeping with local guidelines and procedures.

To avoid multiple venipunctures in a single day, blood samples may be obtained via a peripheral intravenous (IV) catheter. For this study, a peripherally inserted central catheter (PICC) is not considered to be a peripheral IV catheter.

***Use of existing central line***

If a participant in this addendum already has central venous access, for example, via a port or PICC line, as part of their non-COVID-19 clinical care, intervention may be infused (single infusion) via this route if these requirements are met:

- The participant's parents or legal guardians give their permission to use the established central intravenous access route to administer study intervention, AND
- The site consults with the medical team that is using the established central intravenous access route to provide clinical care and obtains their permission to use this route to administer study intervention, AND
- The site investigator determines who is appropriately trained and qualified to access and infuse study intervention via central venous access routes in pediatric participants and delegates the authority to do such procedures to those individuals, AND
- The delegated site personnel follow good clinical practices (GCPs) and the site's established procedure for preventing infections and administering drugs via a central intravenous access route.

***Use of existing central line for mobile study visits***

During mobile study visits, study nurses may obtain blood samples via a central venous access route (for example, port or PICC line) if these requirements are met:

- The participant's parents or legal guardians give their permission to use the established central intravenous access route (for example, port or PICC line) to obtain blood samples during mobile study visits, AND

- The site staff consults with the medical team that is using the established central venous access route to provide clinical care and obtains their permission to use this route to obtain blood samples during mobile study visits, AND
- The site investigator determines who is appropriately trained and qualified to access and obtain blood samples via central venous access routes in pediatric participants and delegates the authority to do such procedures to those individuals, AND
- The delegated site personnel follow GCPs and the site's established procedure for preventing infections when obtaining blood samples via a central venous access route.

Consult with the Lilly medical monitor if there are any questions about this requirement.

**Use of anesthetics or devices to ease discomfort with venipunctures**

To ease discomfort associated with venipunctures, these options are allowed in the study per local prescribing information,

- local anesthetic creams, for example, EMLA or ELA-max
- needleless devices for injecting local anesthetics, for example, a J-Tip, and
- local vibration devices, for example, a Buzzy.

**Pharmacokinetic sampling**

To avoid contamination with infused intervention, blood samples for pharmacokinetic purposes on the day of infusion should never be obtained using the same venous access site that is used for infusion of study intervention. In addition, pharmacokinetic samples on the day of infusion should be obtained from a venous access site on the opposite side of the body from the site of intervention infusion.

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# 4. Appendix 1: Protocol Addendum Revision History

**Revision 2.1**

**Overall Rationale for the Changes:**
The overall rationale for the changes to this protocol addendum are to

- allow pediatric participants in the study if they are hospitalized for any reason except COVID-19
- allow local testing for specific laboratory tests, and
- modify the hepatic monitoring language specifically for pediatric participants.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.7.1 Section 5.1 Inclusion Criteria | Added statement for criterion #2. | Pediatric participants are allowed in the study if they are hospitalized for any reason except COVID-19. |
| 2.7.2. Section 5.2 Exclusion Criteria | Added criterion #34 | Pediatric participants are not allowed in the study if they are hospitalized for treatment of COVID-19. |
| 2.8.1 Section 8.1.2 Symptom Assessment for Pediatric Participants | Removed "chest pain or discomfort with breathing" symptom | Update to CDC resource page for COVID-19 in Children and Teens |
| 2.9.2 Section 9.2 Sample Size Determination | Removed sentence "Data across all weight ranges will be combined for analysis." | Originally entered in error. Details of analyses are captured elsewhere. |
| 2.11 Section 10.6 Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events | Added section | Needed to add pediatric specific language to the table about using local laboratories depending on the participants age and weight in consultation with the investigator and medical monitor. |
| 3.1 Section 10.7 Appendix 7: Liver Safety Suggested Actions and Follow-up Assessments | Added section | Specific sponsor guidance for pediatric studies. Added pediatric specific language about using local laboratories depending on the participants weight. |
| Throughout the addendum | Minor editorial and formatting changes | Minor, therefore not described |

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