Protocol Addendum 2: 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)

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Title Page

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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: 2

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

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) Electronically Signed and Approved by Lilly on date provided below.

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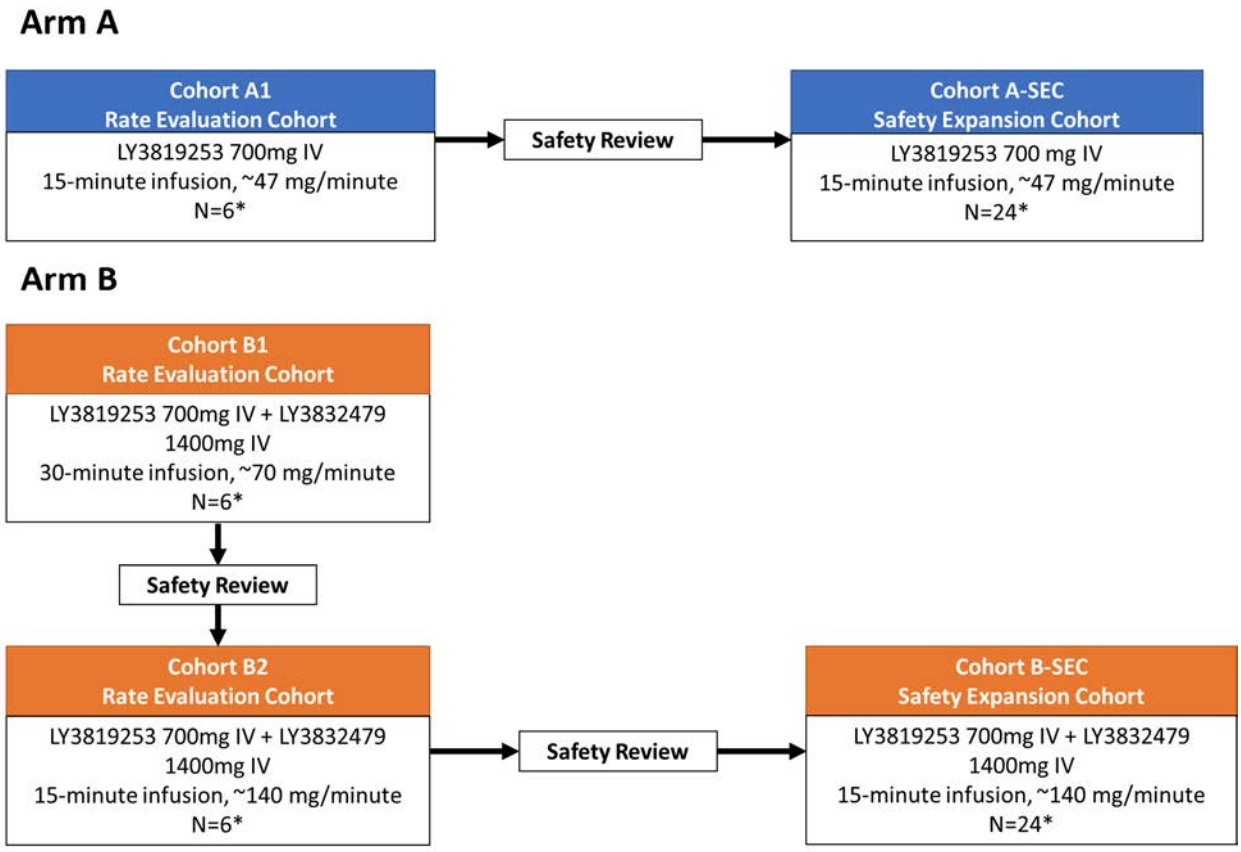
1. Rationale for Addendum

This addendum has been added to explore the safety of accelerated intravenous (IV) administration of LY3819253 alone and in combination with LY3832479. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the global pandemic spread of coronavirus disease 2019 (COVID-19), which has placed significant strain on healthcare resources. A more rapid administration time for LY3819253 alone, or in combination with LY3832479, would decrease the required contact time with healthcare professionals and therefore allow for more efficient use of limited resources, in addition to improving participant convenience and potentially also compliance.

2. Protocol Additions

2.1. Schema for Substudy

Participants enrolled into this addendum will follow the schema below in place of the schema in the J2X-MC-PYAH (PYAH) protocol.



* Based on emerging safety and tolerability data, additional participants may be added to existing dosing cohorts, or new cohorts may be added to evaluate alternative administration rates (see Section 2.5 and 2.11)

Note: Sentinel dosing will be used for the first participant in each new rate evaluation cohort.

Abbreviations: IV = intravenous; N= number of participants; SEC = safety expansion cohort.

2.2. Schedule of Activities

Participants enrolled into this substudy will follow the PYAH protocol Schedule of Activities (SOA). Clarifications for this substudy include:

- This is an open-label substudy and therefore no blinding of investigators or participants is required.
- For treatment administration times of 15 minutes, record vital signs immediately after administration is complete, in addition to the times listed in the SOA.

2.3. Benefit/Risk Assessment

The administration of therapeutic monoclonal antibodies (mAbs) has the potential for hypersensitivity including anaphylaxis and infusion related reactions. Increased rates of administration may be associated with an increased risk of such reactions.

LY3819253 has been evaluated as a monotherapy at doses up to 7000 mg, at a rate of up to ~117 mg/minute. LY3832479 has been evaluated as a monotherapy at doses up to 7000 mg, at a rate of up to ~67 mg/minute. As of 2 October 2020, 727 participants have received blinded treatment with LY3819253 700 mg, 2800 mg, or 7000 mg, or placebo. Serious infusion-related reactions, including events consistent with anaphylaxis, have been reported in the blinded ongoing studies. Refer to the monotherapy EUA fact sheet for details (https://www.fda.gov/media/143603/download).

Combination therapy of 2800 mg LY3819253 and 2800 mg LY3832479 administered at a rate of ~93 mg/minute is being evaluated in a randomized, placebo-controlled, double-blind Phase 2 study in participants with mild to moderate COVID-19 (Study J2W-MC-PYAB [PYAB], Treatment Arms 6 and 7). As of 04 November 2020 when 386 participants had received blinded treatment with either placebo or 2800 mg LY3819253 + 2800 mg LY3832479 in combination in J2W-MC-PYAB, 4 participants have reported single immediate non-serious events of pruritis flushing and dyspnea.

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 and/or the infusion stopped, if indicated. Additional information regarding infusion reaction management options is in Section 6.1.1 of the PYAH protocol.

Participants treated with LY3819253 in combination with LY3832479 had decreased hospitalizations, more rapid viral clearance, and more rapid improvement in symptoms. Decreasing administration times to 15 minutes or less may improve participant compliance, decrease the required contact time with healthcare professionals and other patients in infusion facilities, and increase the number of participants that may be treated in a day. Overall, these factors allow for more efficient use of limited resources.

2.4. Objectives and Endpoints

The table below is to be used in place of the table outlined in Section 3 of the PYAH protocol.

Primary	
Characterize the safety and tolerability of LY3819253 alone, and in combination with LY3832479	• Safety assessments such as AEs and SAEs
Secondary	
Characterize the pharmacokinetics of LY3819253 and LY3832479	Mean concentration of LY3819253 and LY3832479 on Day 29

Characterize the SARS-CoV-2 viral load and viral clearance for participants who received LY3819253 alone, and in combination with LY3832479	• Change from baseline to
	  o Day 3 (+1 day)
	  o Day 5 (±2 days)
	  o Day 7 (±2 days)
	  o Day 11 (±2 days)
	• Proportion of participants with viral load greater than 5.27 on Day 7 (+2 days) among participants enrolled with ≤ 8 days of symptoms prior to randomization
	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11)
	• Time to SARS-CoV-2 clearance
	• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11

Exploratory	

Characterize overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29
	  o COVID-19 related hospitalization (defined as ≥24 hours of acute care)
	  o Death

Characterize symptom resolution and improvement	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 3, 5, 7, and 11 • Change in symptom score (total of ratings) from baseline up to Day 11. • Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 3, 5, 7, and 11

Characterize overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60 and 85
	  o COVID-19 related hospitalization (defined as ≥24 hours of acute care)
	  o Death

Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events through Day 29:
	  o COVID-19 related hospitalization (defined as ≥24 hours of acute care),
	  o COVID-19 related emergency room visit, or
	  o death

Characterize emergence of viral resistance to LY3819253 and LY3819253 in combination with LY3832479	• Comparison from baseline to the last evaluable time point up to Day 29

Abbreviations: AE = adverse event; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2.5. Study Design

This addendum, which will be introduced at selected sites, adds an open-label substudy to explore accelerated IV administration of LY3819253 alone, and in combination with LY3832479.

This substudy comprises two arms. In Arm A, all participants will receive LY3819253 700 mg monotherapy IV. In Arm B all participants will receive the combination of LY3819253 700 mg and LY3832479 1400 mg IV.

Sentinel dosing will be used for the first participant in each rate evaluation cohort that represents a rate increase from the preceding cohort. Safety and tolerability will be reviewed for sentinel participants at least 2 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 in that cohort. Sentinel dosing is not required for the Safety Expansion Cohorts.

The decision to dose the next cohort, either a rate evaluation cohort or a safety expansion cohort (SEC) at the same rate, will be made when at least 5 participants from the previous cohort have been dosed and safety data is assessed for at least 24 hours after the IV infusion by the investigator(s) and Lilly sponsor team.

In total, at least 66 participants will be included in Arms A and B. Based on emerging safety and tolerability data, additional participants may be added to existing dosing cohorts, or new cohorts may be added to evaluate alternative administration rates (see Section 2.9). However, the minimum administration time studied in Arms A and B will be 15 minutes.

Arm A (Monotherapy)

The initial cohort (A1, n=6) of Arm A will evaluate administration of 700 mg LY3819253 IV in 15 minutes (~47 mg/minute). After the first participant in the cohort has been evaluated for 2 hours, additional participants may be dosed in this cohort. Once at least 5 participants have been dosed, and following a safety review after at least 24 hours, additional participants may be dosed in a new cohort. If no stopping criteria are met, the next cohort will be an Arm A Safety Expansion Cohort (A-SEC), to ensure that a total of at least 30 participants are evaluated at the final administration rate selected. If temporary stopping criteria are met in Cohort A1, additional participants may be added to Cohort A1, or a new cohort may be added to evaluate a longer administration time.

Arm B (Combination Therapy)

The initial cohort (B1, n=6) of Arm B will evaluate administration of 700mg LY3819253 and 1400 mg LY3832479 IV in 30 minutes (~70 mg/minute). After the first participant in the cohort has been evaluated for 2 hours, additional participants may be dosed. Once at least 5 participants have been dosed, and following a safety review after at least 24 hours, additional participants may receive study treatment in either a new rate cohort, or a Safety Expansion Cohort (SEC) at the same rate if warranted by emerging safety and tolerability data, or if temporary stopping criteria are met.

Subsequent cohorts in Arm B will evaluate administration of 700 mg LY3819253 and 1400 mg LY3832479 IV in 15 minutes (B2, n=6, ~140 mg/minute). If no stopping criteria are met, the next cohort will be an Arm B Safety Expansion Cohort (B-SEC), to ensure that a total of at least 30 participants are evaluated at the final administration rate selected. If temporary stopping criteria are met in Cohorts B1 or B2, additional participants may be added to an existing cohort, or a new cohort may be added to evaluate a longer administration time.

Screening

Screening will be performed as detailed in the main body of the protocol (Section 1.3 and 4.1).

Open-Label Treatment and Assessment Period

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

- Complete baseline procedures and sample collection
- Participants will be allocated to the monotherapy treatment cohorts prior to the combination treatment cohorts
- Participants receive study intervention, and
- Complete all safety monitoring and post-treatment sample collection.

For additional details on the assessment period, see the main body of the PYAH protocol (Section 1.3 and 4.1).

Post-treatment follow-up

Post-treatment follow-up assessments will be conducted as detailed in the main body of the PYAH protocol (Section 1.3 and 4.1).

2.6. Scientific Rationale for Study Design

This substudy to PYAH is designed to explore the safety and tolerability of accelerated IV administration of LY3819253 alone, or in combination with LY3832479, that will inform the clinical drug development plan.

The sequential cohort, single-dose, rate evaluation design with safety reviews before each new cohort will minimize safety risks to participants during administration rate exploration. Sentinel dosing is included to minimize the risk of any unanticipated acute tolerability or safety concerns in participants administered either LY3819253 alone, or LY3819253 in combination with LY3832479.

The 24-hour safety review after dosing is sufficient to monitor for an acute hypersensitivity response to treatment with LY3819253 alone, or in combination with LY3832479, given the extent of prior clinical experience with these therapeutics.

Participants with mild to moderate COVID-19 illness have been selected for this sub-study to enable the evaluation of the safety and tolerability of accelerated IV administration of LY3819253 alone, or in combination with LY3832479, in a clinically relevant population. Participants with risk factors for severe disease are excluded to enable their enrollment in a study

specifically evaluating the combination therapy in the high-risk population (BLAZE-1, J2W-MC-PYAB).

2.7. Justification of Dose

The 700 mg is authorized as the maximum therapeutic dose for LY3819253. For combination therapy, to provide coverage of the different but overlapping epitopes on SARS-CoV-2 receptor binding domain sites for LY3819253 and LY3832479, the dose selection rationale for each single mAb in the combination is the same as for the dose rationale for a single mAb. Therefore, the dose of 700 mg LY3819253 and 1400 mg LY3832479 are proposed as the maximum therapeutic doses to reduce viral load based on viral dynamic PK/PD modeling and has a sustained concentration above the respective IC90 of viral neutralization for at least 28 days in 90% of the participant population.

2.8. Study Population

No changes to the study population or inclusion/exclusion criteria are required for this substudy.

2.9. Cohort Escalation/Expansion Criteria

As an unblinded rate-evaluation study, data will be evaluated on an ongoing basis until the highest planned rate has been administered.

The decision to dose the next cohort in a Treatment Arm will be made when at least 5 participants from the previous cohort have been dosed and safety data is assessed, including safety laboratory data, AEs and vital signs, from at least 24 hours after the administration by the investigator(s) and Lilly sponsor team. The next cohort may either be a cohort to evaluate a new rate of administration, or a Safety Expansion Cohort to evaluate a larger number of participants at the same rate.

2.10. Temporary Stopping Criteria

Dosing will be temporarily halted, and no further participants will be dosed in that Treatment Arm until a full safety review of the study has taken place if either:

- 2 or more participants in a rate evaluation cohort (e.g. Cohorts A1, B1, B2), or 4 or more participants in an SEC have symptoms consistent with a moderate Acute Allergic reaction or Cytokine Release Syndrome (according to Division of AIDS [DAIDS] criteria [DAIDS 2017]), OR
- 1 or more participants in a rate evaluation cohort (e.g. Cohorts A1, B1, B2), or 2 or more participants in an SEC, have symptoms consistent with Severe Acute Allergic reactions or Cytokine Release Syndrome (according to DAIDS criteria [DAIDS 2017]).

If temporary stopping criteria are met, the assessment committee (AC) will be engaged for a full safety review with the sponsor. The AC may recommend expanding to a safety expansion cohort at that administration rate, or the addition of cohorts to evaluate slower administration rates. See Section 10.1.5 of the PYAH protocol for additional details.

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

This table describes the location of AE-related information in the PYAH protocol.

Topic	PYAH Protocol Location
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

Abbreviations: AE = adverse event; DAIDS = Division of AIDS.

2.11. Preparation/Handling/Storage/Accountability

Blinding is not required for the purposes of this open-label substudy. For additional details see guidance in Section 6.2 of the PYAH protocol.

2.12. Study Assessments and Procedures

As an open-label rate-evaluation study, unblinded data will be evaluated on an ongoing basis by study team members. For additional information on assessments and procedures see Section 8 of the PYAH protocol.

2.13. Measures to Minimize Bias

This is an open-label study. No blinding will be performed.

Participants will be allocated to the currently open treatment arm and cohort through IWRS assignment.

2.14. Statistics

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

This table defines the populations for analysis.

Population	Description
Entered - Addendum	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 allocated. (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 actually received.
Pharmacokinetic - Addendum	All participants who were allocated and received study intervention in the addendum and have evaluable PK sample. Participants will be analyzed according to the intervention they received.

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

3. References

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. National Institute of Allergy and Infectious Diseases. National Institutes of Health. US Department of Health and Human Services. Corrected version 2.1. July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed: 05 October 2020.

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