University of California, Los Angeles
Clinical Research Protocol
Phase I/II, Open-Label Dose-Finding Trial of High-Dose mRNA-1273 Booster for Lung Transplant Recipients

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Sponsor/Investigator:	Yusaku Michael Shino, MD
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Principal Investigator:	Yusaku Michael Shino, MD Department of Medicine – Pulmonary Disease University of California, Los Angeles Box 951690, 43-229 CHS Los Angeles, CA 90095
Medical Monitors:	Yusaku Michael Shino, MD Department of Medicine – Pulmonary Disease University of California, Los Angeles Box 951690, 43-229 CHS Los Angeles, CA 90095 Name: S. Sam Weigt, MD Department of Medicine – Pulmonary Disease University of California, Los Angeles Box 951690, 43-229 CHS Los Angeles, CA 90095

Principal Investigator	Yusaku Michael Shino, MD Associate Professor, Division of Pulmonary and Critical Care
Co- Investigator	Otto Yang, MD Professor, Division of Infectious Disease
Co- Investigator	Stephen Samuel Weigt, MD Associate Professor, Division of Pulmonary and Critical Care
Co- Investigator	Jesse Lawton Clark, MD Associate Professor in Residence, Department of Infectious Diseases
Co- Investigator	Name: John A. Belperio, MD Professor, Division of Pulmonary and Critical Care
Co- Investigator	Name: David Elashoff, PhD Professor, Department of Biostatistics

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Title: Phase I/II, Open-label Dose-finding Trial of High-Dose mRNA-1273 Booster for Lung Transplant Recipients

Protocol Date: 4/9/2022

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BNP	brain naturetic peptide
Bid	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CK	creatinine kinase
CKMB	creatinine kinase myocardial band
cm	centimeter
cMRI	cardiac magnetic resonance imaging
CONSORT	Consolidated Standard of Reporting Trials
COVID-19	coronavirus disease 2019
Cr	creatinine
CrCL	creatinine clearance
CRF	case report form
CTSI	Clinical & Translational Science Institute
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DMF	drug master file
EC	European Commission
ECG	electrocardiogram
eCRF	electronic case report form
EKG	electrocardiogram
EOS	end of study
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GMC	geometric mean concentrations
GMT	geometric mean titers
HEENT	head, ears, eyes, nose, throat
Hg	Mercury
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HTN	Hypertension
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	Intramuscular
IND	investigational new drug
IRB	Institutional Review Board
ITT	intent to treat
IU	international unit
IV	Intravenous
IVIG	intravenous immune globulin
Kg	Kilogram
LLOQ	Lower limit of quantification
LNP	lipid non-particle
LOA	letter of authorization
LTOS	long term outcome study
MAAE	medically attended adverse event
MD	medical doctor
mg	milligram
mL	milliliter
mm	millimeter
mRNA	messenger RNA
m2	square meter
NaCl	sodium chloride
Ng	Nanogram
NOCM	new onset chronic medical condition
NP	nurse practitioner
ORA	Office of Regulatory Affairs
PA	Physician's assistant
PBMC	peripheral blood mononuclear cell
PI	Principal Investigator
Plt	platelet
PP	per protocol

PT	prothrombin time
PTT	partial prothrombin time
RBD	receptor binding domain
RN	registered nurse
SAE	serious adverse experience
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
S-2P	spike protein
T Bili	total Bilirubin
UCLA	University of California, Los Angeles
ug	microgram
USP	United States Pharmacopeia
WBC	white blood cells

PROTOCOL SYNOPSIS

TITLE	**Phase I/II, Open-label Dose-Finding Trial of High-Dose mRNA-1273 Booster for Lung Transplant Recipients**
SPONSOR/INVESTIGATOR	Yusaku Michael Shino, MD Department of Medicine – Pulmonary Disease University of California, Los Angeles Box 951690, 43-229 CHS Los Angeles, CA 90095 Telephone: 310-866-6327 Fax: 310-206-8622 E-mail: MShino@mednet.ucla.edu
FUNDING ORGANIZATIONS	Departmental funding
NUMBER OF SITES	Single site
RATIONALE	Lung transplant recipients have poor outcomes after COVID-19 infection with case fatality rates ranging between 14-39% (1–4). In contrast to immunocompetent participants in vaccine trials, solid organ transplant recipients have had poor responses to SARS-CoV-2 vaccines with several studies reporting anti-SARS-CoV-2 antibody detection in only 34-54% after the second dose (5–7). Lung transplant recipients generally require higher levels of immunosuppression due to the allograft's exposure to the external environment and active immune surveillance. Thus, vaccine responses have been even weaker for lung transplant recipients with several studies reporting antibody responses in less than 20% after the second dose (5, 8–10). Booster vaccines (3rd dose) appear to improve immune responses for solid organ recipients (11–13), but has not been studied specifically for lung transplant recipients.
STUDY DESIGN	This is a Phase I/II open-label dose-finding trial among lung transplant recipients who received three or four mRNA vaccine doses (mRNA-1273 or BNT162b2) after lung transplantation to: standard-dose (50 ug), mid-dose (100 ug) or high-dose (200 ug) mRNA-1273 booster vaccine. Sixty participants will be enrolled into three dose groups: 1) Standard-dose – 20 participants, 2) Mid-dose – 20 participants, 3) High-dose – 20 participants. The first 2 participants in both the mid-dose and high dose groups will be considered the 'sentinel' group. Participants in the sentinel group will receive the vaccine and undergo a 7-day observation period for safety and reactogenicity before additional participants are enrolled into that dose group.

	Overall study enrollment will begin with the mid-dose sentinel group (n=2). During the observation period for the mid-dose sentinel group, we will enroll two participants into the standard-dose group. Once the mid-dose sentinel group completes their 7-day observation period without triggering halting rules and is approved to proceed by the DSMB, we will enroll the next 27 participants (Cohort 1) with a 2:1 randomization into the mid-dose (n=18) and standard-dose (n=9) groups. Once all 20 participants have received their mid-dose vaccine without triggering halting rules and is approved to proceed by the DSMB, we will enroll the high-dose sentinel group (n=2). Once the high-dose sentinel group completes their 7-day observation period without triggering halting rules and is approved to proceed by the DSMB, we will enroll the next 27 participants (Cohort 2) with a 2:1 randomization into the high-dose (n=18) and standard-dose (n=9) groups. All 20 participants in the mid-dose group will be enrolled prior to the enrollment of the high-dose group. We will perform stratified randomization for the two cohorts based on: 1) the number of prior doses, and 2) prior receipt of any BNT162b2 vaccines. Randomization with be done by the UCLA Clinical and Translational Science Institute (CTSI) statistics team based on scheduled participants prior to the study visit. The 6 participants in the sentinel (n=4) and initial (n=2) groups (Table 1) will be assigned into the 3 groups based on their scheduled visit day.
PRIMARY OBJECTIVE	1. Evaluate safety of high-dose mRNA-1273 vaccine among lung transplant recipients measured by incidence of adverse events. 2. Evaluate reactogenicity of high-dose mRNA-1273 vaccine among lung transplant recipients measured by FDA Toxicity Grading scale.
SECONDARY OBJECTIVES	1. Evaluate humoral immunogenicity measured by anti-RBD and anti-spike (S-2P) IgG levels at Day 30. 2. Evaluate humoral immunogenicity measured by neutralizing antibody titers from a pseudovirus neutralization assay at Day 30. 3. Evaluate cellular immunogenicity measured by cellular response assays including flow cytometry with intracellular staining at Day 30.

NUMBER OF PARTICIPANTS	**60 Total:**
PARTICIPANT SELECTION CRITERIA	**Inclusion Criteria:**

The following numbers of participants will be enrolled:		
1A) Standard-dose – Initial Group	2	50 ug
1B) Standard-dose – Full Group	18	50 ug
2A) Mid-dose – Sentinel Group	2	100 ug
2B) Mid-dose – Full Group	18	100 ug
3A) High-dose – Sentinel Group	2	200 ug
3B) High-dose – Full Group	18	200 ug

1. All adult lung transplant recipients (age ≥ 18 at the time of consent) who received all of their COVID-19 vaccines after lung transplantation.
2. Received three or four doses of either the Moderna mRNA-1273 or Pfizer BNT162b2 vaccine with the last dose received at least 4 months prior to study enrollment.
3. Currently receiving standard regimen of three drug immunosuppression with prednisone, tacrolimus and mycophenolate mofetil (cellcept, minimum 250 mg bid) or mycophenolate sodium (myfortic, minimum 180 mg bid).
4. Agrees not to receive other investigational agents for prophylaxis against COVID-19 including Evusheld monoclonal antibodies for at least 30 days after the study vaccine.
5. Understands and agrees to comply with the study procedures and provides written informed consent.
6. Is in stable health without any new or worsening medical conditions in the opinion of the Investigator.
7. Female participants of childbearing potential (<1 year since start of menopause) may be enrolled in the study if the participant fulfills all the following criteria:
    a. Has a negative pregnancy test at Visit 1 Day 1.
    b. Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
    c. Has agreed to continue adequate contraception or practice abstinence through 3 months following the booster injection (Day 90).

d. Is not currently breastfeeding.
e. Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:
    i. Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
    ii. Intrauterine device
    iii. Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
    iv. Sterilization of a female participant's monogamous male partner prior to entry into the study
    v. Note: periodic abstinence (e.g., calendar, ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

1. Previous documented COVID-19 infection.
2. Use of investigational agents for prophylaxis against COVID-19 within 90 days of the start of the study, including Evusheld monoclonal antibodies.
3. Ongoing therapy for acute cellular or antibody mediated rejection.
4. Intravenous immunoglobulins (IVIG) administration within the prior 3 months or ongoing IVIG therapy.
5. Anaphylaxis or allergic reaction to any prior vaccines.
6. History of anaphylaxis or other significant adverse reaction requiring medical intervention after receipt of a vaccine.
7. Is acutely ill or febrile 24 hours prior to or at the Day 1 visit. Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
8. Pregnant or breastfeeding.
9. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
10. Known history of hypertension (HTN) with systolic blood pressure (BP) > 180 mm Hg at the Day 1 visit.

	11. Known history of hypotension with systolic blood pressure < 85 mm Hg at the Day 1 visit. 12. Bleeding disorder considered a contraindication to IM injection or phlebotomy. 13. Active malignancy diagnosed within previous 4 years (excluding non-melanoma skin cancer). 14. Received a major surgery including lung transplantation in the past 3 months.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	1. mRNA-1273 is an LNP dispersion containing an mRNA that encodes for the pre-fusion stabilized spike protein 2019-nCoV. 2. mRNA-1273 will be received at a concentration of 0.2 mg/ml. The investigational pharmacy will prepare doses of 50 ug (0.25 ml) standard-dose, 100 ug (0.5 ml) mid-dose and 200 ug (1 ml) high-dose.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	The mRNA-1273 vaccine, provided as a sterile liquid at a concentration of 0.2 mg per milliliter, will be administered by injection into the deltoid muscle in a volume of 0.25 ml (50 ug), 0.5 ml (100 ug) or 1.0 ml (200 ug). Vaccine mRNA-1273 will be stored at 2° to 8°C (35.6° to 46.4°F) at clinical sites before preparation and vaccination. No dilution was required. Doses could be held in syringes for up to 8 hours at room temperature before administration.
DURATION OF PARTICIPANT PARTICIPATION AND DURATION OF STUDY	**Treatment:** Day 1 intramuscular injection **Follow-up:** 6 months Participants will be on study for up to 7 months. The total duration of the study for recruitment and completion of participants is expected to be up to 12 months.
CONCOMMITANT MEDICATIONS	Based on inclusion criteria, participants will be required to be on a regimen of triple immunosuppression including prednisone, mycophenolate mofetil (minimum 250 mg bid) or mycophenolate sodium (minimum 180 mg bid), and tacrolimus at the Day 1 study visit. Participants receiving IVIG or augmented immunosuppression for treatment of acute cellular rejection or antibody mediated rejection will be excluded from the study.
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	1. Frequency and grade of each solicited local and systemic reactogenicity AE will be recorded on a daily diary using the FDA Toxicity Grading Scale and collected from Day 1 until Day 7. 2. Frequency and grade of each unsolicited adverse events will be recorded on a daily diary and collected from Day 1 until Day 30.

	3. Frequency of any serious adverse experiences (SAEs) and adverse events of special interests (AESIs) will be collected from Day 1 until Day 180.
SECONDARY ENDPOINTS	1. Humoral immunogenicity measured by anti-RBD and anti-spike (S-2P) IgG levels at Day 30. 2. Humoral immunogenicity measured by neutralizing antibody titers from a pseudovirus neutralization assay at Day 30. 3. Cellular immunogenicity measured by cellular response assays including flow cytometry with intracellular staining at Day 30.
SAFETY EVALUATIONS	The study will use a Data and Safety Monitoring Board (DSMB). DSMB reviews are required for study halting and restarting. Reporting to regulatory bodies (IRB, FDA) will only be required for serious adverse events judged by the treating physician and study investigators to be potentially related to the administration of the study drug. All other adverse events will be reviewed by the study investigators and reported per FDA and IRB regulations. The study will be overseen by CTSI Data and Safety monitoring Board. By allowing CTSI DSMB to oversee the study, the PI agrees to abide by the CTSI DSMB's policies and procedures as outlined in the DSMB charter.
PLANNED INTERIM ANALYSES	Interim analysis of the secondary immunogenicity endpoints (humoral and cellular immunogenicity) may be conducted once all study participants have completed their Day 30 visit and blood draw.
Statistical Analysis Plan	**Primary Objective Analysis:** **1. Safety:** will be measured by the frequency and grade of AEs (solicited and unsolicited), SAEs, AESIs, MAAEs. **2. Reactogenicity:** will be measured by the occurrence of solicited injection site and systemic reactions. Simple descriptive statistics will be used to summarize toxicities in terms of type, severity and minimum or maximum values for laboratory measures, time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects. Safety Analyses will be performed on Safety Analysis Set. **Secondary Objective Analysis:** 1. **Binding antibody:** The anti-RBD and anti-spike (S-2P) IgG concentrations (log10 and geometric mean concentrations (GMC)) at Day 30 will be evaluated with comparisons between the standard-dose versus high-dose groups. T-tests with two-sided $p<0.05$ significance will be used (overall α level of 0.1). Changes in the anti-RBC and anti-spike IgG concentrations at Day 30 will be compared between the standard-dose versus high-dose groups using two sample T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). The percent of participants with detectable antibody

	levels (greater than the LLOQ) at Day 30 will also be evaluated using Fisher's exact tests. Pairwise comparisons of binding antibodies will also be evaluated between the standard-dose versus mid-dose groups. 2. **Neutralizing antibody:** Neutralizing antibody titers (geometric mean titers (GMT)) from a pseudovirus neutralization assay at Day 30 will be compared between the standard-dose versus high-dose groups using T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). Changes in the neutralizing antibody titers at Day 30 will be compared between the standard-dose versus high-dose groups using two sample T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). The percent of participants with detectable neutralizing antibody levels (greater than the LLOQ) at Day 30 will also be evaluated using Fisher's exact tests. Pairwise comparisons of neutralizing antibodies will also be evaluated between the standard-dose versus mid-dose groups. 3. **Cellular immunogenicity:** The change in the frequency of target cytokine producing T-cells by flow cytometry with intracellular staining at Day 30 will be compared using the Kruskal-Wallis Test for the standard-dose versus high-dose groups. A comparison of T-cell frequencies between the standard-dose versus high-dose groups will be evaluated using the Wilcoxon rank-sum test. Pairwise comparisons of cellular immunogenicity will also be evaluated between the standard-dose versus mid-dose groups.
Rationale for Number of Participants	The overall mean log10 IgG increase after the third (100 ug) vaccine dose was 0.46 with standard deviation (SD) 0.63. Assuming participants have a 50% lower response to the 50 ug fourth-dose, the expected mean log10 IgG increase is 0.23. Assuming participants have a 100% higher response to the 200 ug fourth-dose, their expected mean log10 IgG increase is 0.91. For 80% power to detect this difference between high-dose and standard-dose groups with a SD of 0.63 for a two-sample t-test with two-sided $\alpha<0.05$ significance, the minimum required sample size is 15 per group. Thus, we will enroll 20 participants into each group. The first 2 participants in the mid and high-dose groups will be enrolled as the sentinel group to ensure an acceptable safety profile before the full group is enrolled.

1 BACKGROUND

The Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) emerged in December 2019 and has caused a global pandemic of unparalleled proportion with a respiratory illness named Coronavirus Disease 2019 (Covid-19). The urgent need for interventions to reduce the high morbidity and mortality associated with Covid-19 has led to numerous vaccine candidates based on traditional and new platforms. mRNA-1273 is

a lipid-nanoparticle (LNP) encapsulated mRNA vaccine encoding a pre-fusion stabilized form of the SARS-CoV-2 spike protein (S-2P).

1.1 Overview of Non-Clinical Studies

Non-clinical studies have demonstrated the immunogenicity, safety and vaccine efficacy of the mRNA-1273 vaccine. Early studies in non-human primates showed robust SARS-CoV-2 neutralizing activity with rapid protection from high-dose SARS-CoV-2 challenge (1). Subsequent non-human primate studies showed a dose-response relationship between increasing mRNA-1273 doses and both serum anti-S-2P IgG levels as well as protection from viral challenge (2). No animals with anti-S-2P IgG > 645 international units (IU)/mL had nasal swab positivity > 100,000 copies/swab. Furthermore, passive transfer of vaccine-induced IgG from non-human primates to naïve hamsters was protective against infection (2).

1.2 Overview of Clinical Studies

Efficacy of the mRNA-1273 vaccine was demonstrated in a phase 3 randomized trial of 30,420 participants in the COVE Study (3, 4). Vaccine efficacy in was 94.1% at preventing COVID-19 illness, including severe disease. Local and systemic reactions to the vaccine were common and included pain at injection site, headache, fatigue, myalgias and arthralgias. However, these reactions were transitory and there were no serious adverse events, episodes of thrombosis or myocarditis associated with the vaccine (3, 4). Hypersensitivity reactions were reported in 1.5% and 1.1% of participants in the vaccine and placebo groups, respectively.

Several medical conditions have been reported in temporal association with COVID-19 vaccines. Thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barre syndrome (GBS) have been reported after the Johnson & Johnson Janssen vaccine (5), although these conditions have not been associated with the mRNA vaccines (Pfizer-BioNTech and Moderna). The mRNA vaccines have been associated with an increased risk of myocarditis and pericarditis, particularly among young males after the second dose (6–9). The incidence of myocarditis/pericarditis is low and estimated at 3.5 cases per million doses after second dose mRNA among all adults, and 24.3 cases per million among individuals 12 to 29 years of age (10). Most reported cases of myocarditis/pericarditis occurred within the first 7 days of vaccination (7–9). Despite the potential for these rare but serious conditions, the benefit-risk assessment for Covid-19 vaccination remains strongly in favor of vaccination for those over age 5.

The phase 1 mRNA-1273 clinical trial evaluated three doses: 25 ug, 100 ug and 250 ug. There was a dose-response relationship between increasing mRNA-1273 doses and serum anti-S-2P antibody levels. Systemic adverse reactions including fatigue, chills, headache, myalgia and injection site pain occurred in more than half the participants, and occurred more frequently with the 250 ug dose. Thus, the 100 ug dose was eventually chosen for the phase 3 clinical trial.

2 STUDY RATIONALE

In contrast to immunocompetent participants in vaccine trials, solid organ transplant recipients have poor responses to SARS-CoV-2 vaccines with studies reporting anti-S-protein antibody detection in only 34-

54% after the second dose (11–13). Lung transplant recipients in particular have weak responses to the vaccine with antibody responses observed in less than 20% after the second dose (11, 14–16). Due to the allograft's exposure to the external environment and active immune surveillance, lung transplant recipients generally require higher levels of immunosuppression. Lung transplantation is also unique among the solid organ transplants in the direct infection and injury of the allograft by SARS-CoV-2.

Thus, lung transplant recipients have had poor outcomes after COVID-19 infection with case fatality rates ranging between 14-39% (17–20). Third vaccine doses appear to improve immune responses for solid organ recipients (21–23), but has not been studied specifically for lung transplant recipients.

The objectives of this study are to determine the safety, reactogenicity and immunogenicity of a mid-dose (100 ug) and high-dose (200 ug) booster mRNA-1273 vaccine among lung transplant recipients who previously received three or four mRNA-1273 vaccine doses.

A single-center observational cohort study of 165 pts at UCLA found that only 35% of lung transplant recipients mounted an anti-RBD IgG antibody response after the second mRNA vaccine dose (Pfizer or Moderna), with an increase to 59% after the third dose. In contrast, lung transplant recipients who were either: 1) infected with COVID-19 or 2) received at least one vaccine dose before transplant, had higher antibody levels approaching those of healthy participants. This suggests that lung transplant recipients may be able to mount a stronger immune response to higher antigen exposure, and may be able to retain their antibody response afterwards. Importantly, we found that reactogenicity was significantly less for lung transplant recipients after both the second and third dose of the vaccine compared with healthy vaccine recipients. The frequency of any systemic adverse reaction (fever, fatigue, headache, myalgia, arthralgia, chills or nausea) was 46% after the third dose for lung transplant recipients compared with 80% for healthy vaccine recipients.

In summary, lung transplant recipients have weak antibody responses to the mRNA-1273 vaccine and remain at high risk for morbidity and mortality due to Covid-19. The 100 ug third dose was associated with significantly less systemic adverse reactions compared with healthy vaccine recipients. Thus, we hypothesize that we can safely improve the immunogenicity of the mRNA-1273 vaccine by administering a 100 ug or 200 ug booster dose to lung transplant recipients, instead of the currently recommended 50 ug booster dose. We will conduct the study as an open-label dose-finding trial comparing: standard-dose (50 ug) booster, mid-dose (100 ug) and high-dose (200 ug) mRNA-1273 booster as described below.

2.1 Risk / Benefit Assessment

Efficacy of the mRNA-1273 vaccine was demonstrated in a phase 3 randomized trial of 30,420 participants in the COVD Study (3, 4). Vaccine efficacy in was 94.1% at preventing COVID-19 illness, including severe disease. Local and systemic reactions to the vaccine were common and included pain at injection site, headache, fatigue, myalgias and arthralgias. However, these reactions were transitory and there were no serious adverse events, episodes of thrombosis or myocarditis associated with the vaccine (3, 4). Hypersensitivity reactions were reported in 1.5% and 1.1% of participants in the vaccine and placebo groups, respectively.

Rare episodes of myocarditis and pericarditis have been reported after the mRNA vaccines (Pfizer-BioNTech and Moderna), particularly among young males after the second dose (9, 24, 25). The incidence of myocarditis/pericarditis is low and estimated at 3.5 cases per million doses after second dose mRNA among all adults, and 24.3 cases per million among individuals 12 to 29 years of age (10) . Most

reported cases of myocarditis/pericarditis occurred within the first 7 days of vaccination (7–9). Despite the potential for these rare but serious conditions, the benefit-risk assessment for Covid-19 vaccination remains strongly in favor of vaccination for those over age 5. Of note, myocarditis has also been associated with COVID-19 infection at a higher incidence than with the mRNA vaccines (6, 26). Analysis of a large national database found the risk ratio of myocarditis after vaccination to be 3.2 (95% CI 1.6-12.4) compared with those who were unvaccinated (6). After COVID-19 infection, the risk ratio of myocarditis was 18.3 (95% CI 4.0-25.1) compared with those who were unvaccinated.

The phase 1 mRNA-1273 clinical trial evaluated three doses: 25 ug, 100 ug and 250 ug. There was a dose-response relationship between increasing mRNA-1273 doses and serum anti-S-2P antibody levels. Systemic adverse reactions including fatigue, chills, headache, myalgia and injection site pain occurred in more than half the participants, and occurred more frequently with the 250 ug dose. Thus, the 100 ug dose was eventually chosen for the phase 3 clinical trial.

Lung transplant recipients, due to their immune suppression medicines, have had weak responses to the COVID-19 vaccines with antibody responses noted in less than 20% after the second vaccine dose (16–18). Lung transplantation is also unique among the solid organ transplants in the direct infection and injury of the allograft by SARS-CoV-2. Thus, lung transplant recipients have poor outcomes following COVID-19 infection with a high mortality rate. Third dose vaccines appear to improve immune responses for solid organ recipients, but has not been studied specifically for lung transplant recipients.

The current CDC guidance is for moderately or severely immunocompromised patients to receive a 50 ug booster: 1) At least 3 months after 3rd dose (first booster), and 2) At least 4 months after 4th dose (2nd booster). We believe that this dosing will be insufficient for many lung transplant recipients, particularly in those who did not receive any vaccine doses prior to their lung transplant, and leave them at high risk of poor COVID-19 outcomes. Importantly, due to their immunosuppression, lung recipients appear to have decreased side effects and reactogenicity to the SARS-CoV-2 vaccine.

We hypothesize that a 100 ug mid-dose and 200 ug high-dose mRNA-1273 booster dose can be safely administered to lung transplant recipients who previously received all of their vaccine doses after their lung transplant. We further hypothesize that the higher dose boosters will induce a stronger immune response to SARS-COV-2 as measured by humoral and cellular response assays. The objectives of this study are to test these two hypotheses.

3 STUDY OBJECTIVES

3.1 Primary Objective

1. Evaluate safety of high-dose mRNA-1273 booster vaccine among lung transplant recipients measured by incidence of adverse events.
2. Evaluate reactogenicity of high-dose mRNA-1273 booster vaccine among lung transplant recipients measured by the FDA Toxicity Grading scale.

3.2 Secondary Objectives

1. Evaluate humoral immunogenicity measured by anti-RBD and anti-spike (S-2P) IgG levels at Day 30.

2. Evaluate humoral immunogenicity measured by neutralizing antibody titers from a pseudovirus neutralization assay at Day 30.
3. Evaluate cellular immunogenicity measured by cellular response assays including flow cytometry with intracellular staining at Day 30.

4 STUDY DESIGN

4.1 Study Overview

This is a Phase I/II open-label dose-finding trial among lung transplant recipients who received three or four mRNA vaccine doses (mRNA-1273 or BNT162b2) after lung transplantation to: standard-dose (50 ug), mid-dose (100 ug) or high-dose (200 ug) mRNA-1273 booster vaccine. Participants will be enrolled into three dose groups: 1) Standard-dose (50 ug) – 20 participants, 2) Mid-dose (100 ug) – 20 participants, 3) High-dose (200 ug) – 20 participants. The first 2 participants in both the mid-dose and high dose groups will be considered the 'sentinel' group. Participants in the sentinel group will receive the vaccine and undergo a 7-day observation period for safety and reactogenicity before additional participants are enrolled into that dose group.

Overall study enrollment will begin with the mid-dose sentinel group (n=2). During the observation period for the mid-dose sentinel group, we will enroll two participants into the standard-dose group. Once the mid-dose sentinel group completes their 7-day observation period without triggering halting rules and is approved to proceed by the DSMB, we will enroll the next 27 participants (Cohort 1) with a 2:1 randomization into the mid-dose (n=18) and standard-dose (n=9) groups.

Once all 20 participants have received their mid-dose vaccine without triggering halting rules and is approved to proceed by the DSMB, we will enroll the high-dose sentinel group (n=2). Once the high-dose sentinel group completes their 7-day observation period without triggering halting rules and is approved to proceed by the DSMB, we will enroll the next 27 participants (Cohort 2) with a 2:1 randomization into the high-dose (n=18) and standard-dose (n=9) groups. Thus, all 20 participants in the mid-dose group will be enrolled prior to enrollment of the high-dose group.

We will perform stratified randomization for the two cohorts based on: 1) the number of prior doses, and 2) prior receipt of any BNT162b2 vaccines. Randomization with be done by the UCLA Clinical and Translational Science Institute (CTSI) statistics team based on scheduled participants prior to the study visit. The 6 participants in the sentinel (n=4) and initial (n=2) groups (Table 1) will be assigned into the 3 groups based on their scheduled visit day.

This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of mid and high-dose mRNA-1273 vaccine among lung transplant recipients who have received three or four prior mRNA vaccines.

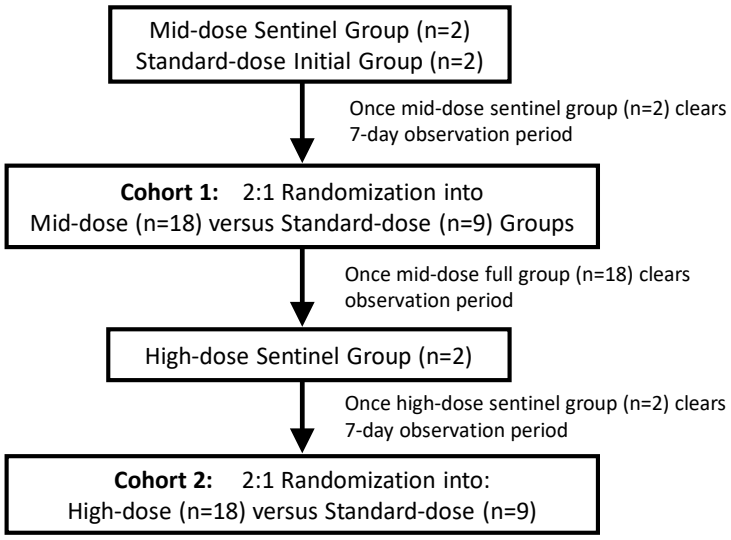
In-person visits will occur on Days 1 (booster vaccine), 7 and 30. Telephone visits will occur on Days 3, 90 and 180. Adverse events will be assessed in person (Days 1, 7 and 30) and by telephone calls (Days 3, 90 and 180). All follow-up visits will include a detailed review for serious adverse experiences (SAEs), adverse events of special interest (AESIs) and medically attended adverse events (MAAEs).

Table 1: Treatment Arms:

Groups will be enrolled as follows:	**n**	**Dose**
1) Mid-dose – Sentinel group	2	100 ug
2) Standard-dose – Initial group	2	50 ug
3) Cohort 1: 2:1 Randomization into		
Mid-dose group	18	100 ug
Standard-dose group	9	50 ug
4) High-dose – Sentinel group	2	200 ug
5) Cohort 2: 2:1 Randomization into		
High-dose group	18	200 ug
Standard-dose group	9	50 ug

Cohorts 1 and 2 will be randomized to their dose and considered the full group.

Figure 1. Study enrollment flow diagram



5 CRITERIA FOR EVALUATION

5.1 Primary Safety Endpoint

Safety will be measured by the frequency and grade of solicited and unsolicited adverse events (AEs), SAEs, AESIs and MAAEs. Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions.

1. Frequency and grade of each solicited local and systemic reactogenicity AE will be recorded on a daily diary using the FDA Toxicity Grading Scale and collected from Day 1 until Day 7.
2. Frequency and grade of each unsolicited AEs will be recorded on a daily diary and collected from Day 1 until Day 30.
3. Frequency of any SAEs, AESIs and MAAEs will be collected from Day 1 until Day 180.

Simple descriptive statistics will be used to summarize toxicities in terms of type, severity and minimum or maximum values for laboratory measures, time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects. Safety Analyses will be performed on the Safety Analysis Set.

5.2 Secondary Immunogenicity Endpoints

1. **Binding antibody:** The anti-RBD and anti-spike (S-2P) IgG concentrations (log10 and geometric mean concentrations (GMC)) at Day 30 will be evaluated with comparisons between the standard-dose versus high-dose groups. T-tests with two-sided $p<0.05$ significance will be used (overall α level of 0.1). Changes in the anti-RBC and anti-spike IgG concentrations at Day 30 will be compared pairwise between the standard-dose versus high-dose groups using two sample T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). The percent of participants with detectable antibody levels (greater than the LLOQ) at Day 30 will also be evaluated using Fisher's exact tests. Pairwise comparisons of binding antibodies will also be evaluated between the standard-dose versus mid-dose groups.

2. **Neutralizing antibody:** Neutralizing antibody titers (geometric mean titers (GMT)) from a pseudovirus neutralization assay at Day 30 will be compared between the standard-dose versus high-dose groups using T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). Changes in the neutralizing antibody titers at Day 30 will be compared between the standard-dose versus high-dose groups using two sample T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). The percent of participants with detectable neutralizing antibody levels (greater than the LLOQ) at Day 30 will also be evaluated using Fisher's exact tests. Pairwise comparisons of neutralizing antibodies will also be evaluated between the standard-dose versus mid-dose groups.

3. **Cellular immunogenicity:** The change in the frequency of target cytokine producing T-cells by flow cytometry with intracellular staining at Day 30 will be compared using the Kruskal-Wallis Test for standard-dose versus high-dose groups. A comparison of T-cell frequencies between the standard-dose versus high-dose groups will be evaluated using the Wilcoxon rank-sum test. Pairwise comparisons of cellular immunogenicity will also be evaluated between the standard-dose versus mid-dose groups.

5.3 Safety Evaluations

The study will use a Data and Safety Monitoring Board (DSMB). DSMB reviews are required for study halting and restarting. Reporting to regulatory bodies (IRB, FDA) will only be required for serious adverse events judged by the treating physician and study investigators to be potentially related to the administration of the study drug, including suspected, unexpected, serious adverse reactions (SUSAR, Section 11). All other adverse events will be reviewed by the study investigators and reported per FDA and IRB regulations. The study will be overseen by CTSI Data and Safety monitoring Board. By allowing CTSI DSMB to oversee the study, the PI agrees to abide by the CTSI DSMB's policies and procedures as outlined in the DSMB charter.

Safety evaluations:

1. **Visit 1**: Day 1 (booster day): informed consent, med history, inclusion criteria review, physical exam, blood draw, administration of booster, 30-minute observation.
2. **Telephone visit Day 3:** Review for AEs, SAEs, AESIs and MAAEs.
3. **Visit 2:** Day 7 - blood draw, physical exam and review for AEs, SAEs, AESIs and MAAEs.
4. **Visit 3**: Day 30 - blood draw, physical exam and review for AEs, SAEs, AESIs and MAAEs.
5. **Telephone visit Day 90**: Review for AEs, SAEs, AESIs and MAAEs.
6. **Telephone visit Day 180**: Review for AEs, SAEs, AESIs and MAAEs.

The following labs will be collected at baseline and clinic follow-up visits.

1. Serum collected for antibody levels.
2. PBMCs collected for cellular response assays including flow cytometry with intracellular staining.
3. Whole blood collected for cellular response assays.
4. Troponin, CK and cytokines banked from Day 0, 7 and 30.

6 PARTICIPANT SELECTION

6.1 Study Population

Participants post lung transplant who previously received three or four mRNA-1273 or BNT162b2 COVID-19 vaccines who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. All adult lung transplant recipients (age ≥ 18 at the time of consent) who received all of their COVID-19 vaccines after lung transplantation.
2. Received three or four doses of either the Moderna mRNA-1273 or Pfizer BNT162b2 vaccine with the last dose received at least 4 months prior to study enrollment.
3. Currently receiving standard regimen of three drug immunosuppression with prednisone, tacrolimus and mycophenolate mofetil (minimum 250 mg bid) or mycophenolate sodium (minimum 180 mg bid).

4. Agrees not to receive other investigational agents for prophylaxis against COVID-19 including Evusheld monoclonal antibodies for at least 30 days after the study vaccine.
5. Understands and agrees to comply with the study procedures and provides written informed consent.
6. Is in stable health without any new or worsening medical conditions in the opinion of the Investigator.
7. Female participants of childbearing potential (<1 year since start of menopause) may be enrolled in the study if the participant fulfills all the following criteria:
    a. Has a negative pregnancy test at Visit 1 Day 1.
    b. Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
    c. Has agreed to continue adequate contraception or practice abstinence through 3 months following the booster injection (Day 90).
    d. Is not currently breastfeeding.
    e. Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:
        i. Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
        ii. Intrauterine device
        iii. Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
        iv. Sterilization of a female participant's monogamous male partner prior to entry into the study
        v. Note: periodic abstinence (e.g., calendar, ovulation methods) and withdrawal are not acceptable methods of contraception.

6.3 Exclusion Criteria

1. Previous documented COVID-19 infection.
2. Use of investigational agents for prophylaxis against COVID-19 within 90 days of the start of the study, including Evusheld monoclonal antibodies.
3. Ongoing therapy for acute cellular or antibody mediated rejection.
4. Intravenous immunoglobulins (IVIG) administration within the prior 3 months or ongoing IVIG therapy.
5. Anaphylaxis or allergic reaction to any prior vaccines.
6. History of anaphylaxis or other significant adverse reaction requiring medical intervention after receipt of a vaccine.
7. Is acutely ill or febrile 24 hours prior to or at the Day 1 visit. Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the

relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

8. Pregnant or breastfeeding.
9. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
10. Known history of hypertension (HTN) with systolic blood pressure (BP) > 180 mm Hg at the Day 1 visit.
11. Known history of hypotension with systolic blood pressure < 85 mm Hg at the Day 1 visit.
12. Bleeding disorder considered a contraindication to IM injection or phlebotomy.
13. Active malignancy diagnosed within previous 4 years (excluding non-melanoma skin cancer).
14. Received a major surgery including lung transplantation in the past 3 months.

Exclusion of Specific Populations:
Because the effects on the fetus are not known, pregnant women will not be eligible for the trial. Women of childbearing potential (<1 year since start of menopause) must utilize a highly effective method of contraception and will be required to have a negative urine or serum pregnancy test within 24 hours prior to the vaccination. Children will not be included in this trial as presently there are no children receiving lung transplantation at UCLA. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including those in other populations.

7 CONCURRENT MEDICATIONS

This trial design allows for participants in all study arms to receive other investigational drugs for COVID-19 after Day 45 of the study.

7.1 Allowed Medications and Treatments

Standard therapy for COVID-19 is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below. Based on inclusion criteria, participants will be required to be on a regimen of triple immunosuppression including prednisone, mycophenolate mofetil (minimum 250 mg bid) or mycophenolate sodium (minimum 180 mg bid), and tacrolimus at the Day 1 study visit. Participants receiving IVIG or augmented immunosuppression for treatment of acute rejection or antibody mediated rejection will be excluded from the study.

7.2 Prohibited Medications and Treatments

Use of investigational agents for prophylaxis against COVID-19 within 90 days of the start of the study, including Evusheld monoclonal antibodies. Use of investigational agents for prophylaxis including Evusheld against COVID-19 for at least 30 days after study vaccination, since this will affect the antibody-based secondary endpoints.

8 STUDY TREATMENTS

8.1 Method of Assigning Participants to Treatment Groups

This is a Phase I/II open-label dose-finding trial among lung transplant recipients who received three or four mRNA vaccine doses (mRNA-1273 or BNT162b2) after lung transplantation to: standard-dose (50 ug), mid-dose (100 ug) or high-dose (200 ug) mRNA-1273 booster vaccine. Participants will be enrolled into three dose groups: 1) Standard-dose – 20 participants, 2) Mid-dose – 20 participants, 3) High-dose – 20 participants. The first 2 participants in both the mid-dose and high dose groups will be considered the 'sentinel' group. Participants in the sentinel group will receive the vaccine and undergo a 7-day observation period for safety and reactogenicity before additional participants are enrolled into that dose group.

Overall study enrollment will begin with the mid-dose sentinel group (n=2). During the observation period for the mid-dose sentinel group, we will enroll two participants into the standard-dose group. Once the mid-dose sentinel group completes their 7-day observation period without triggering halting rules and is approved to proceed by the DSMB, we will enroll the next 27 participants (Cohort 1) with a 2:1 randomization into the mid-dose (n=18) and standard-dose (n=9) groups.

Once all 20 participants have received their mid-dose vaccine without triggering halting rules and is approved to proceed by the DSMB, we will enroll the high-dose sentinel group (n=2). Once the high-dose sentinel group completes their 7-day observation period without triggering halting rules and is approved to proceed by the DSMB, we will enroll the next 27 participants (Cohort 2) with a 2:1 randomization into the high-dose (n=18) and standard-dose (n=9) groups. All 20 participants in the mid-dose group will be enrolled prior to enrollment of the high-dose group.

We will perform stratified randomization for the two cohorts based on: 1) the number of prior doses, and 2) prior receipt of any BNT162b2 vaccines. Randomization with be done by the UCLA Clinical and Translational Science Institute (CTSI) statistics team based on scheduled participants prior to the study visit. The 6 participants in the sentinel (n=4) and initial (n=2) groups (Table 1) will be assigned into the 3 groups based on their scheduled visit day.

If the halting criteria is triggered for the high-dose group and further enrollment of this group is not recommended by the study investigators, DSMB or IRB, the study will continue randomized enrollment into the mid-dose and standard-dose groups with a 1:2 ratio to complete the enrollment of 60 participants total. Since the expected immunogenicity difference between the mid-dose and standard-dose group is smaller, we will require more participants to detect a difference between these two groups. The 1:2 enrollment ratio into the mid-dose and standard-dose groups will even the distribution of participants into these two groups. The primary endpoint analysis for safety and reactogencity will not be affected by a restriction of participants into the mid-dose and standard-dose groups.

8.2 Formulation

mRNA-1273 is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.2 mg/ml. Please refer to letter of authorization (LOA) from to cross-reference the drug master file (DMF).

8.3 Packaging and Labeling

Each of the study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal Law to Investigational Use." Sterile empty vials will be provided with latex-free stoppers.

8.4 Supply of Study Drug at the Site

mRNA-1273 will be stored as per manufacturer guidelines, dispensed, and accounted for by the investigational pharmacy.

8.4.1 Dosage/Dosage Regimen

Investigational product mRNA-1273 will be administered via intramuscular injection (IM) at three doses: standard-dose (50 ug), mid-dose (100 ug) or high-dose (200 ug).

Table 2: Dosing and Administration

Group	Sample Size	Dose	Route	Frequency
1 Standard	20	50 ug	IM	Day 1
2 Mid-dose	20	100 ug	IM	Day 1
3 High-dose	20	200 ug	IM	Day 1

8.4.2 Dispensing

Investigational product mRNA-1273 will be received at 0.2 mg/ml concentration and dispensed by the investigational pharmacy undiluted at three dosages: 50 ug (0.25 ml), 100 ug (0.5 ml) and 200 ug (1 ml).

8.4.3 Administration Instructions

Each dose will be administered via IM injection into the deltoid muscle on Day 1.

8.5 Supply of Study Drug at the Site

Study drug will be supplied by Moderna and stored at the UCLA investigational pharmacy as per manufacturer guidelines, dispensed, and accounted for by the investigational pharmacy.

8.5.1 Storage

Vaccine mRNA-1273 will be stored at 2° to 8°C (35.6° to 46.4°F) at clinical sites before preparation and vaccination. No dilution will be required. Doses could be held in syringes for up to 8 hours at room temperature before administration.

The number of study drug dispensed will be recorded on the Investigational Drug Accountability Record. The UCLA Clinical & Translational Science Institute - Office of Regulatory Affairs (CTSI ORA) will verify these documents throughout the course of the study.

8.6 Measures of Treatment Compliance

Not applicable

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the participant or participant's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

Based on inclusion criteria, participants will be required to be on a regimen of triple immunosuppression including prednisone, mycophenolate mofetil (minimum 250 mg bid) or mycophenolate sodium (minimum 180 mg bid), and tacrolimus at the Day 1 study visit. Participants receiving IVIG or augmented immunosuppression for treatment of acute rejection, antibody mediated rejection or chronic rejection will be excluded from the study.

9.1.2 Demographics

Demographic information will be recorded at enrollment including race, ethnicity, sex, age, BMI, medication history, co-morbidities including cardiovascular disease, risk factors for cardiovascular disease, and immunosuppressive agents.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying risk factors will be recorded at screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician or a qualified member (NP) of the study team at Day 1. Qualified members of the study team (MD, NP, RN and PA) will perform a symptom directed physical exam on Days 7 and 30. New abnormal physical exam findings will be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse oximetry, and respiratory rate will be performed and recorded.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Research Labs

Blood will be obtained and sent to the research lab for:

1. Total immunoglobulins: IgG, IgA, IgM.
2. Anti-RBD, anti-spike binding and neutralizing antibody levels
3. PBMCs collected for cellular response assays including flow cytometry with intracellular staining.
4. Whole blood collected for cellular response assays.
5. Troponin / CK and cytokines for storage on Days 0, 7 and 30.

9.2.2 Clinical Labs

The following may be checked for any unscheduled visits: Complete blood count with differential, comprehensive metabolic panel, tacrolimus / sirolimus level, C-reactive protein, erythrocyte sedimentation rate (ESR), total immunoglobulins (IgG, IgA, IgM), anti-RBD, anti-spike and neutralizing antibody levels, PBMCs collected for cellular response assays including flow cytometry with intracellular staining, whole blood collected for cellular response assays, troponin / CK, cytokines, PT, PTT, INR (16 mL of venous blood).

10 EVALUATIONS BY VISIT

10.1 Screening/Enrollment Day -30 to 0 (Phone)

1. Pre-screen participants via chart review using HIPAA waiver.
2. Invite eligible participants by phone to participate in study.
3. A qualified member of the study team will review study and provide ICF form. Participants will be asked to sign consent at Visit 1 prior to initiating any study-related procedures.
4. Assign the participant a unique screening number.

10.2 Visit 1 Day 1 (Clinic): Booster Vaccine Day

1. For participants who meet inclusion/exclusion criteria, the investigator team will again review the study with the participant (or participant's legal representative) in person and obtain written informed consent and HIPAA authorization.
2. Record demographic data.
3. Record medical history.
4. Review of birth control history with female participants of childbearing potential (<1 year since start of menopause).

5. For women of childbearing potential, counsel participants to use adequate birth control methods required during the trial to avoid pregnancy.
6. For women of childbearing potential, urine pregnancy test will be checked prior to study drug administration on Visit 1 (Day 1).
7. Confirmation participants meet all inclusion criteria and no exclusion criteria review.
8. Review pre-study concomitant medications and therapies and record on the appropriate CRF.
9. Review of influenza and any all 2019-CoV vaccinations or other experimental coronavirus vaccines.
10. Vital signs (HR, BP, temperature, oximetry), and height and weight for determination of BMI.
11. Full physical exam will include assessments of the following organs and organ systems: skin, head, ears, eyes, nose, and throat (HEENT), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
12. Obtain blood samples for baseline: Total immunoglobulins (IgG, IgA, IgM), anti-RBD, anti-spike binding and neutralizing antibody levels, PBMCs collected for cellular response assays including flow cytometry with intracellular staining, whole blood collected for cellular response assays, troponin / CK and cytokines for storage.
13. Confirm group assignment: standard-dose, mid-dose or high-dose group.
14. Inform participants of their designated dose.
15. Administration of booster vaccine.
16. Participants will be observed for 30-minutes post injection administration.
17. Dispense daily diary of symptoms for first 7 days after injection dispensed to participant measuring FDA Toxicity Grading Scale and adverse events.

10.3 Visit 2 Day 3 +/-1 Day (Phone – 2 days post booster):

1. All participants will complete a daily diary of solicited and unsolicited AEs from the vaccination until 7 days post-vaccination. Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions for the first 7 days post-vaccination utilizing the FDA Toxicity Grading Scale.
2. Participants will be contacted by telephone to query for safety events and review daily diaries. Based on the information collected, participants may be asked to return to the clinic for evaluation for an unscheduled visit.
3. Review daily diaries, AEs (solicited and unsolicited), SAEs, AESIs and MAAEs.
4. Participants will contact their primary care doctor, lung transplant pulmonologist or study principal investigator with any SAEs, AESIs or MAAEs.

10.4 Visit 3 Day 7 +/-2 Days (Clinic Visit – 6 days post booster):

1. Vital signs (HR, BP, temperature, oximetry), and height and weight for determination of BMI.
2. Symptom-directed (targeted) physical exam. Targeted physical examinations should also include an assessment for signs suggestive of AEs and AESIs. Interim or unscheduled physical examinations will be performed at the discretion of the PI or appropriate sub-investigator, if necessary, to evaluate AEs or abnormal clinical laboratory test results.
3. Obtain blood samples for follow-up: Total immunoglobulins (IgG, IgA, IgM), anti-RBD, anti-spike binding and neutralizing antibody levels, PBMCs collected for cellular response assays including flow cytometry with intracellular staining, whole blood collected for cellular response assays, troponin / CK and cytokines for storage.

5. Review daily diaries, AEs (solicited and unsolicited), SAEs, AESIs and MAAEs.

10.5 Visit 4 Day 30 +/- 7 Days (Clinic – 29 days post booster):

1. Vital signs (HR, BP, temperature, oximetry), and height and weight for determination of BMI.
2. Symptom-directed (targeted) physical exam. Targeted physical examinations should also include an assessment for signs suggestive of AEs and AESIs. Interim or unscheduled physical examinations will be performed at the discretion of the PI or appropriate sub-investigator, if necessary, to evaluate AEs or abnormal clinical laboratory test results.
3. Obtain blood samples for follow-up: Total immunoglobulins (IgG, IgA, IgM), anti-RBD, anti-spike binding and neutralizing antibody levels, PBMCs collected for cellular response assays including flow cytometry with intracellular staining, whole blood collected for cellular response assays, troponin / CK and cytokines for storage.
4. Review daily diaries, AEs (solicited and unsolicited), SAEs, AESIs and MAAEs.

10.6 Visit 5 Day 90 +/- 7 Days (Phone – 89 days post booster):

1. Participants will be contacted by telephone to query for safety events. AEs (solicited and unsolicited), SAEs, AESIs and MAAEs will be reviewed. Based on the information collected, participants may be asked to return to the clinic for evaluation.

10.7 Visit 6 Day 180 +/- 7 Days (Phone – 179 days post booster): End of study

1. Participants will be contacted by telephone to query for safety events. AEs (solicited and unsolicited), SAEs, AESIs and MAAEs will be reviewed. Based on the information collected, participants may be asked to return to the clinic for evaluation.

10.8 Unscheduled Additional Visit as needed

1. Clinical evaluation for symptoms to include physical exam and ECG as needed.
2. Obtain blood samples for evaluation: Complete blood count with differential, comprehensive metabolic panel, tacrolimus / sirolimus level, C-reactive protein, erythrocyte sedimentation rate (ESR), total immunoglobulins (IgG, IgA, IgM), anti-RBD, anti-spike and neutralizing antibody levels, PBMCs collected for cellular response assays including flow cytometry with intracellular staining, whole blood collected for cellular response assays, troponin / CK, cytokines, PT, PTT, INR (16 mL of venous blood).
3. AEs (solicited and unsolicited), SAEs, AESIs and MAAEs will be reviewed. Based on the information collected, participants may be asked to return to the clinic for evaluation.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory

finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it will be recorded as an AE.

AEs can be further divided into solicited AEs and unsolicited AEs. Solicited AEs are those for which the study team will specifically query the subject whether they occurred. Unsolicited AEs are those events that the subject report occurring without being queried about the specific event.

A suspected adverse event is one for which there is a 'reasonable possibility' that the drug caused the adverse event. A 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event, but implies a lesser degree of certainty about causality compared with an adverse event. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure. All AEs will be assessed for severity and relationship to study intervention (Tables 3 and 4). Suspected, Unexpected, Serious Adverse Reactions (SUSAR) is an adverse event where a causal relationship with the study drug is at least possible but not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics and includes any of the following: suspected AE, unexpected AE and serious adverse experience (SAE). Episodes of myocarditis or pericarditis occurring in temporal association with vaccination will be reported as a SUSAR. Medically attended adverse event (MAAE) is defined as hospitalization, an emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason.

Frequency and grade of each solicited AE (local and systemic reactogenicity) will be collected until Day 7 using the FDA Toxicity Grading Scale to be recorded on a daily diary. Frequency and grade of each unsolicited AEs will be collected until Day 30. Frequency of any SAEs, AESIs and MAAEs will be collected until Day 180. After Day 30 through the end of study on Day 180, only SAEs, AESIs and MAAEs will be reported as AEs. All AEs, solicited and unsolicited, will be captured on the appropriate CRF. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate possible etiology, date of resolution, seriousness, and outcome. AEs occurring during the study-collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed to resolution or stabilization.

Solicited Adverse Events:
Solicited AEs are anticipated local and systemic AEs for which consistent collection of information is desired. Study clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 7 days. Solicited AEs (i.e., reactogenicity) will be collected using a daily diary and recorded on the appropriate CRF from the time of the vaccination until 7 days post vaccination (Days 1-7). For this study, solicited AEs will be defined and graded as follows (Tables 3):

Table 3: Solicited Adverse Reactions and Grading

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > (greater than) 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< (less than) 25 mm or < 2.5 cm	25 - 50 mm or 2.5 - 5 cm	51 - 100 mm or 5.1 - 10 cm	> 100 mm or > 10 cm	Necrosis or exfoliative dermatitis (severe skin rash causing skin discoloration or peeling)
Injection site swelling/induration (hardness)	< 25 mm or < 2.5 cm	25 - 50 mm or 2.5 - 5 cm	51 - 100 mm or 5.1 - 10 cm	> 100 mm or > 10 cm	Necrosis (severe swelling with skin discoloration, blistering, or peeling)
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
					hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration (fluids given through blood veins)	Requires emergency room visit or hospitalization for low blood pressure
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F
Rash	No rash	Localized rash, without associated symptoms	Maculopapular rash (bumpy and red rash) covering < 50% body surface area	Generalized urticarial rash (hives or itchy rash) covering > 50% body surface area	Generalized exfoliative, ulcerative or bullous dermatitis (severe skin rash causing skin discoloration, peeling or blistering)

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
If you experience any grade 4 symptom from your daily diary, or any other severe symptoms that prevents your daily activity AND requires you to see a doctor, please call Dr. Michael Shino immediately at 310-206-6766. The operator will answer the call, please tell them that you would like to "page Dr Shino". Dr Shino or another covering Dr will call you back.					

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Unsolicited Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from study staff or revealed by observation, physical examination or other diagnostic procedures must be recorded on the appropriate CRF. Unsolicited AEs of all severities will be reported from the time of study product administration through Day 30. After Day 30, only SAEs and AESIs will be reported through the end of the study (Day 180).

AE Severity

"Table 3: Solicited Adverse Reactions and Grading" will be used to assess and grade solicited AE severity. "Appendix 3: Table of Laboratory Abnormalities" will be used to grade any laboratory abnormalities observed. If the adverse event is not covered in Table 3 and Appendix 3, the guidelines shown in Table 4 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 4. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	These events do not interfere with the participant's daily activities.
Moderate (2)	These events cause some interference with the participant's daily activities and require limited or no medical intervention.
Severe (3)	These events prevent the participant's daily activity and require intensive therapeutic intervention.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following guidelines in Table 5.

Table 5. AE Relationship to Study Drug

Relationship to Drug	Comment

Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

1. death
2. a life-threatening adverse experience
3. inpatient hospitalization or prolongation of existing hospitalization
4. a persistent or significant disability/incapacity
5. a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

Participants will be instructed to call a study team line (attended 24-hours per day) if they experience any grade 4 symptom from the "Solicited Adverse Reactions and Grading" table (Table 3), any severe unsolicited AE (Table 4), or any SAE. The study team member will interview, document and triage the participant for further evaluation.

11.2.1 Serious Adverse Experience Reporting

All SAEs that occur (whether or not related to study drug) will be reported per UCLA OHRPP IRB guidelines and policy. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB and FDA.

11.3 Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical topic of interest, for which ongoing monitoring and immediate notification by the investigator is required and documentation is in the form of a case narrative. Such events may require further investigation to characterize and understand them. Refer to Appendix 2 for a list of AESIs pertinent to this study. All AESIs will be collected through the entire

study period and must be reported immediately and in all circumstances within 7 days of becoming aware of the event. AESIs were identified as immunologically driven sequelae of COVID-19 and thus topics of interest/AESIs for all COVID vaccines.

Anaphylaxis

All suspected cases of anaphylaxis should be recorded and reported as an SAE and AESI, based on criteria for a medically important event, unless the event meets other serious criteria. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition (27).

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by:

1. Sudden onset AND
2. Rapid progression of signs and symptoms AND
3. Involving 2 or more organ systems, as follows:
    a. Skin/mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes
    b. Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation
    c. Respiratory: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea
    d. Gastrointestinal: diarrhea, abdominal pain, nausea, vomiting

Acute Myocarditis and/or Pericarditis

All suspected cases of probable or confirmed myocarditis, pericarditis, or myopericarditis should be recorded as an AESI, and reported as an SAE, if the event meets seriousness criteria. As an SAE, the event should be reported immediately and in all circumstances within 72 hours. The investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data within 72 hours of it being available. For reporting purposes, a participant who displays signs/symptoms consistent with the CDC case definitions as described below (27), should be reported as a potential case of confirmed or probable myocarditis, pericarditis, or myopericarditis.

The CDC case definitions are intended to serve as a guide to help in the diagnosis and reporting of suspected cases of myocarditis and/or pericarditis; however, the diagnosis of suspected cases is left to the investigator's clinical judgement.

Acute Myocarditis Case Definition

Presence of ≥ 1 new or worsening of the following clinical symptoms (persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis [probable or confirmed]):

1. Chest pain/pressure/discomfort

2. Dyspnea/shortness of breath/pain with breathing
3. Palpitations
4. Syncope

AND

For PROBABLE CASE:

Presence of ≥ 1 new finding of the following:

1. Troponin level above upper limit of normal (any type of troponin)
2. Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis

   To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of the following:

   a. ST segment or T-wave abnormalities
   b. Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias
   c. AV nodal conduction delays or intraventricular conduction defects

3. Abnormal cardiac function or wall motion abnormalities on echocardiogram
4. Cardiac magnetic resonance imaging (cMRI) finding consistent with myocarditis (28).

AND

1. No other identifiable cause of the symptoms and findings

For CONFIRMED CASE:

1. Histopathologic confirmation of myocarditis (using Dallas criteria (29))

OR

2. cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin).

AND

1. No other identifiable cause of the symptoms and findings

Acute Pericarditis Case Definition

Presence of ≥ 2 new or worsening of the following clinical features (30):

1. Acute chest pain (Typically described as pain made worse by lying down, deep inspiration, or cough; and relieved by sitting up or leaning forward, although other types of chest pain may occur)
2. Pericardial rub on examination
3. New ST-elevation or PR-depression on EKG
4. New or worsening pericardial effusion on echocardiogram or magnetic resonance imaging

Myopericarditis Case Definition

Participants who meet criteria for both myocarditis and pericarditis may be described under myopericarditis.

11.4 Medical Monitoring

Michael Shino, MD or S. Sam Weigt, MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Yusaku Michael Shino, MD
Telephone: 310-866-6327
Pager: 310-206-6766 Pgr#24405

S. Sam Weigt, MD
Telephone: 310-825-8599
Pager: 310-206-6766 Pgr#20928

12 DISCONTINUATION AND REPLACEMENT OF PARTICIPANTS

12.1 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

After the screening assessments have been completed, the PI or qualified designee is to review the inclusion and exclusion criteria and determine the participant's eligibility for the study. Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race, BMI, medication history, co-morbidities including cardiovascular disease, risk factors for cardiovascular disease, and immunosuppressive agents) and reason for ineligibility. Participants who are found to be ineligible will be told the reason for ineligibility.

12.2 Halting Criteria for Sentinel Group

The study will be paused if any of the following events occur in the mid-dose (n=2) or high-dose (n=2) sentinel groups and enrollment may resume only after the DSMB reviews the events and permits the study to continue.

1. Any grade 4 (Table 3) solicited local or systemic reaction considered to be at least possibly related to vaccination within 7 days after administration of the vaccine.
2. Two or more grade 3 (Table 3) solicited local or systemic reaction in the same dose group considered to be at least possibly related to vaccination that lasted at least 48 hours within 7 days after administration of the vaccine.
3. Any severe allergic reaction that is at least possibly related to vaccination within 24 hours after administration of the vaccine.

4. Any SAE within 28 days after administration of the vaccine considered to be at least possibly related to vaccination.
5. Any episode of myocarditis / pericarditis within 28 days after administration of the vaccine.
6. Any new episodes of elevated troponin, ECG and physical exam findings concerning for myocarditis / pericarditis within 28 days after administration of the vaccine.
7. Any death unless determined to be definitely not related to vaccination within 90 days after administration of the vaccine.

12.3 Halting Criteria for Full Group (Cohorts 1 and 2)

The study will be paused if any of the following events occur in the full group (standard (n=18), mid (n=18) and high dose (n=18) groups) and enrollment may resume only after the DSMB reviews the events and permits the study to continue.

1. Any grade 4 (Table 3) solicited local or systemic reaction in the mid or high-dose groups considered to be at least possibly related to vaccination within 7 days after administration of the vaccine.
2. Three or more grade 3 (Table 3) solicited local or systemic reaction in the same dose group considered to be at least possibly related to vaccination that lasted at least 48 hours within 7 days after administration of the vaccine.
3. Any three participants with severe allergic reaction that is at least possibly related to vaccination within 24 hours after administration of the vaccine.
4. Any SAE within 28 days after administration of the vaccine considered to be at least possibly related to vaccination.
5. Any episode of myocarditis / pericarditis within 28 days after administration of the vaccine.
6. Any new episodes of elevated troponin, ECG and physical exam findings concerning for myocarditis / pericarditis within 28 days after administration of the vaccine.
7. Any death unless determined to be definitely not related to vaccination within 90 days after administration of the vaccine.

If the halting criteria is triggered for the high-dose group and further enrollment of this group is not recommended by the study investigators, DSMB or IRB, the study will continue randomized enrollment into the mid-dose and standard-dose groups with a 1:2 ratio to complete the enrollment of 60 participants total. Since the expected immunogencity difference between these two groups will be smaller, we will require more participants to detect a difference between these two groups. The 1:2 enrollment ratio into the mid-dose and standard-dose groups will even the distribution of participants into these two groups. The primary endpoint analysis for safety and reactogencity will not be affected by a restriction of participants into the mid-dose and standard-dose groups.

12.4 Early Discontinuation of Study

A participant may be discontinued from study treatment at any time if the participant or study team determines that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

1. Participant withdrawal of consent
2. Participant is not adherent with study procedures
3. Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
4. Protocol violation requiring discontinuation of study treatment
5. Loss to follow-up

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be recorded in the study.

12.5 Withdrawal of Participants from the Study

A participant may be withdrawn from the study at any time if the participant, the sponsor/investigator, or the study team determines that it is not in the participant's best interest to continue.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents. As noted above, participants who discontinue study early (i.e., they withdraw prior to the last visit) should have an early discontinuation visit if they have been discharged from the hospital. Participants who withdraw should be encouraged to come in for a final laboratory visit.

When a participant withdraws or is withdrawn from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the eCRF. These participants will be requested to complete the EOS assessments scheduled for end of participation.

12.6 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the study site for a required study visit:

1. The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
2. Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (e.g., dates of telephone calls and registered letters) should be documented in the participant's study source document.

3. Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
4. A participant should not be considered lost to follow-up until due diligence has been completed. Date of withdrawal/lost to follow-up should be the date of last contact with the participant where safety status of the participant was assessed (e.g., study site visit, telephone call).

12.7 Replacement of Participants

Any participant who is withdrawn or who is lost to follow-up from the study may be replaced at the principal investigator's discretion.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the participant, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

1. Failure to meet inclusion/exclusion criteria
2. Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a participant.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. The form will be sent to the IRB and a copy will be filed in the site's regulatory binder.

14 STATISTICAL METHODS AND CONSIDERATIONS

14.1 General Considerations

Data collected in this study will be presented using summary tables and participant data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. Data Sets Analyzed:

- **Intent-to-Treat (ITT) Analysis Set**

The ITT analysis set includes all participants who are enrolled into a treatment (dose) group regardless of whether participants receive any study drug(s), or receive a different regimen from the regimen they were randomized to. Participants will be assigned into a dose group as described above.

- **Safety Analysis Set**

A safety analysis set will include data from participants who receive at least one dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set will be used in the analyses of safety variables (primary endpoint) as well as study treatment administration.

- **Per-Protocol (PP) Analysis Set**

The PP analysis set includes data from participants in the ITT analysis set who meet the general criteria defining the target population for this study, are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Treatment assignment will be designated according to the actual treatment received. The PP analysis set will be used in the analyses of the secondary endpoints. The PP analysis set will only include participants randomized to the dose-group (Cohorts 1 and 2, Figure 1). The PP analysis set will exclude participants in the sentinel mid-dose (n=2), sentinel high-dose (n=2) and initial standard-dose groups (n=2) who were not randomized to their dose-group. Participants who are found to have detectable anti-N-protein IgG antibody levels (representing prior infection) at their Day 1 (baseline) visit will be excluded from the PP analysis set.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be included: race, ethnicity, sex, age, BMI, medication history, co-morbidities including cardiovascular disease, risk factors for cardiovascular disease, and immunosuppressive agents.

14.3 Analysis of Primary Endpoint

Safety will be measured by the frequency and grade of AEs (solicited and unsolicited), SAEs, AESIs, MAAEs. Reactogenicity will be measured by the occurrence and severity of solicited injection site and systemic reactions. Simple descriptive statistics will be used to summarize toxicities in terms of type, severity and minimum or maximum values for laboratory measures, time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects. Safety Analyses will be performed on Safety Analysis Set.

14.4 Analysis of Secondary Endpoints

1. **Binding antibody:** The anti-RBD and anti-spike (S-2P) IgG concentrations (log10 and geometric mean concentrations (GMC)) at Day 30 will be evaluated with comparisons between the standard-dose versus high-dose groups. T-tests with two-sided $p<0.05$ significance will be used (overall α level of 0.1). Changes in the anti-RBC and anti-spike IgG concentrations at Day 30 will be compared between the standard-dose versus high-dose groups using two sample T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). The percent of participants with detectable antibody levels (greater than the LLOQ) at Day 30 will also be evaluated using Fisher's exact tests. Pairwise comparisons of binding antibodies will also be evaluated between the standard-dose versus mid-dose groups.

2. **Neutralizing antibody:** Neutralizing antibody titers (geometric mean titers (GMT)) from a pseudovirus neutralization assay at Day 30 will be compared between the standard-dose versus high-dose groups using T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). Changes in the neutralizing antibody titers at Day 30 will be compared between the standard-dose versus high-dose using two sample T-tests with two-sided $p<0.05$ significance (overall α level of 0.1). The percent of participants with detectable neutralizing antibody levels (greater than the LLOQ) at Day 30 will also be evaluated using Fisher's exact tests. Pairwise comparisons of neutralizing antibodies will also be evaluated between the standard-dose versus mid-dose groups.

3. **Cellular immunogenicity:** The change in the frequency of target cytokine producing T-cells by flow cytometry with intracellular staining at Day 30 will be compared using the Kruskal-Wallis Test for the standard-dose versus high-dose groups. A comparison of T-cell frequencies between the standard-dose versus high-dose groups will be evaluated using the Wilcoxon rank-sum test. Pairwise comparisons of cellular immunogenicity will also be evaluated between the standard-dose versus mid-dose groups.

14.5 Analysis of Safety

Safety is the primary endpoint and described above. Simple descriptive statistics will be used to summarize frequency and grade of AEs (solicited and unsolicited), SAEs, AESIs and MAAEs. Safety Analyses will be performed on Safety Analysis Set.

14.6 Sample Size Justification

The overall mean log10 IgG increase after the third (100 ug) vaccine dose was 0.46 with standard deviation (SD) 0.63. Assuming participants have a 50% lower response to the 50 ug fourth-dose, the expected mean log10 IgG increase is 0.23. Assuming participants have a 100% higher response to the 200 ug fourth-dose, their expected mean log10 IgG increase is 0.91. For 80% power to detect this difference between high-dose and standard-dose groups with a SD of 0.63 for a two-sample t-test with two-sided $\alpha<0.05$ significance, the minimum required sample size is 15 per group. Thus, we will enroll 20 participants in each group. The first 2 participants in the mid and high-dose groups will be enrolled as the sentinel group to ensure an acceptable safety profile before the full group is enrolled.

If the halting criteria is triggered for the high-dose group and further enrollment of this group is not recommended by the study investigators, DSMB or IRB, the study will continue randomized enrollment into the mid-dose and standard-dose groups with a 1:2 ratio to complete the enrollment of 60 participants total. Since the expected immunogenicity difference between the mid-dose and standard-dose group is smaller, we will require more participants to detect a difference between these two groups. The 1:2 enrollment ratio into the mid-dose and standard-dose groups will even the distribution of participants into these two groups. The primary endpoint analysis for safety and reactogencity will not be affected by a restriction of participants into the mid-dose and standard-dose groups.

14.7 Interim Analysis

Interim analysis of the secondary immunogenicity endpoints (humoral and cellular immunogenicity) may be conducted once all study participants have completed their Day 30 visit and blood draw.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with the study drug.

Study personnel will enter data from source documents corresponding to each participant into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Participants will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a participant number.

The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a secure, de-identified, database. The study coordinators will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Sponsor/Investigator must make study data accessible to the monitor, IRB/ and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each participant must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (participant files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor/Investigator is required to maintain study records.

15.6 Monitoring

This study will be monitored by the UCLA Clinical & Translational Science Institute – Office of Regulatory Affairs (CTSI ORA). Monitoring visits will be conducted according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Sponsor/Investigator grants permission to the appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Participant Confidentiality

In order to maintain participant confidentiality, only a participant number will identify all study participants on CRFs and other documentation.

ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a participant's name to a participant identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

15.8 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor/Investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to participants. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRBs are notified within five working days.

15.9 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning participant recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The

IRB unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the participants of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.10 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, and HIPAA authorization and provide the documents to the IRB/. The consent form generated by the Investigator must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will include the IRB/ -approved copy of the Informed Consent Form in the study file.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. Information should be given in both oral and written form and participants (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a participant is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the participant. A copy of the signed consent form) will be given to the participant or legal representative of the participant and the original will be maintained with the participant's records.

15.11 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.12 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of participants.
2. Personally, conduct or supervise the study (or investigation).

3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to participants or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the participants.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SCHEDULE OF EVENTS

	Screening Day -30 to Day 0	Visit 1 Day 1 Clinic	Visit 2 Day 3 Phone +/-1 day	Visit 3 Day 7 Clinic +/-2 days	Visit 4 Day 30 Clinic +/-7 days	Visit 5 Day 90 Phone +/-7 days	Visit 6 Day 180 Phone +/-7 days	Unscheduled visit as needed
Informed Consent		X						
Demographic data		X						
Medical History		X						
Eligibility review	X	X						
Con meds		X						
Pre-study meds		X						
Review CoV vaccinations		X						
Height		X						
Weight		X		X	X			
Vital Signs (HR, BP, temperature, oximetry)		X		X	X			
Full physical exam		X						X

Targeted physical exam				X	X			
Blood draw*		X		X	X			X
Group assignment		X						
IP administration		X						
30-minute post-dose observation		X						
Review AEs, SAEs, AESIs, MAAEs			X	X	X	X	X	X
Review myocarditis and pericarditis symptoms			X	X	X	X	X	X
Dispense daily diary		X						
Diary review			X	X				
Pregnancy test (women of child-bearing potential)		X						
Birth control history (women of child-bearing potential)		X						
Review participants' use of appropriate birth control (if applicable)		X						

*Baseline labs must be drawn before vaccine dose. Day 7 must be drawn +/- 2 days. All other labs can be drawn +/- 7 days.

APPENDIX 2: ADVERSE EVENTS OF SPECIAL INTEREST (AESI) TERMS

The Investigator's medical judgement must be applied to assess an event as an AESI, as most AESIs are based on medical concepts. The table below does not provide a comprehensive list of terms.

The following table describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, per protocol, even when they occur during/following COVID infection.

Please note: **COVID-19 itself is not an AESI.**

Medical Concept	Medical Concept Descriptions/Guidance
0. Not an AESI	
1. Anosmia, Ageusia	• New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology • DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
2. Subacute thyroiditis	• Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) • DOES NOT INCLUDE new onset of chronic thyroiditis
3. Acute pancreatitis	• New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
4. Appendicitis	• Any event of appendicitis
5. Rhabdomyolysis	• New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
6. Acute respiratory distress syndrome (ARDS)	• New onset of ARDS/respiratory failure due to acute inflammatory lung injury • DOES NOT INCLUDE non-specific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
7. Coagulation disorders	• New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (ex. stroke, DVT, pulmonary embolism, disseminated intravascular coagulation (DIC), etc.)
8. Acute cardiovascular injury	• New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by ECG (ex. atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. • DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.

Medical Concept	Medical Concept Descriptions/Guidance
9. Acute kidney injury	• New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc.; • Increase in serum creatinine by ≥ 0.3 mg/dl (or ≥26.5 µmol/l) within 48 hours; **OR** • Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days
10. Acute liver injury	• New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc.: • >3-fold elevation above the upper normal limit for ALT or AST; **OR** • >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
11. Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rash • Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, Toxic epidermal necrolysis, Drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions
12 Systemic inflammatory syndromes	• Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C) • Kawasaki's disease • Hemophagocytic lymphohistiocytosis (HLH)
13. Thrombocytopenia	• Platelet count < 150 x10^9/L (thrombocytopenia) • New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome
14. Acute aseptic arthritis	Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR. • DOES NOT INCLUDE new onset of chronic arthritic conditions
15. New onset, or worsening, of neurological disease	• Immune-mediated neurological disorders • Guillain-Barre Syndrome • Acute disseminated encephalomyelitis (ADEM) • Peripheral facial nerve palsy (Bell's palsy) • Transverse myelitis • Encephalitis/Encephalomyelitis • Aseptic meningitis • Seizures/convulsions/epilepsy • Narcolepsy/hypersomnia
16. Anaphylaxis	• Anaphylaxis associated with study drug administration

Medical Concept	Medical Concept Descriptions/Guidance
17. Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome • Myalgic encephalomyelitis • Post viral fatigue syndrome • Myasthenia gravis

APPENDIX 3: TABLE OF LABORATORY ABNORMALITIES

Test	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium (Hyponatremia) mEq/L	132 - 134	130 - 131	125 - 129	< 125
Sodium (Hypernatremia) mEq/L	144 - 145	146 - 147	148 - 150	> 150
Potassium (Hyperkalemia) mEq/L	5.4 - 5.6	5.6 - 5.8	5.8 - 6.0	> 6.0
Potassium (Hypokalemia) mEq/L	3.2 - 3.5	3.0 - 3.1	2.8 - 2.9	< 2.8
Glucose (Hypoglycemia) mg/dL	65 - 69	55 - 64	45 - 54	< 45
Glucose (Hyperglycemia) mg/dL				
Fasting	110 - 110	111 - 125	> 125	Requires insulin
Random	110 - 125	126 - 200	> 200	Requires insulin
Blood Urea Nitrogen (BUN) mg/dL	30 - 35	35 - 40	> 40	Requires dialysis
Creatinine (Cr) mg/dL	1.8 - 2.3	2.4 - 2.8	2.9 - 3.2	> 3.2 or Requires dialysis
Calcium (Hypocalcemia) mg/dL	8.0 - 8.4	7.5 - 7.9	7.0 - 7.4	< 7.0
Calcium (Hypercalcemia) mg/dL	10.5 - 11.0	11.1 - 11.5	11.6 - 12.0	> 12.0
Magnesium (Hypomagnesemia) mg/dL	1.3 - 1.5	1.0 - 1.2	0.7 - 0.9	< 0.7
Phosporus (Hypophosphatemia) mg/dL	2.3 - 2.5	2.0 - 2.2	1.6 - 1.9	< 1.6
CPK	1.25 - 1.5 ULN	1.6 - 3.0 x ULN	3.1 - 10 x ULN	> 10 x ULN
Albumin (Hypoalbuminemia) mg/dL	2.5 - 2.8	2.1 - 2.4	< 2.1	---
Protein (Hypoproteinnemia) mg/dL	5.0 - 5.5	4.4 - 4.9	< 4.4	---
Alkaline Phosphatate - **Increase by Factor**	1.1 - 2.0 x ULN	1.6 - 3.0 x ULN	3.1 - 10 x ULN	> 10 x ULN
Liver function Tests (ALT, AST) - **Increase by Factor**	1.1 - 2.5 x ULN	2.6 - 5.0 ULN	5.1 - 10 x ULN	> 10 x ULN
Bilirubin - when accompanied by any increase in LFTs - **Increase by Factor**	1.1 - 1.25 x ULN	1.26 - 1.5 x ULN	1.51 - 1.75 x ULN	>1.75 x ULN
Bilirubin - when LFTs are normal - **Increase by Factor**	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
Pancreatic enzymes (Amylase, lipase)	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.0 - 5.0 x ULN	>5.0 x ULN
Hemoglobin (Female)	8.6 - 9.1	8.1 - 8.5	7.0 - 8.0	< 7.0
Hemoglobin (Female) **change from baseline** value gm/dL	1.2 - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
Hemoglobin (Male)	9.1 - 9.5	8.6 - 9.0	7.5 - 8.5	< 7.5
Hemoglobin (Male) **change from baseline** value gm/dL	1.2 - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
WBC (High) cell/mm^3	15,000 - 20,000	20,001 - 25,000	25,001 - 30,000	> 30,000
WBC (Low) cell/mm^3	1,501 - 2,000	1,001 - 1,500	500 - 1,000	< 500
Lymphocyte (Low) cell/mm^3	601 - 800	401 - 600	200 - 400	< 200
Neutrophil (Low) cell/mm^3	701 - 1,000	501 - 700	401 - 500	< 400
Eosinophils (High) cell/mm^3	650 - 1,500	1,501 - 5,000	> 5,000	Hypereosiniphilic
Platelets (Low) cell/mm^3	60,001 - 80,000	40,001 - 60,000	> 25,000 - 40,000	< 25,000
Prothrombin time (PT) - **Increase by Factor**	1.11 - 1.2	1.21 - 1.3	1.31 - 1.4 x ULN	>1.4 ULN
Partial thrombinplastin time (PTT) - **Increase by Factor**	1.31 - 1.4	1.41 - 1.5	1.51 - 1.6 x ULN	>1.6 ULN
Fibrinogen (High) mg/dL	400 - 500	501 - 600	> 600	---
Fibrinogen (Low) mg/dL	150 - 200	125 - 149	100 - 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation

[1] ULN - Upper limit of normal.

[2] Values highlighted in yellow are adjusted from "Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventitive Vaccine Clinical Trials" to reflect immunosuppressed lung transplant population.

APPENDIX 4: CLAIM FOR CATEGORICAL EXCLUSION

Per 21 CFR 25.15(d) that, to our knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment (EA).

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