Protocol Addendum 4: J2X-MC-PYAH

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Mono and Combination Therapy with Monoclonal Antibodies in Participants with Mild to Moderate COVID-19 Illness (BLAZE-4)

NCT04634409

Approval Date: 16-Mar-2021

Title Page

Protocol Title:

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Mono and Combination Therapy with Monoclonal Antibodies in Participants with Mild to Moderate COVID-19 Illness (BLAZE-4)

Protocol Number: J2X-MC-PYAH

Addendum Number: 4

Addendum Statement: This addendum is to be performed in addition to all procedures required by protocol J2X-MC-PYAH or any subsequent amendments to that protocol.

Compound: LY3819253, LY3832479, LY3853113

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

Regulatory Agency Identifier Number(s)
IND: 150440

Approval Date: Protocol Addendum (4) Electronically Signed and Approved by Lilly on date provided below.

Table of Contents

1. Rationale for Addendum

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

Recently, emergence of mutations to the spike protein of SARS-CoV-2 threaten to render current treatments and vaccines not as effective.

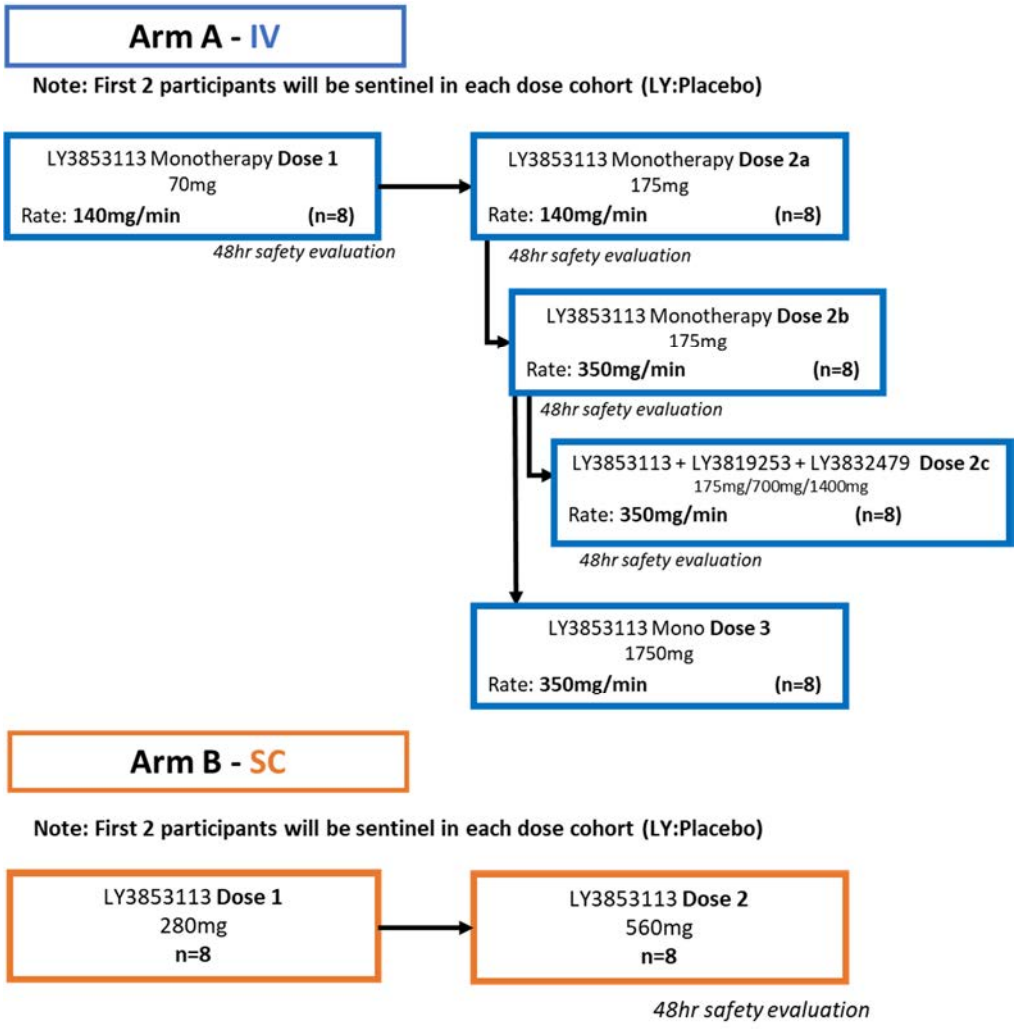
LY3853113 is a novel, highly potent IgG1 neutralizing mAb targeting the spike protein of SARS-CoV-2 that was created in partnership with AbCellera. It binds an epitope within the receptor binding domain that is distinct from those bound by LY3819253 and LY3832479. LY3853113 can neutralize the Wuhan reference strain as well as individual residues present in recent variants of concern (i.e. L452R, D614G, N501Y, N439K, K417N, and E484K). Critically, pseudovirus assays demonstrate that LY3853113 can neutralize variants with the specific combination of receptor binding domain residues of the B.1.1.351 (South African) and B.1.1.28 (P.1/Brazil origin**)** strains. These variants were recently reported in the United States (CDC 2021), thus it is imperative that new treatments for these emerging variants are developed and deployed quickly.

The purpose of this Phase 1, double-blind, randomized, placebo-controlled, ascending dose substudy is to characterize the safety and tolerability of LY3853113 alone by intravenous infusion or subcutaneous injection, and in combination with LY3819253 and LY3832479 by intravenous infusion.

2. Protocol Additions

2.1. Addendum Schema

Participants enrolled into this addendum will follow the schema below in place of the schema in the main protocol.



Note: Safety data from participants administered LY3819253 and LY3832479, expected prior to the start of the addendum, are informing on a maximum rate not exceeding 350 mg/min. The rate from Doses 2b, 2c, and Dose 3 will be defined in the pharmacy preparation instructions.

The first 2 participants in each cohort will be sentinel (LY3853113:placebo). Subsequent participants will be randomized to the remaining treatment allocations, 5 to LY3853113 or LY3853113 in combination with LY3819253 and LY3832479, and 1 to placebo.

Additional participants may be enrolled in case of discontinuation. In case of discontinuation, a newly enrolled participant will have the same treatment assignment as the corresponding discontinued participant.

Abbreviations: IV = intravenous; n = number of participants; SC = subcutaneous.

2.2. Schedule of Activities

Participants enrolled into this addendum will follow the Schedule of Activities below in place of the main protocol schedule(s).

Assessments obtained previously as part of routine clinical care may be used as the baseline assessment if they were done no more than 48 hours before randomization. Visits may be conducted as a telephone call, outpatient clinic or home visit, as long as the protocol SoA is followed.

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
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															
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: vaccination history (including SARS-CoV-2 vaccinations), risk factors and comorbidities associated with severe COVID-19 illness, such as living in a nursing home or long-term care facility.
Prespecified medical history: COVID-19	X															Includes COVID-19 diagnosis date and onset of COVID-19 symptoms.
Height		X														
Weight		X														

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
Visit window (number of days)		--	--	+1	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Prior treatments of special interest within the last 30 days	X															NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments.
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 the main protocol, Section 10.3. Additional details regarding reporting frequency and method of detecting AEs and SAEs can be found in the main protocol, 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.

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
Visit window (number of days)		--	--	+1	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Vital signs and Oxygen Support	X	X		X		X		X	X		X	X	X	X	X	Documentation of hospital-based exam is acceptable. 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. Record SpO2 while participant is at rest. **Screening visit only**: SpO2 while breathing room air. Data not collected on CRF. **Day 1 timing:** • immediately before administration • immediately following completion of infusion if infusion is <15 minutes • every 15 minutes during the infusion, as possible and applicable • every 30 minutes for 1 hour after the end of infusion See Section 2.12.1 for data collected on CRF. **All other study days:** once daily.

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
Visit window (number of days)		--	--	+1	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Hospitalization events		Daily								X	X	X	X	X	X	Record if the following events occur or occurred since prior visit: • Emergency room visits • Hospitalized • ICU admittance, • Extended care facility admittance, and • Discharge
Laboratory Tests and Sample Collection																
Hematology		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory
Clinical Chemistry		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory
C-reactive protein (CRP); high - sensitivity		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
Visit window (number of days)		--	--	+1	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Ferritin		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory
D-dimer		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory
Procalcitonin		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory
Troponin I and Troponin T		X		X					X		X	X				Day 1: before treatment administration All other days: sample may occur at any time during the day No sample needed if participant is hospitalized 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 infusion. Local laboratory and/or Point-of-Care testing.

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
Visit window (number of days)		--	--	+1	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Urine or serum pregnancy	X													X	X	Only for WOCBP as defined in the main protocol, Section 10.4 Appendix 4. Local laboratory
Pharmacokinetic (PK) sample		X		X		X		X	X		X	X		X	X	Day 1: No pre-dose sample needed. IV - one post-dose sample within 30 minutes after the end of IV infusion (may include the flush). SC - one post-dose sample taken as close to the end of the visit as possible. All other scheduled samples may occur at any time during the day. No samples needed if participant is hospitalized. Lilly-designated central laboratory
Immunogenicity (ADA) sample		X							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 Lilly-designated central laboratory
Pharmacodynamic (PD) NP swab		X		X		X		X	X		X	X				Swab is taken from both nostrils. Day 1: swab before treatment administration. No samples needed if participant is hospitalized Lilly-designated central laboratory

J2X-MC-PYAH Addendum 4	**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) for all treatment arms
Visit window (number of days)		--	--	+1	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Exploratory biomarker samples		X		X		X			X		X	X				Day 1: before treatment administration.
Exploratory Serum sample		X												X	X	
Pharmacogenetics sample		X														Lilly-designated central laboratory
Randomization and Dosing																
Randomization		X														
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.
Participant Questionnaire																
Symptoms (Patient Symptom Assessment) and overall clinical status		Daily on Days 1-11 for outpatients only								X	X	X		X	X	Day 1: assess prior to dosing

Abbreviations: ADA = anti-drug antibody; AEs = adverse events; BP = blood pressure; CRF = case report form; ED = early discontinuation visit; FiO2 = fraction of inspired oxygen in the air; ICU = intensive care unit; NP = nasopharyngeal; NSAIDS = non-steroidal anti-inflammatory drugs; PK = pharmacokinetics; SAEs = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen; SC = subcutaneous; WOCBP = women of child-bearing potential.

2.3. Benefit/Risk Assessment

The administration of therapeutic mAbs has the potential for injection site reactions and hypersensitivity, including anaphylaxis and infusion related reactions. Increased rates of administration may be associated with an increased risk of such reactions.

The infusions in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made or the infusion stopped, if indicated. Additional information regarding infusion reaction management options is in Section 6.1.1 of the main protocol.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3819253, LY3832479, and LY3853113 may be found in each respective IB.

2.4. Objectives and Endpoints

Objectives	Endpoints
Primary	
Characterize the safety and tolerability of LY3853113 alone (after IV infusion or SC injection) and in combination with LY3819253 and LY3832479 (after IV infusion)	• Safety assessments such as AEs and SAEs
Secondary	
Characterize the pharmacokinetics of LY3853113 after intravenous infusion or SC injection	• LY3853113 mean concentration on Day 29
Characterize the pharmacodynamics of LY3853113 alone (after IV infusion or SC injection) and in combination with LY3819253 and LY3832479 (after IV infusion)	• Change from baseline in SARS-CoV-2 viral load (Days 3, 5, 7, and 11) • Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 • SARS-CoV-2 viral load AUC assessed through Day 11 • Time to SARS-CoV-2 clearance
Tertiary/Exploratory	
Characterize the participant's clinical status	• Duration (days) of hospitalization • Proportion (percentage) of participants admitted to ICU • Proportion (percentage) of participants requiring mechanical ventilation
Characterize the pharmacodynamics of LY3853113 alone (after IV infusion or SC injection) and in combination with	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, 29) • 75th percentile of SARS-CoV-2 viral load at Day 7

LY3819253 and LY3832479 (after IV infusion)	
Characterize emergence of viral resistance to LY3853113	• Comparison from baseline to the last evaluable time point up to Day 29

Abbreviations: AE = adverse event; ICU = intensive care unit; IV = intravenous; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous.

2.5. Study Design

This is a Phase 1, double-blind, randomized, placebo-controlled, ascending dose substudy that may progress to a Phase 2, double-blind, randomized, placebo-controlled phase.

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures. Screening may be performed up to 48 hours prior to dosing. Screening and Day 1 may occur on the same day.

Treatment and Assessment Period

This is the general sequence of events during the treatment and assessment period:

- Participants are randomized to intervention group
- Baseline procedures and sample collection are completed
- Participants receive study intervention, and
- All safety monitoring and post-administration sample and data collection are performed.

Remote follow-up visits may be conducted to remove the burden of return visits to the clinic and clinical trial staff reflecting limited medical resources in the COVID-19 pandemic.

This addendum will comprise up to 5 dose cohorts to receive study intervention by IV infusion and 2 dose cohorts to receive study intervention by SC injection.

Cohorts will comprise at least 8 participants each:

- 6 randomized to LY3853113 alone or in combination with LY3819253 and LY3832479, and
- 2 randomized to placebo.

Sentinel dosing will be used in each dose cohort that represents a dose increase or infusion rate change (increase in mg/minute) from the preceding cohort. The first 2 participants in each cohort will be randomized 1:1 to LY3853113 and placebo.

Safety and tolerability will be reviewed for sentinel participants up to 24 hours after dosing. The investigator and the Lilly sponsor team are responsible for determining if safety and tolerability is acceptable to continue with dosing subsequent participants.

Subsequent participants will be randomized to the remaining treatment allocations, 5 to LY3853113 and 1 to placebo.

The decision to dose the next cohort will be made when all participants from the previous cohort have been dosed and safety data is assessed for at least 48 hours after the IV infusion or SC injection by the investigator(s) and Lilly sponsor team.

2.6. Justification of Dose

Intravenous dosing for LY3853113

The 175mg dose is the intended target dose for the Phase 2 portion of the study.

The target therapeutic dose of 175 mg was selected using PK/PD modeling in a manner similar to the approaches that were used for LY3819253 and LY3832479. The PK/PD modeling approach includes in vitro potency data (i.e. IC90), predicted human PK, and the expected response in terms of maximal reduction in viral load. The 175 mg dose is expected to result in at least 90% of the population achieving drug concentrations above IC90 through at least 28 days after drug administration, and results in maximum reduction in viral load based on a PK-viral dynamic model.

This Phase 1 addendum will evaluate 3 IV dose levels.

The first dose level is approximately 3 times lower than the target dose level (70 mg). The third dose level is approximately 10 times higher than the target dose (1750 mg) to further evaluate the safety of LY3853113. Based on current knowledge of similar neutralizing mAbs (LY3819253 and LY3832479) that have been studied at doses of up to 7000 mg, the third dose level is anticipated to have an acceptable safety profile. Based on preliminary non-clinical PK results, the PK profile of LY3853113 is similar to that of LY3819253.

Further details about dose selection and coverage of variants of interest may be found in the IB. These doses may be amended if necessary, based on emerging data.

Intravenous dosing for LY3819253 and LY3832479

The IV doses for LY3819253 and LY3832479 will be 700 mg and 1400 mg, respectively. These doses are currently the authorized doses in the EUA.

Subcutaneous dosing for LY3853113

This Phase 1 addendum will evaluate 2 subcutaneous dose levels. The first dose level is 280 mg via 2 × 2 mL injections. This dose is the intended therapeutic dose that would result in viral load reduction similar to IV administration as described above. The upper dose level is 560 mg via 4 × 2 mL injections, and is driven by the feasibility of multiple injections.

2.7. Study Population

2.7.1. Inclusion Criteria

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

Age

1. Are ≥18 and <65 years of age at the time of randomization

Disease Characteristics

2. Are currently not hospitalized
3. Have one or more mild or moderate COVID-19 symptoms (CDC 2020; FDA 2021)
    i. Fever
    ii. Cough
    iii. Sore throat
    iv. Malaise
    v. Headache
    vi. Muscle pain
    vii. Gastrointestinal symptoms
    viii. Shortness of breath with exertion
    ix. Nasal congestion or runny nose
    x. New loss of smell
    xi. Chills
4. Must have sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to the administration of study drug

Sex

5. Men or non-pregnant women
   Reproductive and Contraceptive agreements and requirements are provided in the main protocol, Section 10.4, Appendix 4. Contraceptive use by men or women should be consistent with local regulations for those participating in clinical studies.

Study Procedures

6. Understand and agree to comply with planned study procedures
7. Agree to the collection of nasopharyngeal swabs and venous blood

Informed Consent

8. The participant or legally authorized representative gives signed informed consent as described in the main protocol, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2.7.2. Exclusion Criteria

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

Medical Conditions

9. Have a BMI ≥35
10. Have SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 <300, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA resource page, WWW)
11. Require mechanical ventilation or anticipated impending need for mechanical ventilation
12. Have known allergies to any of the components used in the formulation of the interventions
13. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
14. 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
15. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
16. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study

Other Exclusions

17. Have a history of a positive SARS-CoV-2 serology test
18. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
19. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
20. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
21. Have received convalescent COVID-19 plasma treatment
22. Have participated in a previous SARS-CoV-2 vaccine study or have received a SARS-CoV-2 vaccine
23. 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.
24. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
25. Are pregnant or breast feeding
26. Are investigator site personnel directly affiliated with this study.

2.8. Cohort Escalation Criteria

Data will be evaluated on an ongoing basis until the highest planned dose has been administered.

The decision to dose the next cohort in the addendum will be made when all participants from the previous cohort have been dosed and safety data, including safety laboratory data, AEs and vital signs, are assessed for at least 48 hours after study drug administration by the investigator(s) and Lilly sponsor team.

Available PK and PD data may also be used to guide dose adjustment.

If temporary stopping criteria are met (Section 2.9), dosing will be temporarily stopped and no further participants will be dosed until a full safety review of the study has taken place. The assessment committee (see Section 6.1.2 of main protocol) will be engaged for the full safety review with the sponsor and investigator.

2.9. Temporary Stopping Criteria

Dosing will be temporarily halted, and no further participants will be dosed until a safety review of the study has taken place if:

- Two or more participants at a given dose level develop severe or severe/potentially life-threatening acute AEs related to the administration of study drug (see table in main protocol, Section 6.1.1.2), during or within 2 hours of completion of the administration, that do not resolve with a reduced infusion rate and/or supportive care.
  OR
- Two or more participants at a given dose level develop severe AEs within 4 days of dosing which, in the opinion of the investigator, cannot be attributed to the primary disease, concomitant medications or extraneous circumstances with a reasonable possibility.

Topic	Location in Main Protocol
DAIDS table describing severity of reactions	Section 6.1.1.2
Definition of AEs	Section 10.3.1
Assessment of Intensity/Severity	Section 10.3.3

Changes to the planned dosing schedule must be appropriately documented and communicated with the study personnel and the IRB/IEC before dosing continues.

2.10. Study Interventions(s) Administered

Intervention Name	Placebo	LY3853113	LY3853113	LY3853113 + LY3819253 + LY3832479
Dose Formulation	0.9% sodium chloride solution	Solution	Solution	Solution
Dosage Level(s) (mg)	Not applicable	70, 175, 1750	280, 560	175 + 700 + 1400
Route of Administration	IV infusion, SC injection	IV infusion	SC injection	IV infusion
Use	Placebo	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly	From Lilly	From Lilly

Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately.	Study Intervention will be provided in glass vials and will be labeled appropriately.	Study Intervention will be provided in glass vials and will be labeled appropriately.

Note: Depending on the results of a given internal data review, doses may be adjusted.

Infusion and subcutaneous dose preparation information may be found in the pharmacy preparation instructions.

Arm A IV administration

Single Administration

Participants should be monitored for at least 1 hour after completion of infusion. The infusion rate may be reduced as deemed necessary if an infusion reaction is observed (main protocol, Section 6.1.1.2).

Multiple Administrations

In the event of multiple administrations, participants should receive LY3819253 and LY3832479 or placebo first and should be monitored for at least 30 minutes after completion of the first administration and before administration of LY3853113 or placebo. Participants should be monitored for at least 1 hour after second administration. Further details will be included in the pharmacy preparation incstructions. The infusion rate may be reduced as deemed necessary if an infusion reaction is observed (main protocol, Section 6.1.1.2).

Arm B SC administration

Subcutaneous injections will be administered in the abdomen. The dose will be administered as up to 4 injections of 2-mL each. Different quadrants of the abdomen should be used for each injection.

The site must have resuscitation equipment, emergency drugs and appropriately training staff available for at least 1 hour after the completion of the infusion or SC injection.

2.10.1 Injection volumes and formulation concentrations

Injection volumes are as follows:

Cohort (LY3853113 dose)	Number of injections and volumes
SC Dose Level 1 (280 mg)	2 × 2 mL
SC Dose Level 2 (560 mg)	4 × 2 mL

The LY3853113 formulation concentration will be 70 mg/mL in all cases.

2.11. Injection Site Reactions

For subcutaneous injections, manifestations of a local ISR may include erythema, induration, pain, pruritus, and edema. If an ISR is reported by a participant or site staff, the ISR CRF will be

used to capture additional information about this reaction, for example, injection-site pain, degree and area of erythema, induration, pruritis and edema.

2.12. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 2.2).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

2.12.1 Vital Signs

Vital signs will be measured as specified in the SoA (Section 2.2) and as clinically indicated. Vital signs include

- Body temperature
- Blood pressure
- Pulse rate
- Respiration rate
- Saturation of peripheral oxygen, and
- Supplemental oxygen flow rate, FiO2 if known, and method of delivery, if applicable.

These tables outline Day 1 vital signs data collection on the CRF in relation to the infusion(s). Infusion times may vary depending on the participant.

Single Administration

Timepoint (minutes)	**Collect data on CRF**
Immediately before infusion	Yes
If infusion is <15 minutes, immediately following completion of infusion	Yes
During Infusions > 15 minutes, as possible (if applicable)	--
15	No
30	Yes
45	No
60	Yes
After infusion – every 30 minutes for 1 hour after the end of the infusion	--
end of infusion +30 minutes	Yes
end of infusion +60 minutes	No

Multiple Administrations

Timepoint (minutes)	Collect data on CRF
Immediately before infusion	Yes
If infusion is <15 minutes, immediately following completion of first infusion	Yes
During infusion > 15 minutes, as possible (if applicable)	--
15	No
30	Yes
45	No
60	Yes
After last infusion – every 30 minutes for 1 hour after the end of the last infusion	--
end of infusion +30 minutes	Yes
end of infusion +60 minutes	No

2.13. Statistics

Statistical analyses of this substudy will be the responsibility of the Sponsor or its designee.

Sample Size

The sample size for this addendum is customary for first-in-human studies to evaluate safety.

Populations for Analyses

This table defines the populations for analysis.

Population	Description
Entered	All participants who sign the informed consent form for the addendum.
Efficacy - Addendum	All participants who were allocated and received study intervention in the addendum 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. (Intention to treat).
Safety - Addendum	All participants allocated to treatment in the addendum and who received study intervention. Participants will be analyzed according to the intervention they received.
Pharmacokinetic - Addendum	All participants who were allocated and received addendum intervention in the study and have evaluable PK sample. Participants will be analyzed according to the intervention they received.

Statistical Analyses

All analyses in this addendum will be summarized by cohort and administration method, no inferential statistics will be performed. Data from participants in this addendum will be summarized separately from participants in the main protocol. Refer to the PYAH Statistical Analysis Plan for details on handling dropouts or missing data.

Interim Analyses

An interim analysis of safety data may be conducted at any time for participants who have reached Day 3.

3. References

[CDC] Centers for Disease Control and Prevention. COVID-19 in children and teens. Information for parents and caregivers about COVID-19 in children and teens. Website page last updated December 18, 2020. Accessed March 16, 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html

[CDC] Centers for Disease Control and Prevention. US COVID-19 cases caused by variants. Updated February 21, 2021. Accessed February 21, 2021. https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.html

FDA resource page. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. Food and Drug Administration web site. February 2021. Available at: https:// www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention. Accessed 12 March 2021.

Leo Document ID = ef6e577b-7ace-47ec-b1f2-2e400a08c625

PPD

Approval Date & Time: 16-Mar-2021 21:05:11 GMT

Signature meaning: Approved

PPD

Approval Date & Time: 16-Mar-2021 21:14:37 GMT

Signature meaning: Approved