A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (Trial H1: LY3819253 (LY-CoV555))

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Appendix H1: LY3819253 (LY-CoV555) – version 1.0 (16th July 2020)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between Lilly and NIAID in relation to the ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.1.1. Introduction and rationale for studying the agent

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 monoclonal antibody (mAb) to the receptor binding domain (RBD) of the S protein of SARS-CoV-2 being developed as a potential treatment and prophylaxis for COVID-19. This antibody blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, preventing subsequent viral entry into human cells and viral replication. This is expected to result in a clinically important decrease in viral replication, mitigating the severity of disease in patients in who ongoing viral replication is an important driver of COVID-19 pathophysiology.

LY3819253 is made by Lilly Research Laboratories, Eli Lilly and Company, in partnership with AbCellera Biologics Inc. (AbCellera; Vancouver, Canada), and is derived from a person, who recovered from SARS-CoV-2 infection.

Whereas one antiviral agent (remdesivir) has been demonstrated to have clinical benefit in the target population for this trial and is now part of standard-of-care (see Appendix I), it is plausible that additional antiviral effects from LY3819253 in combination with the antiviral agent may provide additive, if not synergistic, antiviral effects and hence, contribute to improvement in time to sustained recovery.

Lilly is evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3819253 in participants hospitalized for COVID-19, in a randomized, placebo-controlled, double-blind, sponsor-unblinded, single-ascending-dose, Phase 1, first in human study (Study J2W-MC-PYAA [PYAA]) (NCT04411628)(1). Lilly is also evaluating the safety, tolerability, PK and PD of LY3819253 in a phase 2, randomized, double-blind, placebo-controlled, dose ranging study in non-hospitalized participants with mild to moderate COVID-19 Illness (Study J2W-MC-PYAB [BLAZE-1]) (NCT04427501)(2). Both studies are ongoing and preliminary safety, tolerability, PK and PD data from these may inform the dose level administered in this study.

H1.1.1 *Potential risk and benefits from LY3819253*

Anticipated risk is considered low, based on the known mechanism of action for human derived neutralizing antibodies in acute viral disease states. LY3819253 is a highly specific mAb directed at foreign (non-human) epitope(s). The complementarity determining regions (CDRs) of the mAb were derived from B lymphocytes of a naturally convalescent 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, which is further supported by the absence of binding to membranes of human tissue in a tissue cross-reactivity study.

Potential risks for infusion of an IgG1 mAb directed toward a microbial pathogen are mostly associated with either infusion-related immediate and non-immediate hypersensitivity reactions, or infusion-related cytokine release syndrome. Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to: anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticarial, tachycardia, and throat irritation or chest tightness. Additional signs and symptoms associated with cytokine release syndrome may also include fever, headache, myalgia, nausea, and vomiting.

The single infusion in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion paused or stopped as well as any supportive measures instituted as per local practice, if indicated.

A theoretical risk is that LY3819253 may cause antibody-dependent enhancement (ADE) of viral replication (section 3.2). This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases, Dengue and Zika virus infections. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (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 has not indicated safety concerns (3). 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. Both *in vitro* and *in vivo* (non-human primate) experiments have been completed, and no evidence of ADE of infection was observed at sub-neutralizing concentrations of LY3819253.

The potential benefit of LY3819253 is, that the clinical course of COVID-19 may be improved, which may include a faster recovery from COVID-19.

In Study PYAA, 24 adult participants were randomized and received either LY3819253 or placebo through 03 July 2020. A total of 18 participants received LY3819253 (6 participants each receiving either 700 mg, 2800 mg or 7000 mg) and 6 received placebo.

Based on preliminary data from the data cutoff date of 03 July 2020 in Study PYAA, LY3819253 has been well tolerated by participants and no deaths, serious adverse events (SAEs) or discontinuations due to adverse events (AEs) have been reported. No AEs of infusion-related reaction (IRR) considered to be related to LY3819253 by the Principal Investigator (PI) have been reported in this study. Overall, the frequency of treatment-emergent adverse events (TEAEs) in Study PYAA was 23 in 10 participants dosed with LY3819253 (across all doses) or placebo. There were a similar number of

TEAEs across all groups. Most TEAEs reported were mild to moderate in severity. There have been no dose-limiting safety issues identified. Of the data received to date, PK/PD were within expected limits.

In Study PYAB, 26 adult participants entered and were randomized to receive either placebo or LY3819253 at doses of 700 mg or 2800 mg (the 7000mg cohort was initiated on 03 July 2020). Based on the data cutoff date of 03 July 2020, no deaths, SAEs or discontinuations have been reported. The study remains blinded.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3819253 may be found in the Investigator's Brochure, Participant Information Leaflet, and/or Development Safety Update Report.

Given the data on LY3819253 from the on-going Phase 1 and Phase 2 studies, the well-described safety profile of other therapeutic monoclonal antibodies, and the limited disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment of this study is considered favorable.

H1.1.2 *Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)*
The Lilly antibody LY3819253 discovered in partnership with AbCellera was identified from over 400 antibody sequences isolated from blood of a convalescent SARS-CoV-2 infected patient and is a very high affinity binder of the receptor binding domain (RBD) of the viral S-protein. In live virus neutralization *in vitro* assays, LY3819253 has very high potency against SARS-CoV-2. Based on current information available to the TOC, LY3819253 appears to have an excellent potency profile among the RBD antibodies available. Further, the Lilly data demonstrate binding to both the ACE-2-interacting and the resting state of the RBD, neutralization across multiple strains of live virus, and binding across RBD known mutations of SARS-CoV-2, which provides encouraging evidence of a low risk of viral reactivation.

LY3819253 has an open IND, and a single-ascending-dose study in hospitalized patients has already begun (NCT04411628). The Lilly strategy, assuming safety and tolerability, is, to rapidly advance into efficacy studies in hospitalized and ambulatory patients. Clinical trial materials are sufficient to support the general investigative plan, and Lilly will begin drug substance commercial manufacturing at risk at their Branchburg, NJ site with plans for drug product manufacturing at their parenteral fill facility in Indianapolis, IN.

Lilly's statement regarding plans for licensure: Lilly is a global pharmaceutical company and attempts to bring important medical breakthroughs to as many patients in as many countries as possible. It would therefore be our general intent to pursue licensure in countries where the trial occurs. In the case of the COVID-19 pandemic, the actual decision to pursue licensure will be impacted by other factors which may include: status of the COVID pandemic in the country and medical need, availability of other therapies including vaccines, available drug supply and other supply feasibility issues, and other regulatory considerations.

H1.1.3 Justification for dose chosen for LY3819253

The dose levels of LY3819253 administered in this study are informed by Study J2W-MC-PYAA (PYAA) and J2W-MC-PYAB (BLAZE-1). In both studies, 700, 2800, and 7000 mg doses are being evaluated. Based on safety results from the studies mentioned above, the dose to be used is 7000 mg irrespective of body weight.

The projected human half-life is expected to be in the 2-4 weeks range.

This dose is selected to minimize potential concerns about underdosing and thus failing to detect an efficacy signal for an efficacious therapy. There are no significant safety concerns about using the 7000 mg dose, as side effects in antibody therapy are not generally dose-dependent.

H1.2. Agent specific eligibility criteria

In addition to those outlined in the master protocol.

H1.2.1 Inclusion Criteria

1) Non-pregnant female participants who are of reproductive potential and male participants who are able to father a child must abstain from male/female sexual intercourse or 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 and for 90 days after investigational agent is administered.

   Highly effective methods of contraception (less than 1% failure rate) include, but are not limited to:
   - combination oral contraceptives
   - implanted contraceptives
   - intrauterine devices

   Effective methods of contraception include, but are not limited to:
   - diaphragms and cervical caps with spermicide
   - cervical sponges
   - condoms with spermicide

   NOTE:
   - 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), and withdrawal are not acceptable methods of contraception.

   Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.

Participants with pregnant partners should use condoms during vaginal intercourse through 90 days after investigational agent administration.

Participants should refrain from sperm donation through 90 days after investigational agent administration.

NOTE: Reproductive potential is defined as patients who have reached menarche, who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥ 40 IU/ml or 24 consecutive months if an FSH is not available, who have not undergone surgical sterilization, who do not have other clinical condition that could induce amenorrhea, who are not taking medications such as oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea. Individuals with permanent infertility due to an alternate medical cause (e.g. Mullerian agenesis, androgen insensitivity), investigator discretion should be applied.

H1.3. Description of investigational agent

H1.3.1. Administration and duration

See the PIM and Pharmacy Procedures for details. See also section H1.5 below for guidance on the clinical management of the infusion, including infusion-related reactions.

The infusion rate may be reduced as deemed necessary, if an infusion reaction is observed. Participants will be closely monitored every 30 minutes during the infusion and for at least 2 hours after completion of the infusion. Additional monitoring may be necessary based on clinical judgement of the study investigator(s) and/or site staff, and in accordance with the master protocol. The site must have resuscitation equipment, emergency drugs and appropriately trained staff available during the infusion and for at least 2 hours after the completion of the infusion.

If a participant has not already received the relevant dose of remdesivir at the day of enrolment, and has no contraindications to start remdesivir, it is recommended (but not required) that the relevant dose of remdesivir is infused after the infusion of LY3819253 /placebo is completed.

H1.3.2. Formulation and preparation

LY3819253 is provided in vials of 20 ml solution containing 700 mg antibody each. LY3819253 must be stored between 2ºC and 8ºC.

A total of 10 vials is required for dosing of the agent at 7000 mg (see table H1.1). Placebo is normal saline. The study medication is prepared by a unblinded pharmacist at the local pharmacy. To ensure blinding of the participant and clinical staff a colored sleeve will be placed over the infusion bags used (see PIM and Pharmacy Procedures).

LY3819253 should be prepared and dispensed as soon as possible after randomization. Infusions should be completed within 4 hours after the infusion has been prepared by the pharmacist.

Table H1.1. Study medication overview.

Intervention Name	**Placebo**	**LY3819253**
Dose Formulation	0.9% sodium chloride solution	Solution
Dosage Level(s) (mg)	Not applicable	7000
Route of administration	IV infusion	IV infusion
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately

H1.3.3 Supply, distribution, and accountability
Procedures for ordering and accepting drug, for maintaining inventory of LY3819253, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H1.3.4. Contraindicated medications
No medication is known to be contraindicated in patients receiving the investigational agent. Whenever a concomitant medication or the study agent is initiated or a dose changed, investigators must review the concomitant medication's prescribing information and the relevant protocol appendix/appendices, as well as the most recent package insert, Investigator's Brochure, or updated information from DCR, NIAID to obtain the most current information on drug interactions, contraindications, and precautions.

H1.3.5. Precautionary medications
The clinical site should have necessary equipment and medications for the management of any infusion reaction (see section H1.5 below).

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 recommend premedication, if the frequency of infusion reactions among participants warrants it. If minor infusion reactions are observed, 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 participants will be made by the investigator and sponsor and recorded in the study documentation. Any premedications given will be documented as a concomitant therapy.

H1.4. Clinical and laboratory evaluations

H1.4.1 Timing of Assessments

Appendix B outlines the clinical and laboratory monitoring. Assessment and reporting of AEs (section 10.1.1), SAEs (section 10.1.2) and unanticipated problems (section 10.1.3) and their severity, causality (section 10.1.5) and expectedness (section 10.1.6) is performed as outlined in the relevant section of the master protocol.

H1.4.2 Immunogenicity Assessments

At the visits specified in the master protocol (Days 0, 28, and 90) venous blood samples will be collected to determine antibody production against LY3819253. Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of LY3819253 at a laboratory approved by Lilly. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253. Remaining volume from the PK sample may also be used for immunogenicity assessments as needed.

H1.4.3. Pharmacokinetic Assessments

At the visits specified in the master protocol (Days 0, 1, 5, 28, and 90) venous blood samples will be collected to determine LY3819253 serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2mL of the serum collected, as described in the Master Protocol Appendix B as “Research Sample Storage”. PK samples may be assessed by a validated assay at a bioanalytical lab designated by Lilly. The PK assessment will use the same 2ml serum aliquot specified in the Immunogenicity assessment section above (4.2). Analysis of samples from placebo-treated subjects is not planned. Remaining sample used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

H1.5. Clinical management issues

All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

H1.5.1. 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 AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 (July 2017) (Table H1.2).

Table H1.2. Overview of severity grading of infusion-related reactions.

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 OR Mild angioedema with no intervention indicated	Generalized Urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Cytokine Release Syndrome[a]	Mild signs and symptoms AND Therapy (that is, antibody infusion) interruption not indicated	Therapy (that is, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR 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, Corrected Version 2.1 (July 2017)(4).

H1.5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (/adrenaline), acetaminophen (/paracetamol) and antihistamine.

The pharmacy must use amber-colored Ultraviolet Light-Inhibiting (UVLI) protective bags to place over the infusion bag. The pharmacy will be provided with labels to be placed on the IV bag before dispensing (refer to the Pharmacy Procedures).

The pharmacy is required to provide normal saline and IV bags, similarly shrouded.

H1.5.3. Management of Infusion Reactions including Discontinuation

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life-threatening infusion reaction occurs with LY3819253 /placebo, its use should be permanently discontinued.

If a participant is not infused with LY3819253 /placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in the master protocol (Appendix B for overview), should be adhered to as indicated.

H1.5.4. Adverse Events of Special Interest (AESI)

The following are AESIs for the agent LY3819253 or placebo for LY3819253:

- Infusion-related reactions
- Allergic/hypersensitivity reactions

H1.6. References

1. https://clinicaltrials.gov/ct2/show/NCT04411628 (PYAA trial)
2. https://clinicaltrials.gov/ct2/show/NCT04427501 (BLAZE-1 trial)
3. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020;117(17):9490-6.
4. https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one (DAIDS AE severity grading; link also outlined in appendix D)