J2W-MC-PYAB Addendum (4.2)

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

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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: 4.2

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): bebtelovimab (LY3853113)

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

Regulatory Agency Identifier Number(s)
IND: 150440

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Approval Date: Protocol Addendum (4.2) Electronically Signed and Approved by Lilly on date provided below.

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DOCUMENT HISTORY	
Document	**Date**
Version 4.1	29-Apr-2022
Original Protocol Addendum	14-Apr-2022

Revision 4.2

Overall Rationale for the Revision:

The purpose of this revision is to add the collection of body weight for participants at each of the visits where pharmacokinetic (PK) samples are collected: Day 1, Day 5, Day 11, Day 29, ED and Day 60 (in addition to Day 0). This is in order to deliver on the primary objective of assessing pharmacokinetics in the pediatric pharmacokinetic population. This is supported by the following:

- PK of bebtelovimab is impacted by bodyweight. This is known from the adult PK modeling.
- The weight of newborns/infants changes significantly following their first few weeks/months from birth.
- The visits in which PK are collected span approximately 2 months (to Day 60). Because this is an extended time period, the impact of weight changes on PK needs to be captured.
- Therefore, to accurately describe the PK of bebtelovimab in pediatrics down to newborns, their weight must be collected over the 2 month follow-up period after treatment administration.
- After we accurately describe the PK (which is influenced by weight) of bebtelovimab in pediatrics, we will have addressed the primary endpoint of this PK-based study, characterizing the pharmacokinetics of bebtelovimab after intravenous injection.

Section # and Name	Description of Change	Brief Rationale
2.2. Section 1.3. Schedule of Activities	Adjusted weight collection with update to Schedule of Activities	The purpose of this revision is to add the collection of body weight for the participants at each of the visits where PK samples are collected: Day 1, Day 5, Day 11, Day 29, ED and Day 60 (in addition to Day 0) in order to deliver the primary objective to assess the PK in the pediatric pharmacokinetic population after intravenous injection of bebtelovimab.

1. Rationale for Addendum

Eli Lilly and Company (Lilly) has a partnership with AbCellera Biologics Inc. (AbCellera; Vancouver, Canada) to develop neutralizing IgG1 monoclonal antibodies (mAbs) to the Spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a potential treatment for Coronavirus disease 2019 (COVID-19). Candidate antibody gene sequences have been selected from a convalescent COVID-19 United States patient's serum using AbCellera's core platform screening technologies.

Bebtelovimab (LY3853113) is a novel, highly potent IgG1 neutralizing mAb that binds a unique RBD region of the S protein. Bebtelovimab can neutralize the Wuhan reference strain as well as individual residues present in recent variants of concern (e.g. K417N, N439K, L452R, E484K/Q, Q493R, N501Y, and D614G). Critically, pseudovirus and/or authentic SARS-CoV-2 neutralization assays demonstrate that bebtelovimab can neutralize all variants of interest or concern identified as of April 2022, including the Delta variant (B.1.617.2 and related AY sublineages lineages) and Omicron variant (B.1.1.529 [BA.1], BA.1.1 and BA.2 sublineages).

Bebtelovimab is authorized (Emergency Use Authorization [EUA] 111) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 (FDA February 2022). EUA 111 was based on clinical data (BLAZE-4) from patients at low- and high-risk for severe disease as well as the beforementioned in vitro neutralization assay data.

Currently, there are limited authorized treatments for pediatric outpatients under the age of 12 or those 12 to 17 and weighing less than 40 kg. While COVID-19–associated hospitalizations and deaths have occurred more frequently in adults, COVID-19 can also lead to severe outcomes in pediatric patients (Delahoy et al. 2021). As in-person school and activities have increased, hospitalization rates among children have also increased, especially with the emergence of the Omicron variant. During the Delta- and Omicron-predominant periods, pediatric weekly hospitalization rates peaked at 7.1 per 100,000 children and adolescents for Omicron which was four times that of the Delta variant peak (1.8) (Marks et al. 2022). The highest increase in hospitalization rates in children aged 0–4 years was approximately five times as high during the peak week of the Omicron period (15.6) than during the Delta period (2.9) (Marks et al. 2022). Pediatric cases resulting in death have remained at 0.00-0.02% (AAP 2022).

As in adults, outcomes in pediatric patients of all ages are generally worse in the presence of a number of comorbid conditions. Pediatric patients without an underlying medical condition have also been susceptible to Multisystem Inflammatory Syndrome in Children (MIS-C) (CDC 2021; Reiff et al. 2022).

The neutralizing mAbs bamlanivimab and etesevimab have been previously shown to be safe and effective with adult-matched dosing in pediatric patients with COVID-19, and based on this evidence, were given EUA across all pediatric age ranges (EUA 094; Eli Lilly and Company 2022). However, with the emergence of the Omicron variant, there are no neutralizing mAb therapies authorized for use in pediatric patients <12 years of age or those 12 to 17 and weighing <40 kg since April 11, 2022. Considering bebtelovimab's capacity to neutralize Omicron per

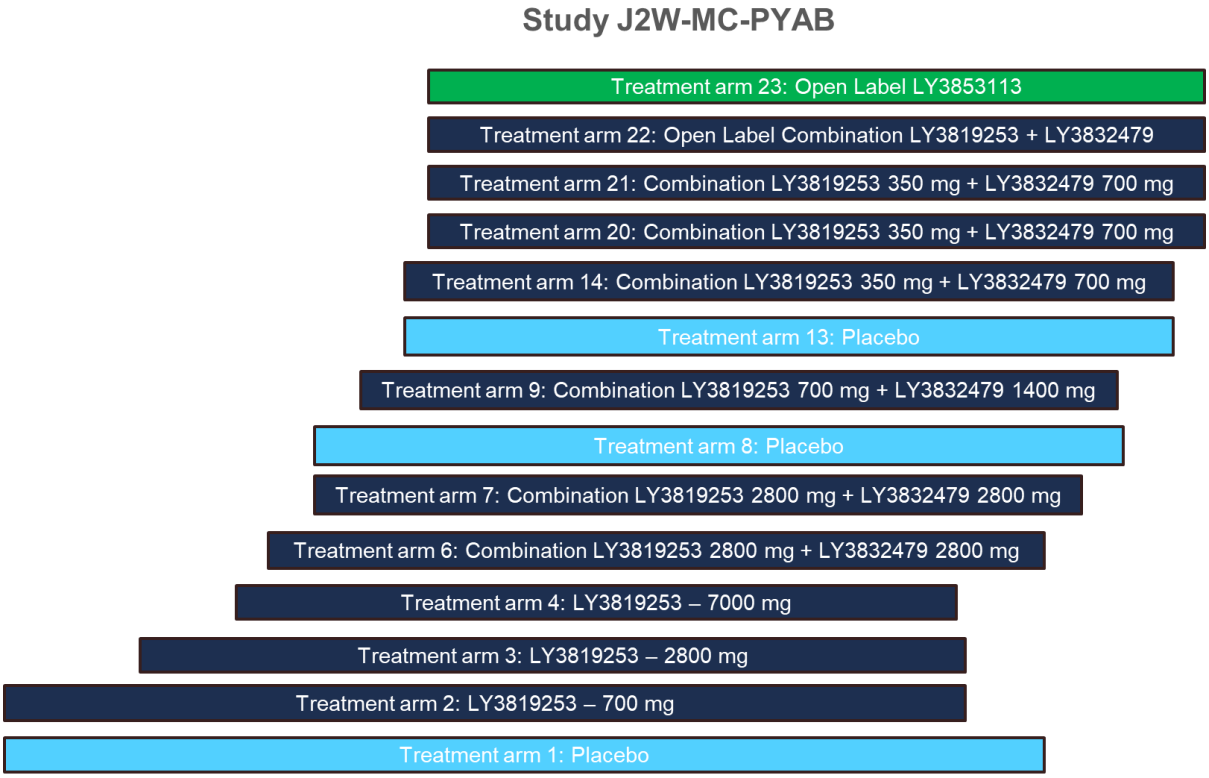
available in vitro neutralization assays and pharmacokinetic (PK) data, this proposed study addendum intends to investigate the PK and safety of bebtelovimab in pediatric patients with COVID-19 <12 years of age or 12 to 17 years of age and weighing <40 kg.

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 23.



Note: Dose levels in treatment arms 22 and 23 are weight dependent.
Addendum 3 contains information for treatment arms 20 and 21. Addendum 2.2 contains information for treatment arm 22.
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 1.3.4. Treatment arm 23

This SoA is for participants in treatment arm 23. Please see Addendum Section 2.14, Appendix 10 for pediatric blood collection restrictions and guidance.

Period I: Screening - Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance (where applicable).

Period II: Treatment Period - For early discontinuations that occur before the last visit in treatment period, see the activities listed for ED in the following table.

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Informed consent	X														The informed consent form must be signed before any protocol-specific tests or procedures are performed. See Appendix 10.1, Section 10.1.3 of the main PYAB protocol for additional details, including assent, as applicable.
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 and confirm	X														Inclusion/Exclusion criteria should be confirmed prior to treatment assignment and administration of first dose of study intervention.
Demographics	X														Includes full date of birth, gender (sex), ethnicity and race
Preexisting conditions and medical history	X														Obtained from interview or available information.
Prespecified medical history	X														Includes COVID-19 diagnosis date, onset of COVID-19

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
															symptoms, and comorbidities associated with severe COVID-19 illness
Prior treatments for indication	X														Within the last 30 days. NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators, monoclonal antibody treatment or any investigational treatments
Prior non-COVID vaccine treatments	X														Within the last 90 days
Prior COVID vaccine treatments	X														
Substance use (alcohol, tobacco use)	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	
Adverse events (AEs)	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 of the main PYAB protocol. Additional details regarding

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
															reporting frequency and method of detecting AEs and SAEs can be found in Section 8.3 of the main PYAB protocol.
Physical Evaluation															
Height	X														For participants ≥2 years of age
Length	X														Only for participants <2 years of age
Weight	X	X		X				X		X	X		X		
Hospitalization events			X	X	X	X	X	X	X	X	X	X	X	X	Record if the following events occur or occurred since prior visit: • Emergency room visits • hospitalized • ICU admittance, and • Discharge
Clinical status and concomitant procedures if participant is hospitalized			X	X	X	X	X	X	X	X	X	X	X	X	Documentation from hospital records is acceptable if hospitalized at any time. Includes: • NEWS 2 Consciousness (ACVPU) • Additional organ support (e.g. ECMO, pressors, renal replacement)

	Period I Screening	**Period II Treatment Period**											**Period III Post-Treatment Follow-Up**		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
															• Supplemental oxygen and any means of ventilatory support, and • Vital signs

	Period I Screening	**Period II Treatment Period**											**Period III Post-Treatment Follow-Up**		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Vital Signs	X	X		X		X		X		X	X		X		Includes: body temperature, pulse rate, BP, respiratory rate, SpO2, and supplemental oxygen flow rate, method of delivery, if applicable, and oxygen support procedures. Documentation of hospital-based exam is acceptable. Record SpO2 while participant is at rest. **Screening visit only:** SpO2 while breathing room air or while on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity. Data not collected on CRF. **Day 1 timing:** • immediately before and after treatment administration • every 30 minutes for 1 hour after the administration. Only record temperature, pulse rate, BP and SpO2. Automation may be used. See Section 8.2.2 of the main PYAB protocol for data collected on CRF. **All other outpatient/home visit study days:** collect once.

	Period I Screening	**Period II Treatment Period**											**Period III Post-Treatment Follow-Up**		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Physical examination	X														
Symptom-directed physical assessment		X													Symptom-directed physical assessment will be conducted at the discretion of the PI or qualified personnel per local regulations, as indicated based on participant status and standard of care. Excluding screening as it includes a physical examination.
COVID-19 Symptoms	X	X	X	X	X	X	X	X	X	X	X				Day 1: assess prior to dosing The presence of absence of symptoms are collected from the participants or their parents/legal guardian.
Laboratory Tests and Sample Collections															
Hematology		X		X				X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day Lilly-designated central laboratory

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Clinical Chemistry		X		X				X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day Lilly-designated central laboratory
Documentation of positive SARS-CoV-2 viral infection	X														Sample for first positive test must be collected within 3 days prior to start of treatment administration. Local laboratory and/or Point-of-Care testing.
PD swab		X		X		X		X		X	X				Swab is taken from both nostrils. Day 1: swab before treatment administration. Methods include nasopharyngeal (preferred) or mid-turbinate. The same method of sample collection must be used per participant for the duration of the study. Switching methods is not allowed. Lilly-designated central laboratory

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Serum or Urine pregnancy (local)	X														Pregnancy tests prior to the first dose of investigational product for females if • aged ≥10 years • <10 years at investigator's discretion • menarche is reached or • there is reason to believe that the patient is sexually active. Local laboratory
PK samples		X*		X				X		X	X		X		***Day 1: immediately after end of treatment administration.*** All other scheduled samples may occur at any time during the day. Pharmacokinetic samples for participants <12 kg may be collected using alternative techniques. For those using a central line on Day 1, please see Addendum Section 2.14, Appendix 10. If participant is hospitalized and if sample is available, collect sample. Lilly-designated central laboratory

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Immunogencity (ADA) samples		X*						X		X	X		X		***Day 1: collect before treatment administration.*** All other scheduled and unscheduled immunogenicity samples should be collected with a time-matched PK sample. No samples needed if participant is hospitalized or <12 kg. Lilly-designated central laboratory
Randomization and Dosing															
Register visit with IWRS	X	X													
Treatment Assignment via IWRS		X													
Dispense Study Drug via IWRS		X													

	Period I Screening	Period II Treatment Period											Period III Post-Treatment Follow-Up		
Study Day from Treatment Assignment		1	2, 3, 4	5	6	7	8, 9, 10	11	22	29	ED	Follow-up if hospital inpatient on Day 29	60	85	
Visit interval tolerance (days)		—	—	±1	—	+1	—	±2	±2	±3	±2	Every 7 days until discharge or Day 60	±4	±4	
Visit Detail		O	T,I	O,H	T,I	O,H	T,I	O,H	T,I	O,H	O,H		O,H	T,I	O = Outpatient clinic, H = Home Visit, T = Telephone, I = IT-Assisted Virtual Visit
Administer Study Intervention		X													Study intervention must be administered within 3 days from the time of first positive SARS-CoV-2 test sample collection. For participants that receive dialysis on the same day as administration of study intervention, complete dialysis first followed by the study treatment. Participants will be monitored for at least 1 hour after completion of treatment administration.

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; ICU = intensive care unit; IWRS = interactive web-response system; NP = nasopharyngeal; NSAIDS = non-steroidal anti-inflammatory drugs; PD = pharmacodynamics; PI = primary investigator; PK = pharmacokinetics; 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 bebtelovimab after intravenous injection	• Area under the concentration-time curve (AUC) from 0 to infinity for bebtelovimab
Secondary	
• Safety description	• Safety assessments such as AEs and SAEs
Exploratory	
• Overall participant clinical status	• Proportion (percentage) of participants who experience the following events by Days 22, 29, 60 and 85 o COVID-19 related hospitalization (defined as ≥24 hours of acute care) or o death from any cause • Proportion (percentage) of participants who experience the following events by Day 29 o a COVID-19 related emergency room visit, or o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or o death from any cause
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 5 o Day 7 o Day 11 • SARS-CoV-2 viral load area under the response-time curve (AUC)
• Symptoms and resolution	• Time to absence of all symptoms • Time to sustained absence of all symptoms • Proportion of participants demonstrating absence of symptoms
• Characterize emergence of viral resistance to bebtelovimab	• Comparison from baseline to the last evaluable time point
• Safety	• Proportion (percentage) of participants who experience MIS-C

Abbreviations: AE = adverse event; MIS-C = multisystem inflammatory syndrome in children; SAE =serious adverse event; 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 (Arm 23) to evaluate bebtelovimab administered as an intravenous injection to pediatric participants.

2.4.1. Section 4.1.1. Design Outline

Careful consideration was given to collect the necessary information to address the key scientific objectives of this pediatric study while also minimizing invasive procedures and overall patient burden, including through the use of comfort measures (e.g., EMLA cream) during blood draws.

This table describes the visit types for this study.

Study Day	Visit Type
1	Outpatient clinic visit
2, 3, 4, 6, 8, 9, 10, 22, and 85 (follow-up visit)	Telephone / IT-assisted virtual visits
5, 7, 11, 29, ED and 60 (follow-up visit	May be conducted as outpatient clinic or home visits

Abbreviation: ED = early discontinuation.

Refer to the SoA (Addendum Section 2.2.1) for the list of procedures in this study.

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. As of April 2022, child COVID-19 cases represented 19.0% of all COVID-19 cases reported, with an overall rate of 17,061 cases per 100,000 children in the US (AAP 2022).

Severity of Disease

While COVID-19–associated hospitalizations and deaths have occurred more frequently in adults (Delahoy et al. 2021), there are still pediatric patients who are infected with SARS-CoV-2 that become hospitalized (0.1-1.5%), and 0.00%-0.02% of all pediatric cases result in death (AAP 2022). There are also concerns about potential later term sequela that may result in pediatric patients from SARS-CoV-2 infections (Hertting et al. 2021), including MIS-C, an uncommon (approximately 2.1 in 100,000 persons <21 years of age [Belay et al. 2021]) but potentially fatal condition that occurs approximately 2 to 6 weeks after infection (CDC 2021).

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,
- obesity,
- diabetes,

- asthma,
- chronic lung disease,
- sickle cell disease, or
- immunosuppression.

However, in severe disease resulting in hospitalization among pediatric patients, approximately one-third of hospitalizations occur in patients that do not have an underlying medical condition (Wanga et al. 2021; Woodruff et al. 2021).

Unmet Need for Treatment

Currently, there are limited authorized or approved therapies effective for the treatment of the Omicron variant of COVID-19 in non-hospitalized pediatric patients under 12 years of age or 12 to 17 and weighing less than 40 kg body weight, which necessitates the urgent need to have access to experimental therapies.

Extrapolation of Efficacy

Efficacy will be fully extrapolated from adult data. The rationale behind this extrapolation of efficacy from adult efficacy studies to pediatric patients is based on

- FDA guidance documents (FDA 2020; FDA February 2021; FDA December 2021)
- the common initial stages of COVID-19 in (adult and pediatric patients when viral infection and replication occurs
- a similar (though usually less severe) course of SARS-CoV-2 infections in pediatric patients as compared to adults (Hoang et al. 2020)
- the mechanism of action of bebtelovimab which, regardless of host, involves direct binding to the SARS-CoV-2 virus S protein at the ACE2 receptor binding site, and
- previous extrapolation of pediatric COVID-19 efficacy from adult COVID-19 efficacy studies with bamlanivimab and etesevimab

This extrapolation approach aligns with the FDA guidance document: Development of Anti-Infective Drug Products for the Pediatric Population (FDA December 2021). This guidance states that extrapolation of effectiveness from adult populations to pediatric populations based on PK may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients. A similar approach for pediatrics is described in the FDA guidance document: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (FDA February 2021).

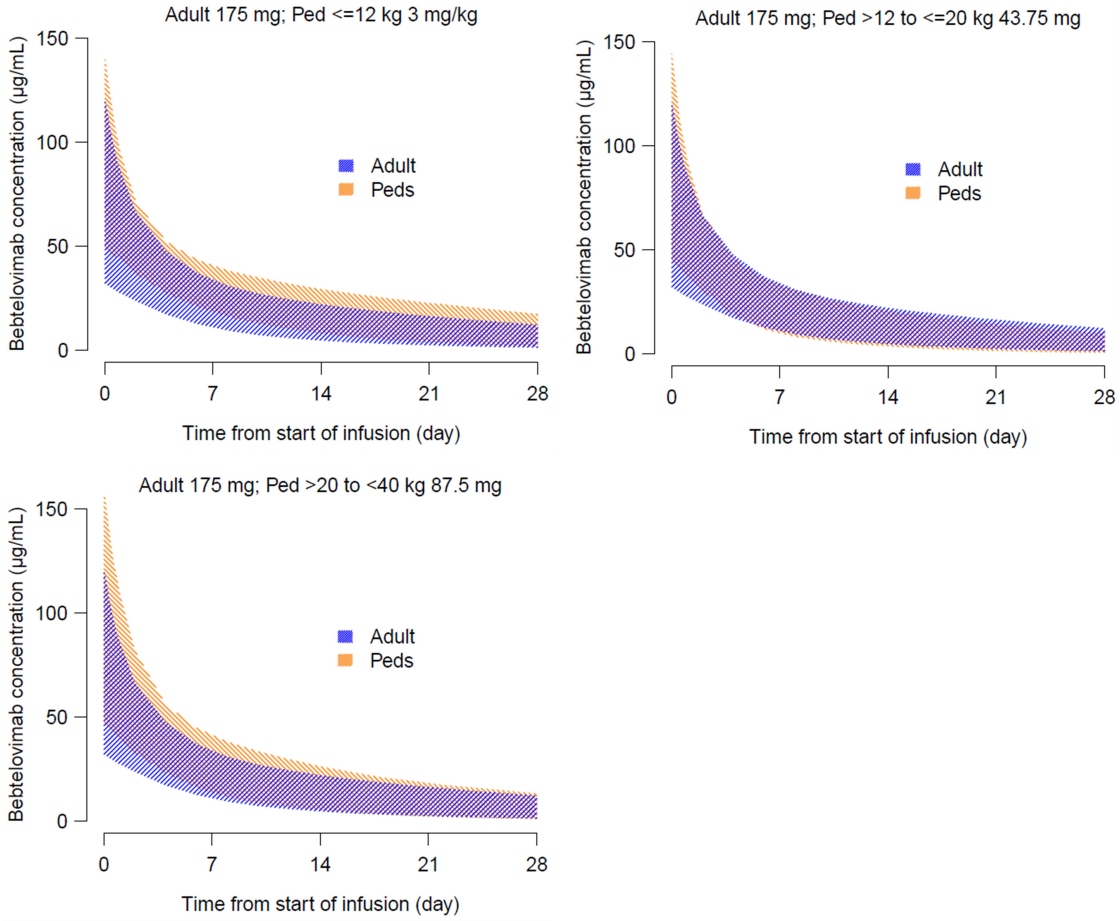
2.6. Section 4.3. Justification for Dose

An exposure-matching approach was implemented to determine pediatric doses that would result in similar serum concentrations to those achieved upon administration of 175 mg that is authorized in adults. The popPK model for bebtelovimab which included allometric scaling on clearance and volume parameters was used to predict the PK in pediatrics. For younger children weighing less than 12 kg (virtual patients drawn using NHANES database), a maturation function was included for clearance (Robbie et al. 2012). Based on exposure-matching, the table

below shows the doses depending on weight category. Due to potential limitations of precision around administrations of doses, bebtelovimab may be diluted for participants at or below 6 kg in body weight. Details for dosing and dilution of bebtelovimab are located within the pharmacy preparation instructions.

Weight group	Bebtelovimab dose
≥3.3 to ≤12 kg	3 mg/kg
>12 to ≤20 kg	43.75 mg
>20 to <40 kg	87.5 mg
≥40 kg	175 mg

Figure 2 shows that the PK model-predicted concentrations for these doses would be similar to adults.



The shaded areas are the 90% prediction interval of each population

Figure 2. Bebtelovimab PK model-predicted comparison of adult and pediatric serum concentrations.

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 first positive result sample of current SARS-CoV-2 viral infection ≤3 days prior to start of the administration
5. Are males or 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. The participant and/or legally authorized representative understand and agree to comply with planned study procedures
7. The participant and/or legally authorized representative 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
36. Are 0 (≥ 38 weeks gestational age and ≥ 3.3 kg) to <12 years of age at the time of screening, or are 12 to 17 and weighing <40 kg.
37. Have mild to moderate COVID-19 disease, including one or more of the following symptoms, within the last 7 days (FDA February 2021; CDC January 2022; CDC March 2022.)
    - shortness of breath or difficulty breathing
    - nasal congestion or runny nose
    - fever
    - chills
    - sore throat
    - malaise
    - nausea
    - vomiting
    - diarrhea
    - cough

- tiredness
- headache
- new loss of taste
- muscle or body aches and pain
- new loss of smell, or
- poor appetite or poor feeding (especially in babies under 1 year old).

2.7.2. Section 5.2. Exclusion Criteria

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

9. SpO2 ≤ 93% on room air at sea level, or while on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity, respiratory rate ≥30 per minute, and 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.
16. This criterion is not applicable for participants in this addendum
17. This criterion is not applicable for participants in this addendum
18. This criterion is not applicable for participants in this addendum
19. Have received treatment with a SARS-CoV-2 specific monoclonal antibody or remdesivir within 90 days before dosing
20. Have received convalescent COVID-19 plasma treatment within 90 days before dosing
21. This criterion is not applicable for participants in this addendum
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. Are currently pregnant or 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. Are currently hospitalized for treatment of COVID-19. Other reasons for hospitalization are acceptable.

2.8. Sectionn 6.1 Study Intervention(s) Administered

Treatment Arm 23

Intervention Name	LY3853113
Dose Formulation	Solution
Dosage Level(s) (mg)	See Addendum Section 2.6
Use	Experimental
IMP and NIMP	IMP
Sourcing	From Lilly
Packaging and Labeling	Study Intervention will be provided in glass vials and will be labeled appropriately.

Abbreviations: IMP = investigational medicinal product.

Dose preparation and administration information may be found in the pharmacy preparation instructions.

Participants should be monitored for at least 1 hour after completion of administration. The administration rate may be reduced as deemed necessary if an injection-related reaction is observed.

Further details will be included in the pharmacy preparation instructions. The site must have resuscitation equipment, emergency drugs and appropriately training staff available during the administration and for at least 1 hour after the completion of the administration.

2.9. Section 8.1. Efficacy Assessments

2.9.1. 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
- malaise
- 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: FDA February 2021; CDC January 2022; CDC March 2022.

2.10. Section 9.0. Statistical Considerations

2.10.1. Section 9.1. Statistical Hypotheses

This is an open-label study with a primary objective of assessing PK and secondary objective of describing safety. The PK of bebtelovimab administered via a weight-adjusting dosing scheme is hypothesized to be well-characterized and consistent with adult exposure.

2.10.2. Section 9.2. Sample Size Determination

There is an urgent unmet need among pediatric patients since there are no approved vaccines for the prevention of COVID-19 in pediatric patients <5 years of age and no FDA-approved therapies effective for treatment of the Omicron variant in patients <12 years or outside the existing bebtelovimab EUA criteria. Consequently, this study will include SARS-CoV-2 positive pediatric patients with mild to moderate disease that are 0 (≥38 weeks gestational age and ≥ 3.3 kg) to <12 years of age, or 12 to 17 years of age and weighing <40 kg.

The planned sample size is approximately 50 participants that are 0 (≥38 weeks gestational age and ≥ 3.3 kg) to 12 years of age, with a minimum of 5 participants in each of these age groups

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

Participants who are 12 to 17 years of age and weighing less than 40 kg can be enrolled into the study until approximately 50 participants that are 0 (≥38 weeks gestational age and and ≥ 3.3 kg) to 12 years of age are fully enrolled.

Fifty participants would provide adequate study power to target a 95% confidence interval within 60% to 140% of the geometric mean estimates of clearance and volume of distribution (Wang et al. 2012) for bebtelovimab as can be seen in Figure 3.

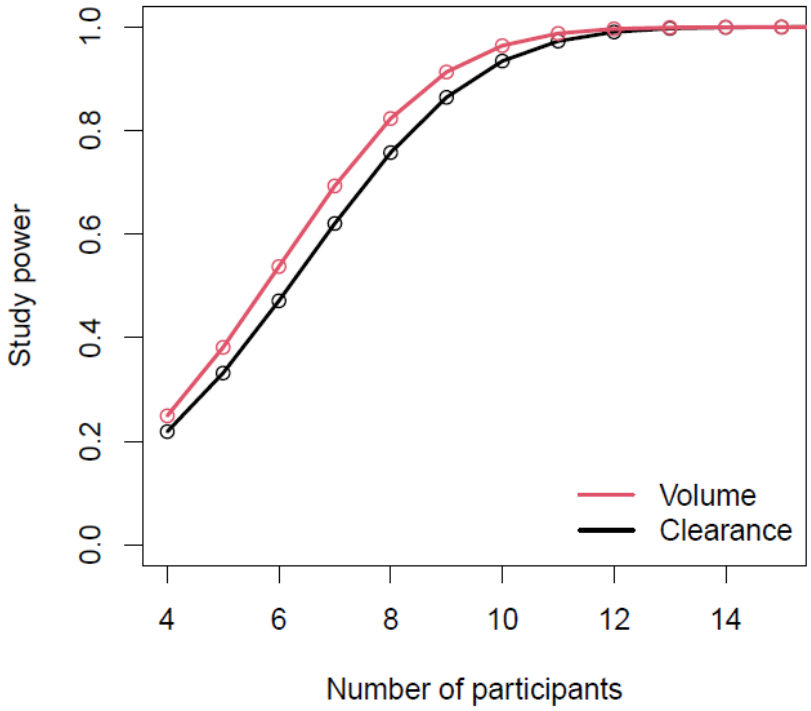


Figure 3. Estimated study power to target a 95% confidence interval within 60% to 140% of the geometric mean estimates of clearance and volume of distribution.

The anticipated risks of bebtelovimab are low, based on the known mechanism of action for human-derived neutralizing antibodies in acute viral disease states. Bebtelovimab is a highly specific mAb directed at a foreign (nonhuman) epitope(s). The complementarity determining regions of this mAb were derived from B lymphocytes of convalescent naturally SARS-CoV-2-infected patients and thus has undergone natural positive and negative selection pressures in vivo. No clinically relevant off-target binding has been observed in tissue cross-reactivity (TCR) studies of membrane targets in human tissues. Therefore, off-target binding and TCR are considered unlikely.

The safety profile of bebtelovimab is expected to be similar to that of bamlanivimab and etesevimab based on their similar mechanism of action. Because the observed safety profile of bamlanivimab and etesevimab was similar between adults and pediatric patients, it is reasonable to expect a similar safety profile with bebtelovimab in pediatric patients. Importantly, clinical trial results of low- and high-risk adults with mild-to-moderate COVID-19 receiving bebtelovimab indicate that the observed risks are monitorable (such as infusion-related reactions, pruritis, rash that were reported in <1% of trial participants) and manageable in the clinical setting.

Efficacy will be fully extrapolated from adult data. Considering there is no expectation that risk status for severe disease has any impact on PK and safety findings, pediatric patients with mild-to-moderate disease are not required to have a risk factor for severe disease to enroll into the study. Benefit in symptom relief is a reasonable expectation for enrolling patients regardless of risk status, and the wider pool of potential participants is expected to expedite enrollment.

2.10.3. Section 9.3. Populations for Analyses

This table defines the pediatric populations for analysis.

Pediatric Population for Analysis	Description
Pharmacokinetic	All pediatric participants who received a full dose of study intervention and have at least one evaluable PK sample.
Safety	All pediatric participants who received study intervention.
Efficacy	All pediatric participants who received study intervention and provided at least one post-baseline measure for the relevant endpoint.

2.10.4. Section 9.4. Statistical Analyses

2.10.4.1. Section 9.4.1. General Considerations

Statistical analysis of this study 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 years,
- 2 to <6 years,
- 6 to <12 years, and
- 12 to 17 and weighing <40kg

Additional details may be provided in the statistical analysis plan.

2.10.4.2. Section 9.4.2. Primary Endpoint

Treatment Arm 23

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.

2.10.4.3. Section 9.4.3. Secondary Endpoints

The secondary objective is to describe safety. The pediatric safety population is described in Addendum Section 2.10.3. Safety analyses will consist of summaries by preferred term within system organ class of treatment-emergent adverse events and serious adverse events (including reason for seriousness). The incidence of any treatment administrations that are interrupted or incomplete due to an adverse event will also be summarized, along with the incidence of immediate or non-immediate hypersensitivity events.

2.10.4.4. Section 9.4.3.4. Pharmacokinetic and Pharmacodynamic Analyses

Bebtelovimab concentration data may 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 and data are available, its impact on bebtelovimab 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 5, 7, and 11)
- AUC.

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

2.10.5. Section 9.5. Interim Analyses

An interim analysis may be conducted to evaluate safety 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 study will be fully described in the statistical analysis plan.

2.10.6. Section 9.6 Assessment Committee (AC)

The sponsor will form an AC to analyze the interim safety data. To minimize any bias introduced into the conduct and analysis of the study, the addendum specific analysis plan will be approved prior to the first interim analysis.

The primary goal of the AC is to review the interim results to facilitate the safety of study participants while maintaining the validity and scientific merit of the study. Information gained

from these analyses will not be reported to study sites or the broader study team beyond the AC until the final DBL for the cohort.

Overall AC structure information is in the main PYAB Protocol Section 10.1.5. Details of the AC will be provided in the Addendum (4) SAP.

2.11. 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.

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

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up pre-dose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

Timing	Sample Type	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	Serum	total tryptase
	Serum	complements (C3, C3a, and C5a)
	Serum	cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. ● Note: If collecting, collect up to 12 hours after the start of the event.	Serum	Bebtelovimab anti-drug antibodies (ADA)
	Serum	Bebtelovimab concentration

a All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

2.13. 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 <1.5× ULN	ALT or AST ≥3× ULN
ALP <1.5× ULN	ALP ≥2× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥1.5× 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 Section 10.2, Appendix 2 of the main PYAB protocol, 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 one or more of the conditions in the table above occur.

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

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 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 <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs/symptoms*, or ALT or AST ≥5× ULN
ALP <1.5× ULN	ALP ≥3× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline with hepatic signs/symptoms*, or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥2× 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 <1.5× ULN	Serum ALT to ≥5× ULN on 2 or more consecutive blood tests
ALT ≥1.5× ULN	Serum ALT to ≥3× ULN on 2 or more consecutive blood tests
TBL <1.5× ULN	TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
TBL ≥1.5× ULN	TBL to ≥2× baseline
ALP <1.5× ULN	Serum ALP to ≥2× ULN on 2 or more consecutive blood tests
ALP ≥1.5× ULN	Serum ALP ≥2× 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.

2.14. 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.

For Day 1 sample collection: It is acceptable to draw the end of infusion sample approximately 1 hour (±15 min) after the end of infusion, but not immediately following the end of the infusion.

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.

For Day 1 sample collection: It is acceptable to draw the end of infusion sample approximately 1 hour (±15 min) after the end of infusion, but not immediately following the end of the infusion.

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. Supporting Documentation

4.1. Protocol Addendum Revision History

Revision 4.1

Overall Rationale for the Revision:
The purpose of this revision is to adjust Inclusion Criterion 36 so that the lower age limit is 38 weeks gestational age, and the lower weight limit is 3.3 kg. This adjustment accounted for the lack of an accepted corrective safety factor to determine acceptable exposure limits for process-related impurities for pre-term infants.

Section # and Name	Description of Change	Brief Rationale
2.6 Section 4.3. Justification for Dose; 2.7.1 Section 5.1. Inclusion Criteria; 2.10.2 Section 9.2. Sample Size Determination	Modified lower age and weight limits for participants	Adjustment made due to the lack of an accepted corrective safety factor to determine acceptable exposure limits for process-related impurities for pre-term infants

Signature Page for VV-CLIN-068441 v1.0

Approval	PPD 01-Jul-2022 18:36:00 GMT+0000

Approval	PPD 01-Jul-2022 23:02:58 GMT+0000

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