Protocol (b): J2W-MC-PYAA

# A Randomized, Placebo-Controlled, Double-Blind, Sponsor Unblinded, Single Ascending Dose, Phase 1 First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous LY3819253 in Participants Hospitalized for COVID-19

NCT04411628

Approval Date: 09-Jun-2020

# Title Page



**Protocol Title:** A Randomized, Placebo-Controlled, Double-Blind, Sponsor Unblinded, Single Ascending Dose, Phase 1 First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous LY3819253 in Participants Hospitalized for COVID-19

**Protocol Number: J2W-MC-PYAA**

**Amendment Number: (b)**

**Compound:** LY3819253

**Study Phase: 1**

**Short Title:** A randomized, placebo-controlled, Phase 1 study to evaluate LY3819253 in participants hospitalized for COVID-19

**Sponsor Name:** Eli Lilly and Company

**Legal Registered Address:** Indianapolis, Indiana USA 46285

**Regulatory Agency Identifier Number(s)**

IND: 150440

**Approval Date:**
Protocol Electronically Signed and Approved by Lilly on 09 May 2020
Protocol Amendment (a) Electronically Signed and Approved by Lilly on 01 June 2020.
Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 09-Jun-2020 GMT

**Medical Monitor Name and Contact Information will be provided separately.**

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Approval Date** |
| Original Protocol | 09 May 2020 |
| Amendment (a) | 01 June 2020 |

## Amendment (b)

## Overall Rationale for the Amendment:

This amendment addresses the United States Food and Drug Administration (FDA) feedback and clinical site feedback.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | Added text for Cohort 4 randomization | Providing information for all 4 cohorts. |
| 1.3 Schedule of Activities | Added clarification to laboratory tests and sample collection that documentation of hospital-based laboratory results are acceptable | Clarification for sites that hospital blood draws and results may be used for this study instead of duplicating blood draws. |
| 1.3 Schedule of Activities | Updated comment for the SARS-Cov-2 viral infection determination | Expanded the time of initial positive determination to 14 days prior to randomization |
| 1.3 Schedule of Activities | Pharmacodynamic sample instructions updated to include mid-turbinate method | Per site feedback |
| 4.2. Scientific Rationale for Study Design | Added text for Cohort 4 | Per FDA feedback. Clarification as to why the study may expand to include the optional Cohort 4. |
| 5.1. Inclusion Criteria | Updated Criterion #4 | Changed 72 hours to 14 days per site feedback. |
| 5.2. Exclusion Criteria | Updated Criterion #21 | Further clarification on timing of measurement |
| 5.2. Exclusion Criteria | Updated Criterion #24 | Clarification that chronic kidney disease is allowed based on the opinion of the investigator, but acute kidney disease is not allowed. |
| 8.6. Pharmacodynamics | Added text to allow mid-turbinate swab method. | Per site feedback |
| 9.5. Interim Analyses | Added text for Cohort 4 and further clarification on safety monitoring | In response to FDA feedback. |
| 10.2. Appendix 2 | Removed nasopharyngeal specific text for the pharmacodynamic sample | Nasopharyngeal or mid-turbinate swabs are now allowed |
| 10.8. Appendix 8 | Updated the contents to only contain the baseline severity categorization | For ease of use. |
| Throughout the protocol | Minor editorial and formatting changes | Minor, therefore not described |

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# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title**: A Randomized, Placebo-Controlled, Double-Blind, Sponsor Unblinded, Single Ascending Dose, Phase 1 First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous LY3819253 in Participants Hospitalized for COVID-19

**Rationale:**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which in critical cases results in progressive pulmonary failure, complications with acute respiratory distress syndrome (ARDS), and can result in death. There is an urgent need for effective therapeutics to modify disease outcomes.

LY3819253 is a neutralizing IgG1 monoclonal antibody (mAb) to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, and to neutralize the virus, potentially treating even established COVID-19 by providing a specific potent, neutralizing antibody to SARS-CoV-2.

Study J2W-MC-PYAA (PYAA) aims to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3819253 following a single dose of LY3819253 administered to participants hospitalized for COVID-19.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| Characterize the safety and tolerability of LY3819253 after intravenous infusion | • Safety assessments such as adverse events and serious adverse events |
| **Secondary** | |
| Characterize the pharmacokinetics of LY3819253 after intravenous infusion | • LY3819253 mean concentration on Day 29 |
| Characterize the pharmacodynamics of LY3819253 after intravenous infusion | • Change from baseline in SARS-CoV-2 viral load (Days 7, 11, 15 and 22)<br>• SARS-CoV-2 viral load AUC<br>• Time to SARS-CoV-2 clearance |

**Overall Design:**

Study PYAA is a Phase 1, double-blind, sponsor unblinded, randomized, placebo-controlled, single ascending dose study in participants hospitalized for Covid-19.

**Double-blind Treatment and Assessment Period**

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

- Participants are randomized to LY3819253 or placebo
- Site completes baseline procedures and sample collection
- Participants begin a single IV infusion of study intervention, and
- Site completes all safety monitoring and post-infusion sample collection.

**Discharge from hospital**

| If hospital discharge… | Then… |
|---|---|
| Occurs prior to Day 29 | participants will be asked to complete the remaining study assessments at the timepoints indicated in the SoA.<br>NOTE: Strategies to manage infection risks and reduce the burden of return visits should be considered by sites, such as home visits. |
| Occurs on the same day as a study assessment visit | hospital discharge assessments do not need to be repeated if the study assessments occurred within 8 hours of discharge and there has been no change in clinical status. |
| Does not occur at or prior to day 29 | assessments will continue to occur weekly up to Day 60 or until hospital discharge, whichever is sooner. |

**Post-treatment follow-up**

Post-treatment follow-up assessments will be conducted at Day 60. Strategies to manage infection risks and reduce the burden of return visits should be considered by sites, such as home visits.

**Disclosure Statement**: This is a first in human, sequential, single ascending dose study with up to 4 cohorts that is participant and investigator blinded.

**Number of Participants:**

Cohorts 1 – 3: Approximately 24 total participants.

Optional Cohort 4: up to 100 total participants.

**Intervention Groups and Duration: Single-Ascending Dose Design**

The study will comprise up to 4 dose cohorts.

Cohorts 1-3 will comprise at least 8 participants:

- 6 randomized to LY3819253 and
- 2 randomized to placebo.

Sentinel dosing will be utilized in any dose cohort that represents a dose increase from the preceding cohort. When sentinel dosing, the first 2 participants in each cohort will be randomized 1:1 to LY3819253 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 LY3819253 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 4 days after the IV infusion by the investigator(s), Lilly sponsor team, and an independent safety assessment committee (ISAC).

The investigator, Lilly sponsor team and ISAC are responsible for determining any dose decisions. The investigator(s) will remain blinded and the Lilly sponsor team and ISAC will be unblinded during these reviews. All available data from previous cohorts will be reviewed. Available PK and PD (virology) data may also be used to guide dose adjustment.

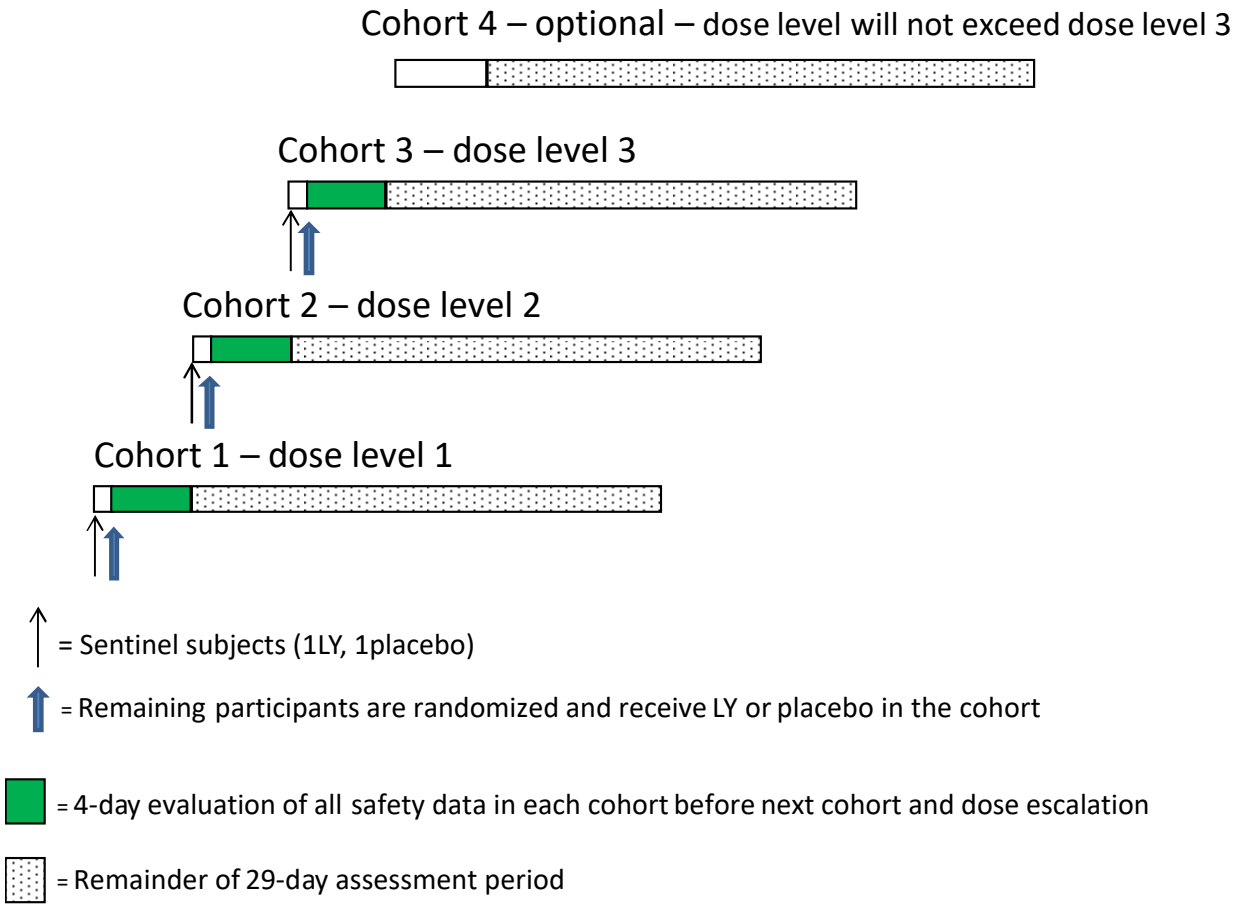
If temporary stopping criteria are met, dosing will be temporarily stopped, and no further participants will be dosed until a full safety review of the study has taken place. The ISAC will be engaged for the full safety review with the sponsor and investigator.

For the optional Cohort 4, up to 100 participants may be randomized in an approximate 1:1 ratio to receive either LY3819253 or placebo.

**Data Monitoring Committee: No**

This study will not have a data monitoring committee. There will be an ISAC.

## 1.2. Schema




Abbreviations: LY = Lilly study intervention

**Figure 1. Sequential single ascending dose schema of study J2W-MC-PYAA**

## 1.3. Schedule of Activities (SoA)

Assessments obtained previously as part of routine clinical care may be used as the baseline assessment as long as they were done no more than 48 hours before randomization.

| **Study J2W-MC-PYAA** | **Screening** | **Double-blind treatment and assessments** | | | | | | | | | **Discharge from hospital or ED** | **Follow-up if inpatient in hospital after Day 29** | **Post-treatment follow-up visit** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | | **1** | **2** | **3** | **4** | **7** | **11** | **15** | **22** | **29** | | Every 7 days until discharge or Day 60 | **60** | |
| **Visit window (± number of days)** | -2 | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 4 | |
| **Procedures** | | | | | | | | | | | | | | **Comments** |
| 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, and including timing of exposure and onset of symptoms suggestive of SARS-CoV-2 infection |
| Prior treatments of special interest within the last 2 weeks | X | | | | | | | | | | | | | NSAIDs, antivirals, antibiotics, antimalarials, corticosteroids, cytokine-directed therapy or other investigational treatments. |
| Tobacco use | | X | | | | | | | | | | | | Includes e-cigarettes. |
| Concomitant medications | | 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 | Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. |

| **Study J2W-MC-PYAA** | **Screening** | **Double-blind treatment and assessments** | | | | | | | | | **Discharge from hospital or ED** | **Follow-up if inpatient in hospital after Day 29** | **Post-treatment follow-up visit** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | | **1** | **2** | **3** | **4** | **7** | **11** | **15** | **22** | **29** | | Every 7 days until discharge or Day 60 | **60** | |
| **Visit window (± number of days)** | -2 | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 4 | |
| | | | | | | | | | | | | | | |
| **Physical Evaluation or Clinical Assessments** | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | Documentation of hospital-based exam is acceptable. |
| Symptom-directed physical exam | | X | X | X | X | X | X | X | X | X | X | X | | Documentation of hospital-based exam is acceptable. |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | Documentation of hospital-based exam is acceptable.<br>Includes: temperature, pulse rate, BP, respiratory rate, SpO2, and where applicable FiO2.<br>**Day 1** timing:<br>• immediately before the infusion,<br>• every 15 minutes during the infusion, as possible<br>• every 30 minutes for 2 hours after infusion and<br>• every 1 hour for the next 4 hours after infusion.<br>Automation may be used.<br>**All other study days:** once daily. |
| Single 12-lead ECG (local) | X | | | | | | | | | | | | | Documentation of hospital-based exam within 72 hours prior to dosing is acceptable. |

| **Study J2W-MC-PYAA** | **Screening** | **Double-blind treatment and assessments** | | | | | | | | | **Discharge from hospital or ED** | **Follow-up if inpatient in hospital after Day 29** | **Post-treatment follow-up visit** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | | **1** | **2** | **3** | **4** | **7** | **11** | **15** | **22** | **29** | | Every 7 days until discharge or Day 60 | **60** | |
| **Visit window (± number of days)** | -2 | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 4 | |
| Chest x-ray (local) | | X | | | | | | | | | | | | Day 1: enter interpretation of most recent chest CT scan or x-ray in CRF if done. No new imaging is required. |
| Hospitalization events | | X | X | X | X | X | X | X | X | X | X | X | | Includes:<br>• hospitalized<br>• ICU admittance, and<br>• discharge |
| Clinical status and concomitant procedures of special interest | | X | X | X | X | X | X | X | X | X | X | X | X | Includes:<br>Limitation on activities due to COVID-19 and requirements for:<br>• Ongoing hospital medical care<br>• Supplemental oxygen<br>• Non-invasive ventilation or high flow oxygen device<br>• Mechanical ventilation<br>• ECMO<br>• Additional organ support (e.g. pressors, renal replacement), or<br>• Consciousness status (ACVPU). |
| Clinical symptoms | | X | X | X | X | X | X | X | X | X | X | X | X | Including presence of fever, cough, shortness of breath at rest or on exertion |
| **Laboratory Tests and Sample Collection** | | | | | | | | | | | | | | |
| Hematology | X | X | | X | | X | X | X | X | X | X | X | | Documentation of hospital-based laboratory results are acceptable.<br>Local laboratory |

| **Study J2W-MC-PYAA** | **Screening** | **Double-blind treatment and assessments** | | | | | | | | | **Discharge from hospital or ED** | **Follow-up if inpatient in hospital after Day 29** | **Post-treatment follow-up visit** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | | **1** | **2** | **3** | **4** | **7** | **11** | **15** | **22** | **29** | | Every 7 days until discharge or Day 60 | **60** | |
| **Visit window (± number of days)** | -2 | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 4 | |
| Clinical Chemistry | X | X | | X | | X | X | X | X | X | X | X | | Documentation of hospital-based laboratory results are acceptable.<br>Local laboratory |
| eGFR | X | | | | | | | | | | | | | Local calculation using CKD-EPI |
| Lactate dehydrogenase (LDH) | | X | | X | | X | X | X | X | X | X | X | | Documentation of hospital-based laboratory results are acceptable.<br>Local laboratory |
| C-reactive protein | | X | | X | | X | X | X | X | X | X | X | | |
| Ferritin | | X | | X | | X | X | X | X | X | X | X | | |
| D-dimer | | X | | X | | X | X | X | X | X | X | X | | |
| Procalcitonin | | X | | X | | X | X | X | X | X | X | X | | |
| Troponin | | X | | X | | X | X | X | X | X | X | X | | |
| SARS-Cov-2 viral infection determination | X | | | | | | | | | | | | | Date and time of initial positive laboratory test was reported for COVID-19 infection ≤14 days prior to randomization<br>Local laboratory |
| Serum pregnancy | X | | | | | | | | | | | | | Only for WOCBP (Section 10.4 Appendix 4) Local laboratory |
| Urine pregnancy | | | | | | | | | | | | | X | Only for WOCBP (Section 10.4 Appendix 4) Local laboratory |
| Pharmacokinetic (PK) sample | | X | | | X | | | X | | X | X | X | X | Day 1: before the infusion and anytime just prior to the end of infusion.<br>All other scheduled samples may be taken at any time during that scheduled day.<br>Lilly-designated laboratory |

| **Study J2W-MC-PYAA** | **Screening** | **Double-blind treatment and assessments** | | | | | | | | | **Discharge from hospital or ED** | **Follow-up if inpatient in hospital after Day 29** | **Post-treatment follow-up visit** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | | **1** | **2** | **3** | **4** | **7** | **11** | **15** | **22** | **29** | | Every 7 days until discharge or Day 60 | **60** | |
| **Visit window (± number of days)** | -2 | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 4 | |
| Immunogenicity (ADA) sample | | X | | | | | | X | | X | X | X | X | Day 1: before the infusion.<br>All other scheduled and unscheduled immunogenicity samples should be collected with a time-matched PK sample.<br>Lilly-designated laboratory |
| Pharmacodynamic sample | | X | | X | | X | X | X | X | X | X | X | | SARS-Cov-2 swab<br>Methods include nasopharygeal (preferred) or mid-turbinate.<br>The same method of sample collection must be used per participant for the duration of the study. Switching methods is not allowed.<br>Day 1: before the infusion.<br>Lilly-designated laboratory |
| Exploratory biomarker samples | | X | | X | | X | X | X | X | X | X | X | | Day 1: before the infusion<br>Lilly-designated laboratory |
| Pharmacogenetics sample | | X | | | | | | | | | | | | Lilly-designated laboratory |
| **Randomization and Dosing** | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Administer study intervention (IV infusion) | | X | | | | | | | | | | | | |

Abbreviations: ACVPU = alert, consciousness, verbal, pain, unresponsive scale; ADA = anti-drug antibody; BP = blood pressure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ED = early discontinuation; FiO2 =

fraction of inspired oxygen in the air; ICU = intensive care unit; IV = intravenous; NSAIDS = non-steroidal anti-inflammatory drugs; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen; WOCBP = women of child-bearing potential.

# 2. Introduction

The efficient community spread of SARS-CoV-2 has resulted in the current pandemic of COVID-19, which in severe and critical cases results in progressive pulmonary infection, complicated by respiratory failure, with a high prevalence of acute respiratory distress syndrome. Although several therapies have been explored in severe COVID-19, none have improved survival, including antivirals, glucocorticoids, and immunoglobulins (Liu et al 2020).

The SARS-CoV-2 gains entry to cells through binding of the spike (S) protein to ACE2 receptors on cells (Hoffmann 2020). 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.

LY3819253 is a neutralizing IgG1 monoclonal antibody (mAb) to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, and to neutralize the virus, potentially treating even established COVID-19 by providing a specific potent, neutralizing antibody to SARS-CoV-2. The blocking of viral entry into respiratory cells and viral replication, and viral neutralization is expected to mitigate the severity of disease in patients in whom ongoing viral spread and replication is the primary driver of COVID-19 pathophysiology. The decrease in viral replication may also shorten a patient's extent and duration of viral shedding and transmission, positively impacting public health.

## 2.1. Study Rationale

LY3819253 is a neutralizing IgG1 mAb to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, and to neutralize the virus, potentially treating even established COVID-19 by providing a specific potent, neutralizing antibody to SARS-CoV-2.

Study J2W-MC-PYAA (PYAA) aims to investigate the safety, tolerability, PK, and PD of LY3819253 following a single dose administered to participants hospitalized for COVID-19. The data from this study will inform decisions for the clinical development of LY3819253.

## 2.2. Background

The global spread of SARS-CoV-2 has resulted in the current pandemic of COVID-19, which in critical cases results in progressive pulmonary failure, complications with ARDS and can result in death.

The SARS-CoV-2 gains entry to cells through binding of the spike (S) protein to ACE2 receptors on cells (Hoffmann 2020). By binding to the S protein, LY3819253 is designed to block interaction with the ACE2 receptors, interfering with viral attachment and entry into human cells, and is also designed to neutralize SARS-CoV-2. These antiviral effects are expected to result in a clinically important decrease in viral replication, mitigating the severity of disease in patients for whom ongoing viral replication is the primary driver of COVID-19 pathophysiology.

Given the current public health emergency and the urgency to discover therapies for COVID-19, additional nonclinical efficacy and safety studies will be conducted in parallel with the first clinical studies. Nonclinical data will be shared as it becomes available.

## 2.3. Benefit/Risk Assessment

LY3819253 has not been administered to humans. Nonclinical information for LY3819253 is described in the Investigator's Brochure (IB).

The potential benefit to humans with COVID-19 disease is considered greater than the likelihood of anticipated and unanticipated risk.

Anticipated risk is considered low and is based on the known mechanism of action for human derived neutralizing antibodies in acute viral disease states. LY3819253 consists of a highly specific mAb directed at foreign (non-human) epitope(s) and will be given to infected patients as a single dose in a controlled, hospitalized setting. The complementarity determining regions (CDRs) of the mAb were derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient and, thus, have undergone natural positive and negative selection pressures *in vivo*, unlike humanized antibodies generated in mice. Therefore, off-target binding and tissue cross-reactivity are considered unlikely.

A theoretical risk is that LY3819253 may cause antibody-dependent enhancement (ADE) of viral replication. This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronaviral infections, such as SARS and MERS, and has not been reported to date with SARS-CoV-2. Additionally, limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 disease has not indicated safety concerns (Shen, 2020; Duan, 2020). LY3819253 will be administered to patients at sufficiently high dose levels to neutralize SARS-CoV-2 and avoid sub-neutralizing concentrations in the presence of virus that are typically associated with ADE.

Additional manageable risks associated with most therapeutic mAbs are the potential for infusion-related hypersensitivity and cytokine release reactions. The single infusion in this study will be at a controlled rate, the study participants will be monitored in the hospital setting, and adjustments in the infusion rate will be made and/or the infusion stopped, if indicated.

Overall, these risks to patients with COVID-19 disease, for which there is no established standard of care treatment, are considered monitorable and manageable in the hospital setting, and the potential benefit outweighs the risks.

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

# 3. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| Characterize the safety and tolerability of LY3819253 after intravenous infusion | • Safety assessments such as AEs and SAEs |
| **Secondary** | |
| Characterize the pharmacokinetics of LY3819253 after intravenous infusion | • LY3819253 mean concentration on Day 29 |
| Characterize the pharmacodynamics of LY3819253 after intravenous infusion | • Change from baseline in SARS-CoV-2 viral load (Days 7, 11, 15 and 22)<br>• SARS-CoV-2 viral load AUC<br>• Time to SARS-CoV-2 clearance |
| **Tertiary/Exploratory** | |
| Characterize the participant's clinical status | • Duration (days) of hospitalization<br>• Proportion (percentage) of participants admitted to ICU<br>• Proportion (percentage) of participants requiring mechanical ventilation<br>• Score using the NIAID and WHO ordinal scales at pre-specified time points<br>• Proportion (percentage) of participants with at least a 2-point improvement on the NIAID and WHO ordinal scale or live discharge from hospital at pre-specified time points<br>• NEWS2 score at pre-specified time points<br>• Proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 15 |
| Characterize the pharmacodynamics of LY3819253 after intravenous infusion | • Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, 22) |
| Characterize emergence of viral resistance to LY3819253 | • Comparison from baseline to Day 29 |

Abbreviations: AE = adverse event; ICU = intensive care unit; NIAID = National Institute of Allergy and Infectious Diseases; NEWS2 = National Early Warning Score; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

# 4. Study Design

## 4.1. Overall Design

Study PYAA is a Phase 1, double-blind, sponsor unblinded, randomized, placebo-controlled, single-ascending dose study.

**Screening**

Interested hospitalized 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.

**Double-blind Treatment and Assessment Period**

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

- Participants are randomized to LY3819253 or placebo
- Site completes baseline procedures and sample collection
- Participants begin a single IV infusion of study intervention, and
- Site completes all safety monitoring and post-infusion sample collection.

**Discharge from hospital**

Participants discharged from the hospital will complete study procedures outlined in the SoA.

| If hospital discharge… | Then… |
|---|---|
| Occurs prior to Day 29 | participants will be asked to complete the remaining study assessments at the timepoints indicated in the SoA.<br>NOTE: Strategies to manage infection risks and reduce the burden of return visits should be considered by sites, such as home visits. |
| Occurs on the same day as a study assessment visit | hospital discharge assessments do not need to be repeated if the study assessments occurred within 8 hours of discharge and there has been no change in clinical status. |
| Does not occur at or prior to day 29 | assessments will continue to occur weekly up to Day 60 or until hospital discharge, whichever is sooner. |

**Post-treatment follow-up**

Post-treatment follow-up assessments will be conducted at Day 60. Strategies to manage infection risks and reduce the burden of return visits should be considered by sites, such as home visits.

### 4.1.1. Single-Ascending Dose Design

The study will comprise up to 4 dose cohorts.

Planned dosing information is provided in Section 6.1.

Dose escalation criteria are provided in Section 6.6.1.

Temporary stopping criteria are provided in Section 6.6.2

Cohorts 1 - 3 will comprise at least 8 participants:

- 6 randomized to LY3819253 and
- 2 randomized to placebo.

Sentinel dosing will be used in any dose cohort that represents a dose increase from the preceding cohort. The first 2 participants in each cohort will be randomized 1:1 to LY3819253 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 LY3819253 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 4 days after the IV infusion by the investigator(s) and Lilly sponsor team.

Cohort 4 may be initiated, at the discretion of the sponsor team, if more data is needed to inform the dose of LY3819253.

## 4.2. Scientific Rationale for Study Design

This study is the first investigation of LY3819253 in humans. The study is designed to explore a range of doses that will inform the clinical drug development plan for LY3819253.

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

The 4-day safety review after dosing is sufficient to monitor for an acute adverse immune response to treatment with LY3819253.

The optional, expansion Cohort 4 allows for additional data collection to detect reduction in the rate of clinical worsening.

In accordance with FDA recommendation (20 March 2020 Pre-IND Meeting), the population for this study are hospitalized patients infected with SARS-CoV-2.

Participants enrolling to this study will have moderate to severe COVID-19 illness according to the Food and Drug Administration (FDA) definitions (FDA resource page [WWW]), but with notable exception in the specific eligibility criterion #21 for severe participants. This exception is intended to limit the severity of the participant enrolling to this study to exclude those at highest risk of respiratory failure. Lilly believes the optimal benefit:risk for LY3819253 may be found in a participant that does not have impending respiratory failure, as this severity of patients with COVID-19 have primary pathology associated with overexuberant inflammatory response where LY3819253 is less likely to be effective. Further, adverse events in this population could potentially confound our ability to discern safety signals in this study.

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

## 4.3. Justification for Dose

The dose levels selected for this study are designed to explore a wide exposure-response range that potentially encompasses a therapeutic dose, and will provide the safety and tolerability underpinnings for the clinical drug development plan for LY3819253.

Up to 4 cohorts will be enrolled to characterize the dose response of LY3819253 on safety, tolerability, PK and PD markers. The first 3 cohorts will explore the efficacious dose range (2 doses) and 1 supratherapeutic dose. The planned dose levels for LY3819253 are 700 mg, 2800 mg and 7000 mg.

Cohort 4 is optional and may be used to characterize the dose-response relationship for dose selection in subsequent studies. The dose for Cohort 4 may be evaluated at a lower or equal level to the maximum investigated dose but will not exceed 7000 mg.

The doses are determined based on these key variables:

- projected human PK of the mAb, including lung tissue distribution
- in vitro binding potency to the viral targets
- neutralization of virus cell entry and replication, and
- antibody-viral dynamic modeling and simulation.

The projected human half-life is expected to be approximately 19 days based on PK/PD modeling.

The starting dose of 700 mg is expected to have a sustained concentration above the *in vitro* IC90 of viral cell-entry neutralization for at least 28 days. The maximum dose of 7000 mg is selected due to uncertainty in model predicted PK concentrations, viral load reduction and consideration of infusion volume in participants.

The dose levels are fixed, not body weight based. Given the planned dose levels, the predicted impact of body weight on therapeutic response will be minimal.

## 4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all required phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant.

# 5. 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 and the setting of this research study, verbal interview of a potential participant, their legal representative or family member, may be the source for preexisting conditions and medical history unless otherwise specified within the eligibility criteria.

## 5.1. Inclusion Criteria

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

**Age**

1. Are ≥18 and ≤85 years of age at the time of randomization

**Type of Participant and Disease Characteristics**

2. In the judgement of the investigator, have moderate or severe COVID-19 illness per the FDA resource page (WWW) (Section 10.8, Appendix 8)
3. This criterion was removed
4. Are hospitalized, or in the process of being admitted to hospital, and have an initial laboratory determination of current COVID-19 infection ≤14 days of randomization.

**Sex**

5. Are men or non-pregnant women
   Reproductive and Contraceptive agreements and guidance is provided in Section 10.4, Appendix 4.
6. Criterion 6 merged with criterion 5.

**Study Procedures**

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

**Informed Consent**

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

## 5.2. Exclusion Criteria

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

**Medical Conditions**

10. Require invasive mechanical ventilation or anticipated impending need for invasive mechanical ventilation
11. Anticipate transfer to another hospital which is not a study site within 5 days of randomization

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. Were resident in a nursing home or long-term care facility immediately prior to current hospitalization
15. 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
16. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
17. Have prior history of hepatic impairment, such as
    a. severe liver cirrhosis Child-Pugh B or worse
    b. cirrhosis with a history of hepatic encephalopathy
    c. clinically meaningful ascites requiring ongoing treatment with diuretics and/or paracentesis, or
    d. history of hepatorenal syndrome.
18. Have any serious concomitant systemic disorder that, in the opinion of the investigator, would preclude participation in the study
19. Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product
20. Received convalescent COVID-19 plasma treatment prior to enrollment

**Diagnostic assessments**

21. Have an SpO2 <88% while breathing room air at rest. If on supplemental oxygen at the time of screening, use the last time point of measurement on room air up to 48 hours prior
22. This criterion was removed
23. Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5X upper limit of normal (ULN)
24. Have acute kidney disease with an eGFR <30 mL/min/1.73 $m^2$ based on the chronic kidney disease epidemiology collaboration equation (CKD-EPI).
    Chronic kidney disease is allowable, if judged to be stable for the past 3 months, in the opinion of the investigator.

**Other Exclusions**

25. Are pregnant or breast feeding
26. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
27. Are Lilly employees
28. Are investigator site personnel directly affiliated with this study or their immediate families.

## 5.3. Lifestyle Considerations

Reproductive and Contraceptive guidance is provided in Section 10.4, Appendix 4.

## 5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

Repeating laboratory tests during the screening period does not constitute rescreening.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

# 6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

This is a single dose study.

| **Intervention Names** | **LY3819253** | **Placebo** |
|---|---|---|
| **Type** | Biologic | Not applicable |
| **Dose Formulation** | solution | 0.9% Sodium chloride solution |
| **Unit Dose Strength(s)** | 700 mg/vial | Placebo |
| **Planned Dosage Level(s)** | Cohort 1: 700 mg<br>Cohort 2: 2800 mg<br>Cohort 3: 7000 mg<br>Optional Cohort 4 may explore lower or equal levels to the max investigated dose, but will not exceed 7000 mg. | Not applicable |
| **Route of Administration** | IV infusion | IV infusion |
| **Use** | experimental | placebo |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | From Lilly | Commercially available 0.9% sodium chloride solution will be used as a placebo for this study |
| **Packaging and Labeling** | Study Intervention will be provided in glass vials and will be labeled appropriately | Commercially available 0.9% sodium chloride solution will be used as a placebo for this study |

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

This table describes the infusion volume and rate for the planned LY3819253 doses. Cohort 4 instructions will be provided in the pharmacy instructions. Placebo volume and rate will match the LY3819253 dose cohort.

| LY3819253 Dose (mg) | Volume (mL) | Start Infusion rate x Time |
|---|---|---|
| 700 | 50 | 100 mL/hr x 30 min |
| 2800 | 75 | 100 mL/hr x 45 min |
| 7000 | 100 | 100 mL/hr x 60 min |

The infusion rate may be reduced as deemed necessary if an infusion reaction is observed.

During the infusion, vital signs will be monitored every 15 minutes as described in the SoA.

After completion of the infusion, participants will be monitored every 30 minutes for 2 hours and then every 1 hour for the next 4 hours.

The site must have resuscitation equipment, emergency drugs and appropriately training staff available during the infusion and for at least 4 hours after the completion of the infusion.

### 6.1.1. Special Treatment Considerations

#### 6.1.1.1. Premedication for Infusions

Premedication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to use premedication for other cohorts if the frequency of infusion reactions among participants warrants it.

If minor infusion reactions are observed, but review of the data suggests that dose escalation may continue, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and sponsor and recorded in the study documentation, along with the dose-escalation decision.

Any premedications given will be documented as a concomitant therapy.

#### 6.1.1.2. Management of Infusion Reactions

All participants should be monitored closely, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

**Symptoms and Signs**

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions severity will be assessed and reported using the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

This table describes the severity of reactions according to DAIDS.

| Parameter | Mild | Moderate | Severe | Severe and Potentially Life-threatening |
|---|---|---|---|---|
| Acute Allergic Reaction | Localized urticaria (wheals) with no medical intervention indicated | Localized urticaria with intervention indicated<br>OR<br>Mild angioedema with no intervention indicated | Generalized Urticaria<br>OR<br>Angioedema with intervention indicated<br>OR<br>Symptoms of mild bronchospasm | Acute anaphylaxis<br>OR<br>Life-threatening bronchospasm<br>OR<br>Laryngeal edema |
| Cytokine Release Syndrome[a] | Mild signs and symptoms<br>AND<br>Therapy, that is, antibody infusion interruption not indicated | Therapy indicated (that is, antibody infusion) interruption indicated<br>AND<br>Responds promptly to symptomatic treatment<br>OR<br>Prophylactic medications indicated for ≤24 hours | Prolonged severe signs and symptoms<br>OR<br>Recurrence of symptoms following initial improvement | Life-threatening consequences (for example, requiring pressor or ventilator support) |

[a] = A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

Source: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (July 2017).

### Site Needs

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

### Management of Infusion Reactions

Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms.

If a participant permanently discontinues from study intervention, they should complete adverse event (AE) monitoring and other procedures as stated in the SoA.

#### 6.1.1.3. In the Event of a Retrospective Positive Sterility Finding from Prepared Study Intervention

If a positive sterility finding occurs in the terminally sterile filtered study intervention, the participants who were dosed from the impacted batch should be contacted immediately and undergo a full physical examination including, but not limited to, blood pressure, pulse rate and body temperature.

A blood sample should be collected for culture and assayed for inflammatory markers such as C-reactive protein and elevations in white blood cell counts.

If the signs and symptoms indicated a participant has a possible infection, they will be clinically managed, treated and followed up until resolution. Any adverse events will be recorded as appropriate.

## 6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

To protect blinding, the interventions must be prepared by an unblinded site personnel qualified to prepare study intervention who are not involved in any other study-related procedures. Instructions for preparation will be provided by the sponsor.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

This is a blinded study.

All participants will be centrally randomized to study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

This table describes general procedures for unblinding.

| | |
|---|---|
| Unblinding (IWRS) | • Emergency unblinding for adverse events may be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS<br>• In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted<br>• Participant safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the sponsor in advance of unblinding<br>• If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance<br>• The date and reason that the blind was broken must be recorded in the source documentation and case report form. |

Abbreviations: IWRS = interactive web-response system.

If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion stopped. If any amount of study intervention was administered, follow procedures according to the SoA as described in Section 7.1.

## 6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the case report form (CRF).

## 6.5. Concomitant Therapy

### Prior Treatment for Indication

Any prior therapy, such as antivirals, antibiotics, or antimalarials used as treatment prior to signing informed consent should be recorded.

Therapy prior to enrollment with antivirals including lopinavir/ritonavir, remdesivir or other therapeutic agents (e.g. corticosteroids) are permitted.

Convalescent COVID-19 plasma treatment is not allowed prior to enrollment.

### Concomitant Therapy

Participants should be treated according to standard of care, even as it evolves, and medications may be part of the treatment paradigm. Therefore, remdesivir may be initiated as standard of care for participants hospitalized with severe disease (if available through the FDA Emergency Use Authorizations) outside of local standard of care per written policies or guidelines.

If the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) includes lopinavir/ritonavir, chloroquine, hydroxychloroquine or other investigational agents, then initiating these during the study is permitted, but may require additional safety monitoring by the site.

Convalescent COVID-19 plasma treatment is not allowed.

Any medication, investigational agent, or vaccine, including over the counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency for concomitant therapy of special interest

Acetaminophen and corticosteroid use are permitted at any time during the study.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor if required.

The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

## 6.6. Dose Modification

### 6.6.1. Dose Escalation Criteria

By nature of being a Phase 1 sponsor unblinded dose-escalation study, data will be evaluated on an ongoing basis until the highest planned dose has been administered.

The decision to dose the next cohort 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 4 days after the IV infusion by the investigator(s), Lilly sponsor team and an independent safety assessment committee (ISAC).

The investigator, Lilly sponsor team and ISAC are responsible for determining any dose decisions. The investigator(s) will remain blinded and the Lilly sponsor team and ISAC will be unblinded during these reviews. All available data from previous cohorts will be reviewed. Available PK and PD data may also be used to guide dose adjustment.

If temporary stopping criteria are met (Section 6.6.2), dosing will be temporarily stopped and no further participants will be dosed until a full safety review of the study has taken place. The ISAC will be engaged for the full safety review with the sponsor and investigator.

### 6.6.2. Temporary Stopping Criteria

Dosing will be temporarily halted, and no further participants will be dosed until a full 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 infusion (see Table in Section 6.1.1.2), during or within 2 hour of completion of the infusion, 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 acute 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.

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

| Topic | 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 |

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

## 6.7. Intervention after the End of the Study

No continued access is planned after completion of this study, as additional efficacy would be needed to demonstrate continued access criteria.

# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

These sections describe reasons for a participant's

- permanent or temporary discontinuation of study drug, or
- discontinuation (withdrawal) from the study.

Discontinuation of specific sites or of the trial as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Section 10.1. Appendix 1.

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If the IV infusion is permanently stopped, the participant will remain in the study for follow-up and further evaluations as described in the SoA.

## 7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

### 7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue study treatment.

If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product.

Safety follow up is as outlined in

- Section 1.3 (Schedule of Activities),
- Section 8.2 (Safety Assessments), and
- Section 8.3 (Adverse Events and Serious Adverse Events).

## 7.3. Lost to Follow up

A participant will be considered lost to follow-up if, after discharge from the hospital, they do not return for scheduled visits and are unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

# 8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed.

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.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 8.1. Efficacy Assessments

This section is not applicable for this study.

## 8.2. Safety Assessments

### 8.2.1. Physical Examinations

A complete physical examination will be performed at the screening visit. This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

A symptom-directed physical examination will be performed at other visits, as specified in the SoA and as clinically indicated.

Investigators should pay special attention to clinical signs related to COVID-19, to ongoing medical conditions and to previous serious illnesses.

### 8.2.2. Vital Signs

Vital signs will be measured as specified in the SoA 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.

Additional vital signs may be measured during the study if warranted, as determined by the investigator.

### 8.2.3. Electrocardiograms

A single, local, 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and corrected QT intervals. Additional ECG readings may occur at investigator discretion.

### 8.2.4. Clinical Laboratory Assessments

See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

The investigator or appropriate designee must review the laboratory report, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Documentation of the review may be completed according to institution processes or by making an entry in the participants' progress notes (medical record) stating that the laboratory results have been reviewed.

The laboratory reports must be filed with the source documents unless a source document agreement or comparable document cites an electronic location that accommodates the expected retention duration.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event [SAE] or AE or dose modification), then the results must be recorded in the CRF.

**Pregnancy Testing**

Women of childbearing potential (WOCBP) must undergo pregnancy testing according to the SoA. Participants who are pregnant will be discontinued from the study (Section 7.2).

### 8.2.5. Hospitalization events

The date of hospitalization events will be recorded in the CRF and includes when the participant is hospitalized, admitted to the ICU, discharged from the ICU, discharged from the hospital, admitted to an extended care facility, discharged to home.

### 8.2.6. Procedures of Special Interest

The participants' clinical status and concurrent procedures of special interest will be recorded in the CRF and include limitation on activities due to COVID-19 and requirements for

- ongoing hospital medical care
- supplemental oxygen
- non-invasive ventilation or a high flow oxygen device
- mechanical ventilation
- ECMO
- additional organ support (e.g. pressors, renal replacement), or
- consciousness status using alert, consciousness, verbal, pain, unresponsive scale (ACVPU).

### 8.2.7. Respiratory Support

Once enrolled in the study, participants may be managed with high-flow nasal cannula, noninvasive positive pressure ventilation or any other form respiratory support as needed per investigator discretion.

## 8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study.

Discontinuation information is in Section 7.

Detailed AE definitions and procedures are in Section 10.3

AEs and SAEs related to COVID-19 are subject to different reporting requirements detailed in Section 10.3.1.

### 8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time of signing of the informed consent form (ICF) until participation in the study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving study intervention, it needs to be reported within the SAE reporting timeframe if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3, Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

### 8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it with the Investigator's Brochure, and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.3.5. Pregnancy

Although normal pregnancy is not an adverse event, details of all pregnancies in female participants will be collected for 90 days after dosing.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4, Appendix 4.

Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.

### 8.3.6. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions.

If such a reaction occurs, additional details describing each symptom should be provided to the sponsor in the infusion-related reaction/hypersensitivity CRF.

If symptoms and/or signs occur during or within 6 hours after infusion of LY3819253 and are believed to be hypersensitivity or due to cytokine release, then investigators are encouraged to report the event as infusion-related immediate hypersensitivity reaction or cytokine release-associated infusion reaction, respectively.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Section 10.6, Appendix 6, "Recommended Laboratory Testing for Hypersensitivity Events". Laboratory results are provided to the sponsor via the central laboratory.

In case of skin lesions or rash consistent with vasculitis, efforts should be made to perform the following as soon as possible

- dermatology consultation
- skin biopsy, and
- photographs of lesions of interest, including skin biopsy site.

### 8.3.7. Infusion-related Reactions

As with other mAbs, infusion-related reactions may occur during or following LY3819253 administration. If an infusion-related reaction occurs, additional data describing each symptom and sign should be provided to the sponsor in the CRF.

This table describes the location of infusion-related reaction information in this protocol.

| Topic | Location |
|---|---|
| Special treatment considerations | Section 6.1.1 |
| Premedication for infusions | Section 6.1.1.1 |
| Management of infusion reactions | Section 6.1.1.2 |
| DAIDS table describing severity | Section 6.1.1.2 |

Symptoms occurring during or after infusion of study intervention may also be defined according to AE categories such as acute allergic reaction or cytokine release syndrome (refer to DAIDS).

### 8.3.8. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention.

The sponsor collects product complaints on study interventions used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study intervention so that the situation can be assessed.

NOTE: Any AEs or SAEs that are associated with a product complaint will follow the processes outlined in Section 8.3.3 and Appendix 10.3 of the protocol.

**Time Period for Detecting Product Complaints**

Product complaints that result in an adverse event will be detected, documented, and reported to the sponsor during all periods of the study in which the study intervention is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to the study intervention, the investigator will promptly notify the sponsor.

**Prompt Reporting of Product Complaints to Sponsor**

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

**Follow-up of Product Complaints**

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

## 8.4. Treatment of Overdose

In case of suspected overdose, participants should be monitored for any signs or symptoms of adverse reactions or effects, and supportive care should be provided as necessary.

## 8.5. Pharmacokinetics

Venous blood samples will be collected as specified in the SoA for determination of concentrations of LY3819253 used to evaluate the PK for LY3819253.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.

Instructions for the collection and handling of biological samples will be provided by Lilly.

Site personnel will record

- The date and time (24-hour clock time) of administration (start and end of infusion), and
- The date and time (24-hour clock time) of each PK sample.

It is essential that the times are recorded accurately.

### 8.5.1. Bioanalytical

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3819253 will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated subjects are not planned.

Sample retention is described in Appendix 1, Section 10.1.12. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

## 8.6. Pharmacodynamics

The SARS-CoV-2 viral RNA level and viral clearance will be evaluated by either a nasopharyngeal swab or mid-turbinate swab at times specified in the SoA. The same method of sample collection must be used per participant for the duration of the study. Switching methods for a participant is not allowed.

The nasopharyngeal swab is the preferred method and will be taken from both nostrils. The nasopharyngeal procedure is described in Section 10.7.

Sample retention is described in Section 10.1.12. Remaining samples may be used for additional exploratory studies to better understand LY3819253 and the disease, which may include sequencing and/or culture of the virus for future studies.

## 8.7. Genetics

A whole blood sample will be collected for pharmacogenetic analysis where local regulations allow.

See Section 10.2 Clinical Laboratory Tests, and Section 1.3 SoA for sample collection information.

See Section 10.5 for genetic research, custody, and sample retention information.

## 8.8. Biomarkers

Blood samples will be collected from all participants for analysis of immune system-related markers. Serum, whole blood for cellular and/or epigenetic analysis, and whole blood RNA samples for exploratory biomarker research will be collected at the time specified in the SoA where local regulations allow.

Samples will be stored and analysis may be performed on biomarkers thought to play a role in immune system related responses to viral infection including, but not limited to, immune pathways, cellular composition, serum analytes, or epigenetic biomarkers, to evaluate their association with observed clinical responses to LY3819253 and the disease state.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the intervention target (S protein), the COVID-19 disease state, pathways associated with disease, and/or the mechanism of action of the study intervention.

Sample retention is described in Section 10.1.12.

## 8.9. Immunogenicity

**Visits and times**

At the visits and times specified in the SoA, venous blood samples will be collected to determine antibody production against LY3819253. The actual date and time (24-hour clock time) of each sample collection will be recorded.

**Sample collection, handling, and use**

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3819253 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253.

**Sample retention**

Sample retention is described in Section 10.1.12.

## 8.10. Health Economics

This section is not applicable for this study.

# 9. Statistical Considerations

## 9.1. Statistical Hypotheses

This is an exploratory study with a primary objective of assessing safety and tolerability. Any hypothesis tests conducted for treatment comparisons will be exploratory in nature and conducted without adjustment for multiplicity.

## 9.2. Sample Size Determination

For Cohorts 1 – 3, approximately 24 participants will be randomized to receive one of three dose levels of LY3819253 or placebo. Additional participants may be required to ensure a minimum of 8 participants in each cohort complete 7 days of study assessments. Up to a maximum of 3 additional participants per cohort may be added.

Participant viral loads over time were simulated using a representative PK/PD model to enable a Monte Carlo assessment of the power of the trial to detect a 30% treatment difference in mean AUC (28 day) of viral load. This assessment revealed greater than 90% probability of meeting the following Bayesian critical success factor:

$$\Pr((\text{mean } AUC_{PL} - \text{mean } AUC_{LY})/\text{ mean } AUC_{PL} > 0.3) > 0.60$$

PL = placebo, LY = LY3819253

Additionally, the anticipated 6 participants per treatment provides greater than 80% probability (within each treatment arm) of observing safety events of reasonable prevalence (that is, at least 25%) to support the primary objective of safety assessment.

For the optional Cohort 4, up to 100 participants may be randomized in an approximate 1:1 ratio to receive either LY3819253 or placebo. The overall numbers of participants randomized to LY3819253 and placebo in this study will provide 60% power to detect a reduction in the rate of clinical worsening from 22% to 9% (one-sided alpha=0.05). Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 15.

A participant is only allowed to receive one IV infusion in one cohort.

## 9.3. Populations for Analyses

This table defines the populations for analysis.

| Population | Description |
|---|---|
| Entered | All participants who sign the informed consent form |
| Safety | All participants randomly assigned and who received study intervention. Participants will be analyzed according to the intervention they actually received. |
| Pharmacokinetic | All randomized participants who received study intervention and have evaluable PK sample. Participants will be analyzed according to the intervention they actually received. |
| Pharmacodynamic | All randomized participants who received study intervention and provided at least one post-baseline measure for the relevant endpoint. Participants will be analyzed according to the intervention they actually received. |

## 9.4. Statistical Analyses

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

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to the first participant dosed and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

### 9.4.1. General Considerations

This table describes the general statistical methods that may be used in this study.

| **Method** | **Analysis** |
|---|---|
| Descriptive Statistics | number of participants, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures |
| Kaplan-Meier curves and summary statistics | Time-to-event analysis |
| Logistic regression analysis | Treatment comparisons of binary variables with treatment in the model. |
| Nonparametric<br>(for example, Mann-Whitney or van Elteren tests) | Treatment comparison of ordinal variables. |
| Analysis of variance or analysis of covariance | Treatment comparisons of continuous variables following appropriate transformations, if necessary |

Adjustments for other factors, if any, will be described in the SAP.

### 9.4.2. Safety Analyses

Safety analyses will be conducted using the safety population described above.

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with intervention as perceived by the investigator. Adverse events reported prior to randomization will be distinguished from those reported as new or increased in severity during the study post-randomization.

Safety parameters that will be assessed include, but are not limited to, safety laboratory parameters, and vital signs. The parameters will be summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

### 9.4.3. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on data from all participants who receive intervention and have evaluable PK.

Pharmacokinetic parameter estimates for LY3819253 will be calculated using standard noncompartmental methods of analysis.

The primary parameter for analysis will be mean concentration on Day 29. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

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 7, 11, 15 and 22)
- Viral load AUC
- Time to SARS-CoV-2 clearance, and
- Proportion of participants that achieve SARS-CoV-2 clearance.

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

### 9.4.4. Exploratory Endpoints

Exploratory endpoints will be summarized using descriptive methodology and treatment comparisons conducted using methods previously described.

Endpoints will include:

- Duration (days) of hospitalization
- Proportion (percentage) of participants admitted to ICU
- Proportion (percentage) of participants requiring mechanical ventilation
- Score on the NIAID ordinal scale at pre-specified time points
- Score on the WHO ordinal scale at pre-specified time points
- Proportion (percentage) of participants with at least a 2-point improvement on the WHO ordinal scale or live discharge from hospital, at pre-specified time points
- Proportion (percentage) of participants with at least a 2-point improvement on the NIAID ordinal scale or live discharge from hospital at pre-specified time points
- NEWS2 score at pre-specified time points
- Proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 15, and
- Comparison from baseline to Day 29 for the emergence of viral resistance to LY3819253.

Mortality and categorical changes on the ordinal scale will be analyzed as discrete variables.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, pharmacodynamic, or

population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

### 9.4.5. Immunogenicity

If data from validated immunogenicity assays are available, treatment-emergent anti-drug antibodies (TE-ADAs) may be assessed.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADA and who are TE-ADA positive (TE-ADA+) to LY3819253 will be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the TE-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, PD response or safety to LY3819253 may also be assessed. Additional details may be provided in the SAP.

## 9.5. Interim Analyses

Periodic, unblinded reviews of PK, PD and safety data will occur throughout the study in addition to the scheduled dose escalation reviews.

If Cohort 4 proceeds, then up to 4 interim analyses may occur.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by the ISAC. Details of the unblinded safety reviews, including the frequency and approximate timing, are specified in the ISAC charter.

The approximate timing, decision criteria, and statistical methods associated with each possible modification to the ongoing study will be fully described in the SAP and ISAC Charter and finalized prior to the first study unblinding.

## 9.6. Data Monitoring Committee (DMC)

This study will not have a data monitoring committee. Independent safety assessment committee information is in Section 10.1.5 and the ISAC charter.

# 10. Supporting Documentation and Operational Considerations

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, and
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

The investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

Due to strict respiratory isolation policies, limited access to COVID-19 patient rooms and SARS-CoV-2 transmissibility via droplet-contaminated paper, verbal consent and alternative methods of obtaining consent (for example, by phone) will be allowed if approved by the IRB.

If a signed paper copy of the ICF is allowed by hospital policy, how it will be obtained and stored will need to be determined. Any variation from the standard consent process due to isolation and infection control should be sent to the IRB for approval prior to enrollment.

The site should document the process in their regulatory files and demonstrate that the process has IRB concurrence or approval.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent and, if applicable, the individual designated to witness a verbal consent, must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

### 10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

### 10.1.5. Committees Structure

The ISAC will consist of a chair external to Lilly and will include at least two other Lilly physicians external to the PYAA study team. The ISAC will be engaged in dosing decisions or if any of the stopping criteria are met, and may also conduct periodic reviews of available data to

make recommendations on study conduct. Details of the ISAC will be provided in the ISAC charter.

### 10.1.6. Dissemination of Clinical Study Data

A clinical study report will be provided for this study and a summary of study information provided on publicly available websites.

### 10.1.7. Data Quality Assurance

**Investigator responsibilities**

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

**Data monitoring and management**

The Monitoring Plan includes

- monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring
- methods
- responsibilities
- requirements
- handling of noncompliance issues, and
- monitoring techniques.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents. They will also ensure that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

**Records retention and audits**

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

The sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and by regulatory agencies at any time. Investigators will be given notice before an audit occurs.

**Data Capture System**

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Data from complaint forms submitted to Sponsor will be encoded and stored in the global product complaint management system.

### 10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must be available.

The definition of what constitutes source data can be found in Section 10.1.7.

### 10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

**Site Closure**

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator, or
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and assure appropriate participant therapy and/or follow-up.

### 10.1.10. Publication Policy

In accordance with the sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

### 10.1.11. Investigator Information

Physicians with a specialty in infectious disease, critical care, or pulmonary disease may participate as investigators.

### 10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of the intervention or after the intervention becomes commercially available.

This table describes the retention period for potential sample types.

| Sample Type | Custodian | Retention Period After Last Participant Visit |
|---|---|---|
| Pharmacogenetics sample | Sponsor or designee | up to 7 years |
| Exploratory Biomarker Samples | Sponsor or designee | up to 7 years |
| Pharmacokinetic (PK) sample | Sponsor or designee | up to 2 years |
| Pharmacodynamic Samples | Sponsor or designee | up to 7 years |
| Immunogenicity (ADA) sample | Sponsor or designee | up to 7 years |

## 10.2. Appendix 2: Clinical Laboratory Tests

Clinical laboratory tests will be performed according to the SoA.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy testing will be performed according to the SoA.

Central and local laboratories will be used. The table below describes when the local or central laboratory will be used.

If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Investigators must document their review of the laboratory safety report as described in Section 8.2.4.

Refer to Section 10.6 for recommended laboratory testing for hypersensitivity events.

| Clinical Laboratory Tests | Comments |
|---|---|
| **Hematology** | Assayed by local laboratory |
| Hemoglobin | |
| Hematocrit | |
| Erythrocyte count (RBCs - Red Blood Cells) | |
| Mean cell volume | |
| Mean cell hemoglobin | |
| Leukocytes (WBCs - White Blood Cells) | |
| Differential | |
| Neutrophils, segmented | |
| Lymphocytes | |
| Monocytes | |
| Eosinophils | |
| Basophils | |
| Platelets | |
| Cell Morphology (RBC and WBC) | |
| **Clinical Chemistry** | Assayed by local laboratory |
| Sodium | |
| Potassium | |
| Chloride | |
| Bicarbonate | |
| Total bilirubin | |
| Direct bilirubin | Record on Day 1 and if abnormal values occur |
| Alkaline phosphatase (ALP) | |
| Alanine aminotransferase (ALT) | |
| Aspartate aminotransferase (AST) | |
| Gamma-glutamyl transferase (GGT) | Record on Day 1 and if abnormal values occur |
| Blood urea nitrogen (BUN) | |
| Creatinine | |
| Creatine kinase (CK) | Record on Day 1 and if abnormal values occur |
| Uric acid | Record on Day 1 and if abnormal values occur |
| Total protein | |
| Albumin | |
| Calcium | Record on Day 1 and if abnormal values occur |
| Phosphorus | Record on Day 1 and if abnormal values occur |
| Glucose | |
| Amylase | Record on Day 1 and if abnormal values occur |
| Lipase | Record on Day 1 and if abnormal values occur |
| Lactate dehydrogenase (LDH) | |
| **Calculations** | Completed locally |
| eGFR | calculated by CKD-EPI equation |
| **SARS-Cov-2 viral infection determination** | Local laboratory |

| Clinical Laboratory Tests | Comments |
|---|---|
| **SARS-Cov-2 Panel** | |
| C-Reactive Protein | |
| Ferritin | |
| D-dimer | |
| Procalcitonin | |
| Troponin | |
| SARS-Cov-2 viral infection confirmation | |
| **Hormones (female)** | Assayed by local laboratory. |
| Serum Pregnancy | |
| Urine Pregnancy | |
| **Pharmacokinetic (PK) Samples** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites. |
| **Pharmacodynamic Sample** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites. |
| SARS-Cov-2 test | |
| **Pharmacogenetics sample** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites. |
| **Exploratory Biomarker Samples** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites. |
| Serum | |
| RNA (PAXGene) | |
| Whole Blood (EDTA) | |
| Whole Blood (EDTA) Epigenetics | |
| **Immunogenicity Samples** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites. |
| Anti-LY3819253 antibodies | |
| Anti-LY3819253 antibodies neutralization | |

## 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1. Definition of AE

| **AE Definition** |
|---|
| An AE is any untoward medical occurrence in a clinical study participant temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br><br>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. |

| **Events <u>NOT</u> Meeting the AE Definition** |
|---|
| • Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.<br>• The following study-specific clinical events related to COVID-19 are exempt from AE reporting unless the investigator deems the event to be related to the administration of intervention:<br>  o Hypoxemia due to COVID-19 requiring supplemental oxygen;<br>  o Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices;<br>  o Respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO |

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease under study, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, such as endoscopy or appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

Please note: If an event is not an AE per definition above, then it cannot be an SAE.

| **An SAE is defined as any AE that:** |
|---|
| **a. Results in death** |
| **b. Is immediately life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>• In general, hospitalization signifies that the participant has been admitted to hospital for >"23 hour observation" and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br>• Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **d. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, |

and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.3. Recording and Follow-Up of AE and/or SAE

**AE and SAE Recording**

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, except the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity/Severity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories, which together with serious criteria on the AE CRF ("results in death" and "life-threatening"), are aligned with the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

**Mild:** Mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated.

**Moderate:** Moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated.

**Severe:** Severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

**Assessment of Causality**

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the investigator's brochure and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always assess the causality for every event before the initial transmission of the SAE data to Sponsor or designee.

The investigator may change their opinion of causality after consideration of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

### 10.3.4. Reporting of SAEs

| **SAE Reporting via Paper CRF** |
|---|
| Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.<br><br>Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.<br><br>Contacts for SAE reporting can be found in site training documents. |

## 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

**Women**

**Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

**Woman not of Childbearing Potential (WOCBP)**

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with either
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy, or
    c. Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female is defined as, women with:
    a. 12 months of amenorrhea for women >55, with no need for FSH
    b. 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced amenorrhea)

**Participation in the Study**

Women of child-bearing potential may participate in this study.

Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit.

Women of child-bearing potential who are completely abstinent or in a same sex relationship, as part of their preferred and usual lifestyle, must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.

All other women of child-bearing potential must agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study.

Abstinence or contraception must continue for 90 days after the last dose of intervention.

**Acceptable Methods of Contraception**

Highly effective methods of contraception (less than 1% failure rate) comprise, but are not limited to

- combination oral contraceptives
- implanted contraceptives, or
- intrauterine devices.

Effective methods of contraception comprise but are not limited to diaphragms with spermicide or cervical sponges.

**Not Acceptable Methods of Contraception**

Use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

**Men**

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with non-pregnant women of child bearing potential partners for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days after the last dose.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure to the fetus, predicted to be 90 days after the last dose.

**Acceptable Methods of Contraception**

Highly effective methods of contraception (less than 1% failure rate) comprise, but are not limited to

- combination oral contraceptives
- implanted contraceptives, or
- intrauterine devices.

Effective methods of contraception comprise but are not limited to diaphragms with spermicide or cervical sponges.

Men and their partners may choose to use a double–barrier method of contraception that must include use of a spermicide.

#### Other Guidance

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days after the last dose.

### Collection of Pregnancy Information

#### Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

#### Female Participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study and will follow the standard discontinuation process.

## 10.5. Appendix 5: Genetics

Sample collection information is found in Appendix 2, Section 10.2 (Clinical Laboratory Tests).

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to SARS-CoV-2 and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3819253 or SARS-CoV-2. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome as appropriate.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3819253 or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained at a facility selected by the sponsor or its designee while research on SARS-CoV-2 continues but no longer than 7 years or other period as per local requirements.

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

Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected.

- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample after approximately 4 weeks.

## Clinical Lab Tests for Hypersensitivity Events

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

Abbreviations: IgE = immunoglobulin E; PK = pharmacokinetic.

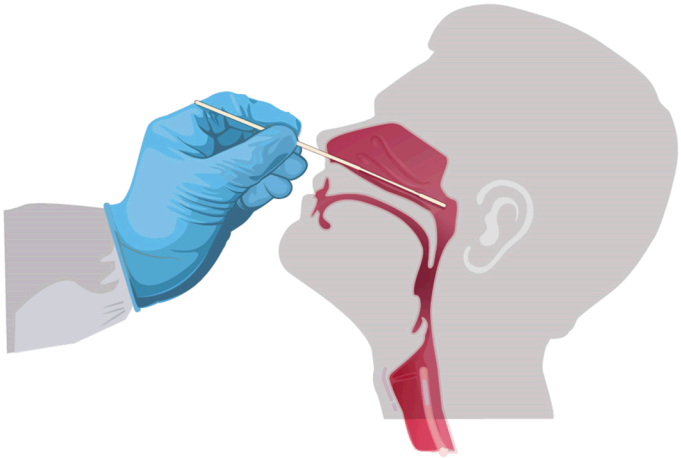
## 10.7. Appendix 7: Nasopharyngeal Swab Instructions

**Personal Protective Equipment for healthcare provider collecting specimen:**

- N95 or higher-level respirator (or facemask if a respirator is not available), eye protection, gloves, and a gown.

**Nasopharyngeal swab:**

- Use only synthetic fiber swabs with plastic or wire shafts.
- Have participant blow nose to clear. Provide tissues for participant in case of sneeze.
- Insert minitip swab with a flexible shaft (wire or plastic) through the nostril parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of the participant, indicating contact with the nasopharynx.
- Swab should reach depth equal to distance from nostrils to outer opening of the ear.
- Gently rub and roll the swab. Leave swab in place for several seconds to absorb secretions.
- Slowly remove swab while rotating it.
- Repeat in other nostril using same swab unless there is an obstruction from a deviated septum or other blockage.
- Swabs should be placed immediately into a sterile transport tube containing 2-3 mL of viral transport medium and stored at 2-8°C for up to 72 hours, then at -70°C or below.



## 10.8. Appendix 8: FDA Guidance for Industry - Baseline Severity Categorization for COVID-19.

This appendix contains pages from the *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry* by the U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER), dated May 2020 (FDA resource page, [WWW]).

**APPENDIX**

**EXAMPLES OF BASELINE SEVERITY CATEGORIZATION**

SARS-CoV-2 infection without symptoms

- Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test
- No symptoms

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate $\geq$ 20 breaths per minute, saturation of oxygen ($SpO_2$) > 93% on room air at sea level, heart rate $\geq$ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19

- Positive testing by standard RT-PCR assay or an equivalent test
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate $\geq$ 30 per minute, heart rate $\geq$ 125 per minute, $SpO_2 \leq$ 93% on room air at sea level or $PaO_2/FiO_2$ < 300
- No criteria for Critical Severity

Critical COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Evidence of critical illness, defined by at least one of the following:
  - Respiratory failure defined based on resource utilization requiring at least one of the following:
    - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
  - Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
  - Multi-organ dysfunction/failure

NOTE: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.

## 10.9. Appendix 9: Abbreviations and Definitions

| Term | Definition |
|---|---|
| **ADA** | anti-drug antibody |
| **ADE** | antibody-dependent enhancement |
| **blinding** | A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **complaint** | A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| **compliance** | Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements. |
| **CRP** | clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer. |
| **ECG** | electrocardiogram |
| **EDC** | electronic data capture system |
| **enroll** | The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment. |
| **enter** | Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **GCP** | good clinical practice |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **Informed consent** | A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. |
| **intervention** | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. |
| **IWRS** | interactive web-response system |

| | |
|---|---|
| **NIAID** | National Institute of Allergy and Infectious Diseases |
| **NIH** | National Institutes of Health |
| **NEWS2** | National Early Warning Score |
| **participant** | Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control |
| **PK/PD** | pharmacokinetics/pharmacodynamics |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **WHO** | World Health Organization |

## 10.10. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

**Amendment (a): 01 June 2020**

**Overall Rationale for Amendment (a):**

This amendment addresses the United States Food and Drug Administration (FDA) feedback. Additional changes were made to address newly available internal or external information. Other changes were made for clarity and consistency. This table describes the changes made for Amendment (a)

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page | Changed PIND to IND | Per FDA |
| Synopsis | Changes to secondary objectives and endpoints | To match changes in Section 3. |
| Synopsis | Updates to general sequence of events during double-blind treatment and assessment period | To more accurately represent the sequence |
| Synopsis | Updated Number of Participants and Intervention Groups and Duration sections. | Based on new internal and external information |
| Synopsis | Updated when the independent safety assessment committee will be engaged | Per FDA feedback |
| Schema | Updates to cohort 4 and sample size | Cohort 4 will not have sentinel dosing because the dose level will not exceed dose level 3. Removed the sample size information for all cohorts that was no longer correct and removed indicator for sentinel dosing for Cohort 4. |
| 1.3 Schedule of Activities | Screening visit window update | Correction to align with randomization and dosing |
| 1.3 Schedule of Activities | Vital Signs - updated comments/instructions | Per FDA feedback |
| 1.3 Schedule of Activities | Clinical symptoms - updated comments/instructions | For clarity |
| 1.3 Schedule of Activities | Pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity and exploratory biomarker samples – updated comments/instructions | For clarity |
| 3 Objectives and Endpoints | Secondary PK objective endpoint changed | More clinically meaningful |
| 3 Objectives and Endpoints | Secondary PD objective endpoint | Added timepoints for analysis |
| 3 Objectives and Endpoints | Moved PD secondary endpoint to exploratory | Decision that viral clearance should be exploratory |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3 Objectives and Endpoints | Added 2 exploratory objectives | Per FDA feedback |
| 4.1. Overall Design | Updates to general sequence of events during double-blind treatment and assessment period | To more accurately represent the sequence |
| 4.1.1. Single-ascending Dose Design | Updated text for the change with Cohort 4 | Cohort 4 increase in sample size |
| 4.2. Scientific Rationale for Study Design | Added text for Cohort 4 | Cohort 4 increase in sample size |
| 4.2. Scientific Rationale for Study Design | Updated text for participant population | The I/E criteria were updated to provide more clarity, and the severity of illness definitions were changed to the FDA definitions. |
| 4.3. Justification for Dose | Updated projected half-life and *in vitro* IC90 | New data available for the updates |
| 5.1 Inclusion Criteria | Increased age limit to 85 years | Based on clinical site feedback |
| 5.1 Inclusion Criteria | Updated disease characteristics | In order to provide more clarity based on clinical site feedback. Severity definitions were updated to those provided by the FDA. |
| 5.1 Inclusion Criteria | Removed criterion describing symptoms | Not needed because of the update to the disease characteristics |
| 5.1 Inclusion Criteria | Updated criterion for hospitalization | Corrected the timing |
| 5.1 Inclusion Criteria | Criterion #6 was merged with Criterion 5 | Correction |
| 5.2. Exclusion Criteria | Updated criterion for mechanical ventilation to state, “invasive mechanical ventilation” | For clarity |
| 5.2. Exclusion Criteria | The timing of SpO2 measurement while breathing room air was changed to occur at screening | SpO2 is measured at screening and instructions were added for participants on supplemental oxygen. |
| 5.2. Exclusion Criteria | Removed respiratory rate criterion | It is covered in the new update to disease characteristics in the inclusion criteria |
| 6.1. Study Intervention(s) Administered | Added information about Cohort 4. | Instructions for infusion volume and rate will be in the pharmacy instructions. |
| 6.1. Study Intervention(s) Administered | Updated the monitoring instructions | Per FDA feedback |
| 6.1.1.2. Management of Infusion Reactions | Removed table of specific guidelines | Investigators should determine the severity of the infusion reaction and manage the reactions based on standard of care and their clinical judgment. |
| 6.5. Concomitant Therapy | Updated text about standard of care and allowing remdesivir during the study | Per FDA feedback |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.6.1. Dose escalation criteria | Updated when the independent safety assessment committee (ISAC) would be engaged for reviews | Per FDA feedback |
| 6.6.2. Temporary Stopping Criteria | Removed redundant text | Already stated in Section 6.6.1. |
| 8.2.4. Clinical Laboratory Assessments | Updated required text | Per Lilly required language |
| 8.3.5. Pregnancy | Updated collection timing to 90 days | New data available for the update |
| 8.3.7. Infusion-related Reactions | Updated table | Removed link to table that was removed in Section 6.1.1.2. |
| 8.9. Immunogenicity | Removed “predose” | Refer to SoA for sample times |
| 8.6. Pharmacodynamics | Updated text to clarify how the samples may be used | Per FDA feedback |
| 9.2. Sample Size Determination | Updated sample size information | Based on new internal and external information |
| 9.2. Sample Size Determination | Corrected Bayesian critical success factor equation | correction |
| 9.4.1. General Considerations | Updated table | corrections |
| 9.4.1. General Considerations | updated one sentence and removed another | corrections |
| 9.4.2. Safety analyses | Removed listings | Parameters will not be listed, only summarized |
| 9.4.4. Exploratory Endpoints | Addition of exploratory endpoint | Per Section 3. Objectives and Endpoints |
| 9.4.3. Pharmacokinetic and Pharmacodynamic Analyses | Updated PK and PD analyses | To match endpoints in Section 3. |
| 9.4.4. Exploratory Endpoints | Updated exploratory endpoints | To match table in Section 3. |
| 10.1.5. Committees Structure | Updated when the Independent Safety Assessment Committee (ISAC) will be engaged | Per FDA feedback |
| 10.1.12. Long-term sample Retention | Updated sample retention times | Per internal Lilly decision |
| 10.2. Appendix 2: Clinical Laboratory Tests | Updates to text | For clarity |
| 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information | Updated collection timing to 90 days | New data available for the update |
| 10.5. Appendix 5: Genetics | Updated sample retention time | Per internal Lilly decision |
| 10.8. Appendix 8 | Added an appendix to contain FDA resource page | The COVID-19 severity criteria from this resource page will be used for inclusion criteria purposes |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 11 References | Added FDA reference | For inclusion criteria |
| Throughout the protocol | Minor editorial and formatting changes | Minor, therefore not described |

# 11. 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: 14 April 2020.

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