A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of Heterologous and Homologous Chimpanzee Adenovirus and Self-Amplifying mRNA Prime-Boost Prophylactic Vaccines Against SARS-CoV-2 in Healthy Adults

DMID Protocol Number: 20-0034

IND Sponsor: Division of Microbiology and Infectious Diseases (DMID)

Draft or Version Number: 10.0

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STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally-funded human subjects research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be subject to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federal wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/Independent or Institutional Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP), and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and Division of Microbiology and Infectious Diseases (DMID)
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award
- Applicable Federal, State, and Local Regulations and Guidance

SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6(R2) Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____

Name, Credentials

Title

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACD	Acid Citrate Dextrose
ACE	Angiotensin-Converting Enzyme
ACIP	Advisory Committee on Immunization Practices
Ad	Adenovirus
ADE	Antibody-Dependent Enhancement
AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
°C	Celsius
CAR	Coxsackie-Adenovirus Receptor
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
ChAd	Chimpanzee Adenovirus
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CK	Creatine Kinase
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services

CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CSR	Clinical Study Report
CVST	Central Venous Sinus Thrombosis
DC	Dendritic Cell
DCC	Data Coordinating Center
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEA	European Economic Area
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immunospot
EMA	European Medicines Agency
EUA	Emergency Use Authorization
°F	Fahrenheit
FDA	Food and Drug Administration
FT	Freeze/Thaw
FWA	Federal Wide Assurance

GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GMFR	Geometric Fold-Rise
GMT	Geometric Mean Titer
GWAS	Genome-Wide Association Studies
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HgB	Hemoglobin
HIT	Heparin-Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRSA	Health Resources and Services Administration
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICS	Intracellular Cytokine Staining
IDCRC	Infectious Diseases Clinical Research Consortium
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G

IgM	Immunoglobulin M
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
LN_2	Liquid Nitrogen
LNP	Lipid Nanoparticles
MAAEs	Medically Attended Adverse Events
MedDRA®	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mL	Milliliter
mM	Millimolar
mmHg	Millimeters of Mercury
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
N	Number (typically refers to subjects) or Nucleocapsid
NDA	New Drug Application
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NOCMCs	New Onset Chronic Medical Conditions
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OHRP	Office for Human Research Protections

PBMCs	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PE	Physical Examination
PEG	Polyethylene Glycol
PHI	Protected Health Information
PI	Principal Investigator
PIMMCs	Potentially Immune-Mediated Medical Conditions
PLT	Platelets
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PREP Act	Public Readiness and Emergency Preparedness Act
PT	Prothrombin time
PTs	Preferred Terms
PTT	Partial thromboplastin time
QA	Quality Assurance
QC	Quality Control
RBD	Receptor-Binding Domain
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
S	Spike
SAE	Serious Adverse Event/Serious Adverse Experience
SAM	Self-Amplifying mRNA
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SGP	Sub-Genomic Promoter
SIV	Simian Immunodeficiency Virus
SNP	Single Nucleotide Polymorphisms
SOC	System Organ Class
SOP	Standard Operating Procedure
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
T Bili	Total Bilirubin
TCE	T Cell Epitope(s)
Th1	T Helper Cell Type 1
Th2	T Helper Cell Type 2
TTS	Thrombosis with Thrombocytopenia Syndrome
µg	Microgram
UK	United Kingdom
URI	Upper Respiratory Illness
US	United States
UTR	Untranslated Regions
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VEEV	Venezuelan Equine Encephalitis Virus
VITT	Vaccine-Induced Immune Thrombotic Thrombocytopenia
VP	Viral Particles

WBC	White Blood Cell
WOCBP	Women of Childbearing Potential
YO	Years Old
YRS	Years

PROTOCOL SUMMARY

Title:	A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of Heterologous and Homologous Chimpanzee Adenovirus and Self-Amplifying mRNA Prime-Boost Prophylactic Vaccines Against SARS-CoV-2 in Healthy Adults
Design of the Study:	Open-label, dose escalation, non-randomized study of the safety, tolerability, and immunogenicity of investigational ChAd-S and SAM-S SARS-CoV-2 vaccines with or without TCE. Stage 1 will study dose escalation of homologous and heterologous prime-boost vaccination schedules in healthy naïve adult subjects. Stage 2 will study booster vaccination(s) in adult subjects who previously received COVID-19 EUA/licensed vaccines (see Table 1).
Study Phase:	1
Study Population:	Men and non-pregnant women who are in good health and meet all eligibility criteria will be enrolled: • Stage 1: 17 subjects, 18-60 yo • Stage 2: up to 118 subjects, ≥18 yo Subjects will be enrolled at one of at least 4 distinct US-based Infectious Diseases Clinical Research Consortium (IDCRC) sites into different groups. Subjects' willingness to receive ChAd vaccines will be assessed and documented at the time of informed consent and considered to determine group assignments.
Number of Sites:	At least 4 domestic clinical research sites
Description of Study Product or Intervention:	ChAd expressing spike alone or spike plus TCE (ChAd-S and ChAd-S-TCE) and SAM expressing spike alone or spike plus TCE (SAM-S and SAM-S-TCE):

- ChAd-S, 5 x 10^{10} viral particles (vp), intramuscular (IM)
- SAM-S, 3 micrograms (µg) and 30 µg, IM
- ChAd-S-TCE, 5 x 10^{10} vp, 1 x 10^{11} vp, and 5 x 10^{11} vp, IM
- SAM-S-TCE, 3 µg, 6 µg, and 10 µg, IM

Study Objectives:

Primary:

- To assess the safety and tolerability of different doses of ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE when administered as:
    - prime-boost in healthy naïve adult subjects.
    - First or second boost in healthy adult subjects previously vaccinated with EUA/licensed mRNA or adenoviral-vectored COVID-19 vaccines.

Secondary:

- To assess the humoral and T cell responses to ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE.

Exploratory:

- To evaluate memory B cell responses to ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE.
- To evaluate neutralizing antibody responses to the ChAd vector.

Duration of Individual Subject Participation: 12 months after the last study vaccination

Estimated Time to Last Subject/Last Study Day: Approximately 24 months

Table 1: Treatment Arms

Stage	Study Population	Group	Sample Size	Vaccination(s)	Day of Dosing/ Interval Between Doses (Days)
1*	Naïve (18-60 yo)	1	4	5 x 10^{10} vp ChAd-S/ 30 µg SAM-S	28
		3A	3	30 µg SAM-S/ 30 µg SAM-S	28
		3B	7	30 µg SAM-S/ 3 µg SAM-S	84-129
		4	3	10 µg SAM-S-TCE/ 3 µg SAM-S-TCE	84-129
2**	SAM-S-TCE Boosts after EUA/licensed mRNA (Groups 5-7) and Ad26 (Group 8) COVID-19 Vaccines (18-60 yo)	5	10	3 µg SAM-S-TCE	≥112
		6	10	6 µg SAM-S-TCE	≥112
		7A&B# ****	8-12	10 µg SAM-S-TCE	≥112
		8A&B# ****	8-12	10 µg SAM-S-TCE/ 10 µg SAM-S-TCE***	≥112/ 56***
	SAM-S-TCE Boosts after approved/licensed mRNA (Groups 9-11) and Ad26 (Group 12) COVID-19 Vaccines (>60 yo)	9	8	3 µg SAM-S-TCE	≥112
		10A&B#	8-12	6 µg SAM-S-TCE	≥112
		11A&B#	8-12	10 µg SAM-S-TCE	≥112
		12A&B#	8-12	10 µg SAM-S-TCE/ 10 µg SAM-S-TCE***	≥112/ 56***
	ChAd-S-TCE Boosts after approved/licensed mRNA COVID-19 Vaccines (>60 yo)	13	7-10	5 x 10^{10} vp ChAd-S-TCE	≥112
		14	7-10	1 x 10^{11} vp ChAd-S-TCE	≥112
		15	7-10	5 x 10^{11} vp ChAd-S-TCE	≥112

*Were enrolled prior to protocol version 5.0. No further enrollment will occur in Stage 1. Group 1A, as noted in protocol version 4.0, is noted above as Group 1. Groups 1B and 2, as noted in protocol version 4.0, have been eliminated, due to anticipated challenges with enrollment of naïve subjects.

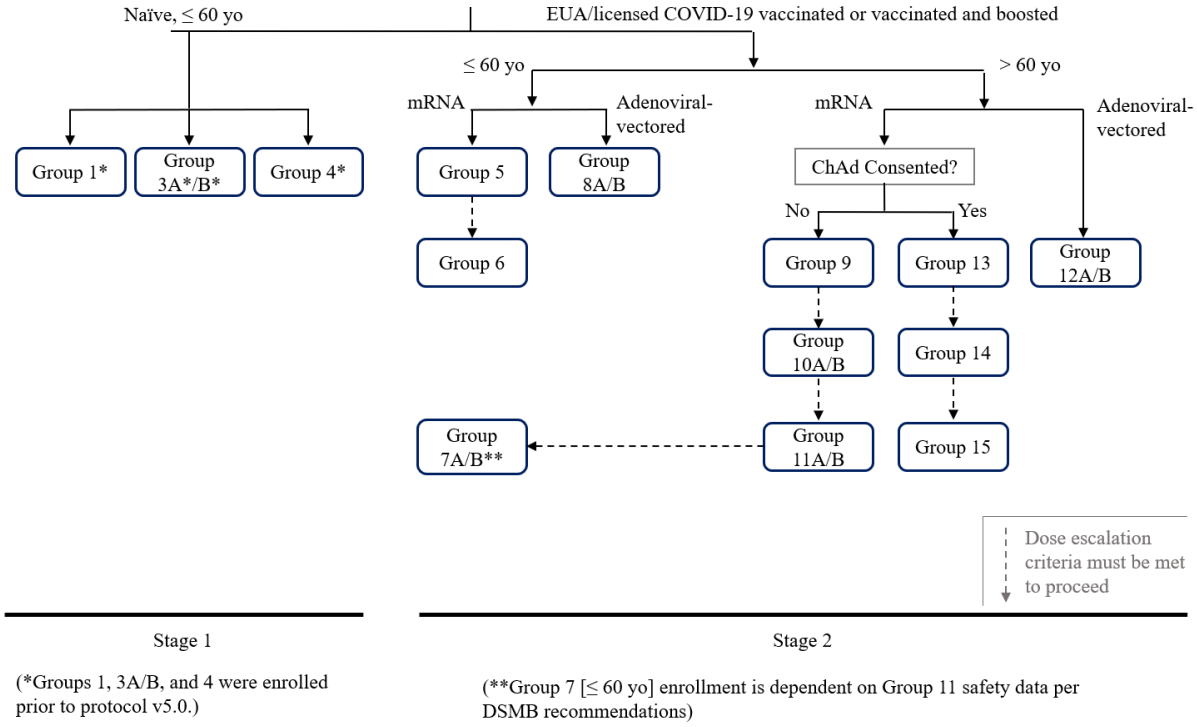
**Will be enrolled under protocol versions 5.0 and later; Stage 2 was redesigned in version 5.0 to focus on subjects previously given primary vaccination series of mRNA or Ad26 COVID-19 vaccines and has now been redesigned to also include those given recommended COVID-19 booster vaccinations. All Stage 2 subjects will receive single or double boosts of SAM-S-TCE or a single boost with ChAd-S-TCE. Groups 5, 6, 8, 9, 10, 12, and 13-15 are dose escalations with 3 sentinels/group (irrespective of subgroup) who will be followed for 72 hours post vaccination. After all 3 sentinels are evaluated for 72 hours and no safety issues are observed, the remainder of the group will be enrolled and followed through Day 8 after study vaccination before dose escalation. Dosing in Groups 7 and 11 (10 µg SAM-S-TCE) will proceed with 3 sentinels/group (irrespective of subgroup) monitored for 7 days post vaccination prior to enrollment of the remainder of the group; enrollment into Group 7 will depend on all safety data from Group 11 generated through 28 days of follow up post-vaccination.

***Will administer the highest tolerable dose as determined by the dose escalations. For the SAM-S-TCE double boosting groups, the interval after the last EUA/licensed COVID-19 vaccination will be ≥112 days and the interval between the 2 SAM-S-TCE boosts will be 56 days.

[#]Participants in Groups 7, 8, 10, 11, and 12 will be enrolled in two subgroups: A (vaccinated, but no prior infection history) and B (vaccinated, and history or evidence of infection, but not within 4 months before enrollment), and the numbers of noninfected and infected subjects will not be pre-specified. For Groups 13-15, 7-10 subjects will be enrolled into each group that have been previously infected with SARS-CoV-2 at least 4 months earlier or not, and the numbers of noninfected and infected subjects to be enrolled will not be pre-specified.

**** After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

Figure 1: Group Enrollment Flow Diagram*



(*Groups 1, 3A/B, and 4 were enrolled prior to protocol v5.0.)

(**Group 7 [≤ 60 yo] enrollment is dependent on Group 11 safety data per DSMB recommendations)

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

1 KEY ROLES AND STUDY GOVERNANCE

This study is sponsored by DMID. Decisions related to this study will be made by the protocol team, which includes representatives from the participating clinical research sites (Principal Investigators (PIs)), DMID (sponsor) and Gritstone bio, Inc. (formerly known as Gritstone Oncology, Inc.), and the Study Steering Committee (SSC), a subset of the protocol team. Key Roles are noted in the protocol-specific manual of procedures (MOP).

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

The ongoing outbreak of Coronavirus Disease 2019 (COVID-19) originally emerged in China during December 2019 (1) and had become a global pandemic by March 2020. COVID-19 is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Two other coronaviruses have caused world-wide outbreaks in the past two decades, namely SARS-CoV (2002-2003) (3) and Middle East respiratory syndrome coronavirus (MERS-CoV) (2012-present) (4). There are no specific treatments or fully licensed vaccines available for SARS-CoV or MERS-CoV. The scale of the current SARS-CoV-2 outbreak has led to extraordinary efforts and measures from national and international organizations in an attempt to effectively treat patients and contain the spread of the disease (5).

2.1.1 Coronaviruses

Coronaviruses are enveloped positive-stranded RNA viruses whose name derives from their characteristic crown-like appearance in electron micrographs (6). These viruses have the largest known viral RNA genomes, with a length of 27 to 32 kilobases. The host-derived membrane is studded with glycoprotein spikes and surrounds the genome, which is encased in a nucleocapsid that is helical in its relaxed form but assumes a roughly spherical shape in the virus particle. Replication of viral RNA occurs in the host cytoplasm by a unique mechanism in which RNA polymerase binds to a leader sequence and then detaches and reattaches at multiple locations, allowing for the production of a nested set of mRNA molecules with common 3′ ends. There are four main sub-groups known as alpha, beta, gamma, and delta coronaviruses. SARS-CoV-2 is a novel *betacoronavirus* similar to SARS-CoV and MERS-CoV. The viral genome of SARS-CoV-2 was sequenced to enable diagnostic testing, epidemiologic tracking, and development of preventive and therapeutic strategies (7-11).

The genomes of SARS-CoV and SARS-CoV-2 possess four genes that encode the S, M, N, and E proteins. The spike (S) protein projects through the viral envelope and forms the characteristic spikes in the coronavirus "crown". The major epitopes that stimulate neutralizing antibody to SARS-CoV are present within the S protein. S-specific epitopes can also induce CD4+ T helper and cytotoxic lymphocytes, but multiple additional SARS-CoV-2 antigens can also induce both CD4+ T helper and CD8+ cytotoxic lymphocytes. The S protein is a heavily glycosylated protein that mediates receptor binding and fusion with the host cell membrane. SARS-CoV-2 binds to the human angiotensin converting enzyme-2 (ACE2) receptor on host cells to mediate internalization. Recent characterization of the spike receptor binding domain (RBD) of SARS-CoV-2 shows a highly conserved cryptic epitope found in the original SARS virus (12).

Structural analysis identified residues in the SARS-CoV-2 RBD that are critical for ACE2 binding, the majority of which either are highly conserved or share similar side chain properties with those in the SARS-CoV receptor-binding domain. Such similarity in structure and sequence strongly argues for convergent evolution between the SARS-CoV-2 and SARS-CoV, which may assist in the identification of cross-reactive antibodies (13). The membrane (M) protein has a short N-terminal domain that projects on the external surface of the envelope and spans the envelope three times, leaving a long C terminus inside the envelope. The M protein plays an important role in viral assembly. The nucleocapsid protein (N) associates with the RNA genome to form the nucleocapsid. It may be involved in the regulation of viral RNA synthesis and may interact with M protein during virus budding. Cytotoxic T lymphocytes recognizing portions of the N protein have been identified (14). The small envelope (E) protein leaves its C terminus inside the envelope and then either spans the envelope or bends around and projects its N terminus internally. Its function is not known, although, in the SARS-CoV, the E protein along with M and N are required for proper assembly and release of the virus.

2.1.2 Need for a SARS-CoV-2 vaccine

SARS-CoV epidemics have occurred in several outbreaks since 2002. Over 8,000 cases and 900 deaths were reported during the 2002-2003 SARS epidemic (3). MERS has reportedly killed approximately 35% of all reported cases, 42% of cases in Saudi Arabia, yet only 19% of cases in South Korea, where mortality ranged from 7% among younger age groups to 40% among those aged >60 years old (15, 16). The current outbreak due to SARS-CoV-2 (COVID-19) has a high age-related mortality rate and has rapidly spread worldwide. To date, public hygiene measures, case isolation and contact quarantine remain the primary methods of infection control for an overwhelming majority of the world population.

Several vaccine candidates have recently been made available under EUA and licensure in a limited number of countries. Studies of the Pfizer and Moderna mRNA vaccines demonstrated high efficacy against all symptomatic and severe disease and received Emergency Use Authorization (EUA) on December 12 and 18, 2020, respectively. The Pfizer mRNA vaccine received approval on April 23, 2021, and will be marketed as Comirnaty, for the prevention of COVID-19 disease in individuals 16 years of age and older. The Moderna mRNA vaccine received approval on January 31, 2022 and will be marketed as Spikevax for the prevention of COVID-19 in individuals 18 years of age and older. On March 29, 2022 the FDA expanded authorization of the Pfizer BNT162b2 and the Moderna mRNA-1273 COVID-19 vaccines to allow immunocompromised individuals (12 years and older) and adults 50 years and older who received an initial booster dose at least 4 months prior to receive a second mRNA booster to increase their protection against severe disease from COVID-19. Key demographic groups for vaccination include healthcare workers and vulnerable populations (the older adults and patients

with co-morbidities) who have accounted for a large proportion of the fatalities to date. The ideal vaccine would generate broadly cross-protective immune responses to help protect vaccinated subjects against the next coronavirus strain to cross from its animal reservoir into humans. In addition, new variants of SARS-CoV-2 are being reported as the pandemic continues and may continue to emerge as first-generation vaccines impose selective pressure for immune escape. Furthermore, the ideal vaccine must induce long lasting humoral and T cell immunity in all age groups without causing any serious adverse effects.

Over the past two decades, the scientific community and the biopharmaceutical industry have been asked to respond urgently to a number of epidemic crises involving outbreaks of H1N1 influenza, Ebola, Zika and several strains of Coronaviruses. Whereas an H1N1 influenza vaccine could be developed relatively rapidly as the core technology was available and already approved by regulatory authorities, availability of specific vaccines for other emergent epidemic pathogens was hindered by several factors: scientific, methodologic, regulatory and commercial (17). Prior efforts to initiate a Phase I clinical trial in healthy subjects to evaluate a candidate SARS-CoV deoxyribonucleic acid (DNA) vaccine required 17 months after the sequence of the virus was initially published (18).

2.1.3 Inducing an optimal and safe immunity against SARS-CoV-2

Multiple platforms are under development for the current SARS-CoV-2 outbreak, with clinical trials of candidate vaccines being initiated within a few weeks of pathogen sequence publication in January 2020. These candidate vaccines will need to demonstrate consistent, safe and, ultimately, long-lasting protective immune responses across strains of SARS-CoV-2 and across patient subsets (the older adults, in particular) with an acceptable safety profile, and be suitable for large-scale manufacturing (17).

A number of SARS-CoV-2 vaccines are currently being evaluated and are largely focused on driving a neutralizing antibody response against the S glycoprotein. Several preclinical studies have shown protection from viral challenge by high titer neutralizing antibodies against the S glycoprotein of the original SARS virus in susceptible hosts (18, 19). Extending this concept into humans, investigations are ongoing to characterize neutralizing antibodies in humans recovering from natural SARS-CoV-2 infection (12, 13). Whether these antibodies can confer durable protection in patients for longer than 6-9 months remains unclear. Neutralizing antibody titers and the associated memory B cell response are short lived in SARS-recovered patients (20). In previous SARS endemics, the SARS-CoV-specific IgM and IgA response lasted less than 6 months, while virus-specific IgG titer peaked four months post infection and markedly declined after 1 year (21-27).

Humoral responses to viral antigens may also lead to the phenomenon of antibody-dependent enhancement (ADE) of infection, wherein antibody bound to viral surface proteins paradoxically increases viral uptake into host cells via FcR recognition of antibody Fc domains (28). This phenomenon has constrained development of a vaccine against dengue (29), and similar biology has been observed in some pre-clinical models with coronavirus vaccines that elicit humoral responses (30, 31).

Unbalanced immune responses to coronavirus vaccines may also cause iatrogenic pulmonary toxicity through other mechanisms, perhaps related to excessive innate immune activation (32, 33). This has been observed in several animal models examining vaccine candidates for SARS and MERS (34, 35), including in non-human primates (NHP) (36). One type of unbalanced responses associated with significant increased pathology is vaccine-associated enhanced respiratory disease (VAERD). VAERD is a distinct clinical syndrome that may occur either when there is a relatively high ratio of binding antibody to neutralizing antibody resulting in a large amount of antibody that binds but does not neutralize which in the presence of a high viral load may result in immune complex deposition and complement activation (37, 38). In addition, accentuated Th2 responses can lead to eosinophilic inflammatory (39). Such an adverse effect appears associated with a type 2 helper T cell (Th2) response, strongly suggesting that a more Th1-biased response is critical for optimal vaccine responses (14, 40-42).

Given the emergence of multiple coronavirus epidemics/pandemics over the last 20 years, the ideal vaccine would generate cross-strain immunity to help protect vaccinated subjects against not only the current but also the next coronavirus strain to cross from its animal reservoir into humans (19). B cell epitopes on viral surface antigens typically mutate at rates higher than internal proteins, rendering antigenic drift a real concern, which might bypass humoral responses (43). T cell epitopes can be derived from more highly conserved viral genes, suggesting that durable $CD8^+$ T cell memory is a highly desirable component of the immune response to an ideal SARS-CoV-2 vaccine (44-55). Indeed, despite the lack of long-lasting, virus-specific memory B cell response, SARS-CoV-specific memory T cells persist in SARS-recovered patients for up to 6 years post-infection (18, 44, 55-58).

In summary, the induction of $CD8^+$ T cells specific to SARS-CoV-2 antigens is not only more likely to synergize with a high neutralizing-antibody response to maximally protect the host but may also be crucial to avoid the risk of serious immunopathology (14, 59). However, none of the vaccine candidates currently in clinical development against SARS-CoV-2 comprehensively target CD8+ T cell epitopes outside of Spike.

2.1.4 Public Readiness and Emergency Preparedness Act

The study of ChAd (GRT-C907, GRT-C909) and SAM (GRT-R908, GRT-R910) vaccines, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services (DHHS) under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributors, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as the ChAd (GRT-C907, GRT-C909) and SAM (GRT-R908, GRT-R910) vaccines. The PREP Act provides immunity for covered persons from liability unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 10, 2020 and is retroactively effective from February 4, 2020.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's (HRSA) CICP (http://www.hrsa.gov/cicp/) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at http://www.hrsa.gov/cicp/. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this study, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under

the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.

2.2 Scientific Rationale

An ideal vaccination approach against viral respiratory infections would induce both neutralizing antibodies (from B cells) as well as effector and memory $CD8^+$ T cell responses for maximum efficacy. Neutralizing antibodies to viral surface proteins serve to prevent viral entry into cells, and virus epitope specific $CD8^+$ T cells kill virally infected cells. SARS-CoV-2 convalescent patients exhibit both elements of this adaptive immune response (60) even though neutralizing antibody titers may be low (61).

Gritstone has developed a potent, proprietary vaccine platform that delivers antigens within viral vectors and drives extremely strong B and T cell responses (both $CD4^+$ and $CD8^+$). To address the challenge of cancer vaccines, we have been delivering neoantigens (mutated "non-self" epitopes) via two vaccine platforms: a replication deficient chimpanzee adenovirus 68 vector (ChAd) for the prime vaccination, and for boost vaccinations, a self-amplifying mRNA vector (SAM) formulated with lipid nanoparticles. We are evaluating this platform in ongoing phase 1-2 clinical trials to administer tumor neoantigens to cancer patients, consistent with the notion that neoantigen-specific T cells can drive tumor elimination and clinical response.

The vaccine regimen, has been well tolerated without any dose limiting toxicities (DLTs) observed in Gritstone's cancer immunotherapy studies, including in older adult patients, and despite the combination with immune checkpoint inhibitors. There is an opportunity to leverage Gritstone's potent, clinical-stage vaccine platform to drive T cell and B cell-mediated immunity to SARS-CoV-2 by changing the antigen payload from cancer neoantigens to a SARS-CoV-2 payload/cassette. This approach enables a vaccine to educate the immune system to recognize SARS-CoV-2 antigens and stimulate both T cell and B cell immunity to protect healthy individuals.

However, in the current study, reactogenicity with a 30 µg SAM-S priming dose and with a 10 µg SAM-S-TCE priming dose has been seen in the younger naïve subjects in Groups 3 and 4. Despite not meeting any halting rules, the levels of reactogenicity were deemed to not support dose escalation with these specific vaccines in a COVID-19 vaccine naïve population. Therefore, dose escalations in Stage 2 will begin with the lowest dosage of SAM-S-TCE supported by product stability and potency testing (3 µg as of the writing of protocol version 5.0), and

increasing to no more than 10 µg, as tolerated. Each dose escalation group will start with 3 sentinels followed for 72 hours before proceeding with the remaining volunteers in each group. At least 7 subjects enrolled in each dose escalation group will be evaluated through Day 8 post-vaccination before the protocol team decides on whether to further dose escalate. Subjects in Groups 3B and 4 who have received the prime vaccination will receive 3 µg of SAM-S or SAM-S-TCE, respectively as the second dose.

Due to the extensive roll-out of the EUA/licensed COVID-19 vaccines, no further enrollment will occur in Stage 1 (naïve subjects). Stage 2 groups focus on the use of SAM-S-TCE and ChAd-S-TCE as boosting vaccines in subjects who previously received a primary EUA/licensed COVID-19 vaccination series, with or without subsequent receipt of an approved COVID-19 booster vaccination. Because of the increasing prevalence of SARS-CoV-2 infection, and the need to understand how booster vaccines may impact pre-existing immunity, enrollment of subjects has also been extended to include both participants with previous but not acute evidence of infection (must be PCR negative at screening and have had no evidence of infection during the previous 4 months before screening), and those without prior infection history.

During the course of this trial the 10 µg dose of the same lot of the Gritstone SAM-S-TCE vaccine being used in DMID 20-0034 has been tested in 10 adults ≥60 years of age in a parallel trial in the UK. The subjects were previously vaccinated with the AstraZeneca ChAdOx1 COVID-19 vaccine and compared to similar subjects given boosts with the Moderna mRNA-1273 vaccine after ChAdOx1 primary vaccination. None of the elderly UK subjects boosted with 10 µg of SAM-S-TCE had any severe graded reactogenicity, and the boosting of neutralizing antibody responses was similar between those boosted with SAM-S-TCE and those boosted with the Moderna mRNA-1273. Concurrently, increasing evidence suggests that the mRNA vaccines are more reactogenic in younger compared with older people. Thus, in version 7.0 of this protocol dosing of SAM-S-TCE in older subjects will precede dosing with 10 µg of SAM-S-TCE in younger subjects.

2.2.1 Gritstone's Adenovirus-vectored vaccine platform

Adenoviruses are excellent vectors for delivering genes or vaccine antigen to the target host tissues and are being tested in several vaccine and gene therapy studies. Adenovirus-based vectors offer several advantages over other viral vectors such as broad range of tissue tropism, well-characterized genome, ease of genetic manipulation including acceptance of large transgene DNA insertions, inherent adjuvant properties, ability to induce robust transgene-specific T cell and antibody responses, non-replicative nature in the host, and ease of production at large scale.

Adenoviruses activate several innate immune-signaling pathways that result in the secretion of a number of proinflammatory cytokines. These proinflammatory cytokines pave the way for

effective immune cell stimulation and result in the induction of robust adaptive humoral and cellular immune responses. A number of human clinical trials have been conducted for adenoviral-vectored vaccines against different infectious agents including Ebola virus, Zika virus, influenza viruses, human immunodeficiency virus (HIV), *Mycobacterium tuberculosis*, malaria and, more recently, SARS-CoV-2. Gritstone has developed a potent antigen delivery system based on ChAd68 which delivers multiple antigens to drive robust T cell responses.

ChAd activates T cells following IM injection by first entering myocytes via the coxsackie-adenovirus receptor (CAR). Adenovirus transduction of myocytes leads to expression of the cassette in the muscle cells. Dendritic cells (DCs) and other inflammatory cells are recruited to the adenovirus-injected muscle, ingest the antigen(s) and migrate to the vaccine draining lymph node where T cell activation occurs. In addition to infection of myocytes, adenovirus can also transduce DCs directly through a CAR-independent mechanism that involves the lectin DC-SIGN. This direct infection of DCs is expected to occur in lower frequency relative to DC uptake of antigen from myocytes, but both pathways result in T cell activation. Humoral responses to adenoviral capsid proteins and encoded antigens are also elicited, with high antibody titers measured after 2 weeks and sustained thereafter for months. ChAd vectors also elicit strong antibody responses to encoded pathogen antigens (62, 63).

Grounded in traditional infectious disease vaccinology, this vector system has been initially deployed by Gritstone in cancer immunotherapy to educate and expand the patient's T cells to detect tumor-specific antigens and destroy tumor cells. In NHP models, we have demonstrated strong and long-lasting $CD8^+$ and $CD4^+$ T cell responses to simian immunodeficiency virus (SIV) epitopes, with memory effector T cells observed beyond 12 months from the initial prime. In mice we have also demonstrated our ChAd elicits strong humoral responses, consistent with prior data in NHP and humans (62, 63). Most importantly, ongoing phase 1-2 trials in patients (including older adult patients) with advanced tumors have confirmed the induction of $CD8^+$ and $CD4^+$ T cells against tumor-specific epitopes contained in the ChAd vaccines.

Immunogenicity in the older adults is crucial since many infectious disease vaccines are largely, if not exclusively, tested in younger healthy subjects, whereas SARS-CoV-2 infection carries greatest risk of mortality in the older adults (1, 64). A strong immune response in older adult subjects, as has been shown with the Gritstone ChAd system in patients with advanced cancers, is likely central to a clinically useful vaccine, especially since older subjects may have impaired or altered T cell functions (65), which in turn may explain the higher mortality rate observed in older adult patients infected with SARS-CoV-2. The demonstrated potent immunological priming ability of the ChAd vector suggests that a single dose may induce substantial and rapid protective immunity, another potential advantage of this vector during the ongoing SARS-CoV-2 pandemic.

Gritstone is developing ChAd based on the similar tolerability and immunogenicity as human adenovirus without the limitation of preexisting neutralizing immunity. Chimpanzee adenoviruses have shown a very similar safety profile to human adenoviruses, such as adenovirus serotype 5 (Ad5), as both are well tolerated in multiple clinical studies, including thousands of patients vaccinated with human adenovirus for infectious diseases such as Ebola and Zika. The use of ChAd is selected to avoid pre-existing immunity to human adenovirus (a common virus in the community that causes cold-like symptoms), which has been shown to blunt immune responses induced by the vaccine vector at prime vaccination. Early data in the two ongoing cancer clinical studies demonstrate that the ChAd vaccine vector is well tolerated at a dose of $1x10^{12}$ vp/vaccination.

The choice of a high dose of $1x10^{12}$ vp in Gritstone's cancer vaccine studies was primarily driven to induce a robust T cell response following immunization with a ChAd containing a non-natural polyepitope expression cassette in patients suffering from advanced cancers, a potential suboptimal immune system following cytotoxic chemoradiation therapy and the usual deleterious tumor microenvironment. While lower doses of adenovirus have induced robust humoral and cellular immune responses against respiratory syncytial virus (RSV) (66) and influenza (67), doses as high as $1 x10^{11}$ of a ChAd3-Ebola glycoprotein vaccine administered in a Phase 2 clinical study were well tolerated with transient side effects and drove strong and robust antibody responses (68). Doses up to $1.6 x10^{11}$ vp of an Ad5 Ebola vaccine have similarly been used safely and induced strong immunogenicity whereas a lower dose of $4 x10^{10}$ vp was also safe but immunogenicity seemed to be more vulnerable to the pre-existing immunity to Ad5 (69). In the same study, the homologous prime-boost regimen with this Ad5 Ebola vaccine at 6 months interval was able to elicit greater antibody responses with longer duration.

A key question is whether induction of strong and long-lasting T cell responses to SARS-CoV viral strains, in particular SARS-CoV-2, will require higher doses of the adenovirus prime and/or the delivery of a boost, and if so, at what interval, particularly in older adult subjects. There is evidence that a sub-therapeutic vaccine response in terms of SARS-CoV neutralizing antibody and T cells may lead to induced hepatic and pulmonary pathologies by generating enhancing antibodies without sufficient levels of protective T cells and neutralizing antibodies (33). Studies that used higher doses of adenoviruses as prime and boost in ferrets and rhesus macaques induced strong B and T cell responses against SARS-CoV (70). Importantly, efficacy was noted only with the prime-boost immunization regimen suggesting that clinical outcome is mainly determined early after exposure to SARS-CoV and may be independent of viral load later on. These data suggest that a certain threshold of neutralizing antibodies together with the possible contribution of virus specific T cells may be necessary for clinically meaningful protection.

ChAd can also be used to boost the immune response after homologous prime, although immunogenicity may be blunted by anti-vector (ChAd hexon) antibodies elicited after the prime. Data using human adenoviral vectors suggest that the longer the interval between prime and boost, the greater the effectiveness of the boost up to 4-6 months after prime. A boost performed 4 weeks after the prime with a chimpanzee PanAd3-RSV vaccine administered intramuscularly in healthy human subjects induced a significant B and T cell response to RSV despite preexisting cross-reactivity to the chimpanzee adenovirus (66). In contrast, a homologous priming-boosting regimen with adenovirus type-5 Ebola vaccine at 6 months interval was able to elicit greater antibody responses with longer duration (69). A key argument for using chimpanzee adenoviruses as vaccine vectors is the absence of preexisting immunity compared to human adenoviruses (71).

Taken together, these data suggest that high doses of a non-human adenovirus homologous prime-boost may induce a strong B and T cell responses in otherwise healthy humans against SARS-CoV-2, thus supporting Gritstone's proposed dose range (5×10^{10} to 5×10^{11} vp) as a prime. When using a ChAd-derived homologous prime-boost vector platform, a ChAd boost administered 4 months post prime appears optimal.

2.2.2 Gritstone's self-amplifying mRNA-vectored vaccine platform (SAM)

Synthetic RNA platforms allow for rapid and scalable manufacturing of prophylactic and therapeutic vaccines (72). Conventional mRNA strategies against infectious diseases and cancers have been investigated in several clinical trials including against SARS-CoV-2 (73-77). With conventional mRNA, antigen expression is proportional to the number of transcripts delivered by the vaccine to the target cells: large doses or repeat administrations may thus be necessary to achieve the desired therapeutic effects, which in turn may induce unwanted toxicities and/or immunogenicity against the vector. SAM vaccines have been designed to circumvent these limitations. SAM are derived from self-replicating, single-stranded RNA viruses and can be delivered as viral replicon particles with the SAM packaged into the viral particle, or as synthetic SAM produced after in vitro transcription. SAM theoretically cannot form infectious viral particles as only the RNA is capable of further amplification and lacks the viral sequences necessary to generate new viral particles.

The Gritstone SAM platform is based on a synthetic RNA molecule derived from Venezuelan Equine Encephalitis Virus (VEEV) replicon with the goal of extending the duration and magnitude of antigen expression. SAM is delivered in a lipid nanoparticle (LNP) formulation. The SAM platform proves to be safe, potent and well-tolerated in preclinical animal models and is now in phase 1-2 trials in patients with advanced cancers. Specifically, Gritstone's SAM is constructed by retaining the untranslated regions (UTRs), non-structural proteins encoding the replication machinery and a sub-genomic promoter (SGP) of the parent VEEV, but the structural

proteins in the sub-genomic region are replaced by the antigens of therapeutic interest. This structural engineering results in high levels of antigen expression without formation of the infectious viral particles that can spread from cell to cell.

Preclinical studies against SARS-CoV-2 and other pathogens show the SAM platform's utility in homologous and heterologous prime-boost vaccine regimens to reliably and potently drive balanced, durable immune responses for optimal protective immunity, demonstrating that this synthetic platform would be particularly useful for the rapid response to a pandemic outbreak or emerging infectious pathogens. Gritstone's SAM has been administered as vaccine boosts to at least 40 patients with advanced cancers in combination with nivolumab, and in some patients, with ipilimumab. Patients have received and well-tolerated up to 8 monthly SAM boosts (dose ranging from 30 to 300 µg) delivered intramuscularly. Following an initial ChAd prime, SAM boosts have induced the maintenance and/or amplification of $CD8^+$ T cells specific to the tumor-derived neoantigens encoded in the ChAd and SAM cassettes. Additional details are provided in Section 2.3.3 and in the Investigator's Brochures (IBs).

2.2.3 Gritstone's EDGE epitope prediction platform

Given the likely importance of $CD8^+$ T cell generation for an optimal vaccine against SARS-CoV-2, identification of strong T cell epitopes within the SARS-CoV-2 genome is key since not all viral genes can be incorporated within the vaccine payload (the viral genome is too large). Identification of critical T cell epitopes is challenging since cytotoxic T cells recognize short peptides (8-12 amino acids) presented by class HLA I molecules which are highly polymorphic within populations, and across ancestries. Gritstone has developed and validated a best-in-class, machine learning/artificial intelligence platform to identify T cell epitopes from nucleic acid sequence, named Gritstone EDGE. We built EDGE with robust HLA class I coverage (covering multiple ethnicities) by training on a large database of human tumor, normal tissue and cell-line HLA-presented peptides, the vast majority of which are wild type sequences derived from the normal cellular proteome. The model captures general processing and presentation in the context of HLA of intracellular peptides with performance comparable across different tissue types (78).

Gritstone's EDGE platform leads the field in the prediction of HLA peptide presentation and has been applied to viral epitope definition. Unpublished analyses demonstrate that EDGE is able to successfully discriminate HIV CD8 epitopes (in the Los Alamos Database) from the rest of the HIV proteome. As human data accrue as to the identity of true epitopes (assessment of convalescent subjects' immune responses plus study of vaccinated patients), we have generated several SARS-CoV-2 antigenic cassettes to ensure inclusion of optimal, immunogenic T cell epitopes in the best format. Whole gene S antigen is also included to drive a neutralizing antibody response. We are utilizing our EDGE platform to ensure that most individuals across major ancestry groups (Caucasian, Asian, African American, and Hispanic) receive a large

number of candidate CD8 epitopes while minimizing our cassette sequence "footprint." The deposition of world-wide SARS-CoV-2 sequence data has also allowed for the incorporation of emerging viral mutations into our design approach.

2.2.4 Purpose of Study

This phase 1 clinical trial will explore the ability of novel vectors (notably self-amplifying mRNA or SAM), a novel schedule (heterologous or homologous prime-boost), and novel SARS-CoV-2 epitope cassettes (extending COVID antigenic vaccine content beyond Spike) to safely drive strong, broad, durable immune responses to SARS-CoV-2. Cassette S contains a codon optimized Spike and will be assessed during Stage 1. An additional Spike-T Cell Epitope (cassette S-TCE) cassette will also be studied in Stage 1 as well as in Stage 2.

The successful EUA/licensed COVID-19 vaccine roll-out campaign has resulted in a diminishing domestic naïve population. Most of the population has received an EUA/licensed mRNA COVID-19 vaccine; to optimize homogeneity of study groups, we propose to focus on the enrollment of EUA/licensed mRNA COVID-19 vaccine experienced subjects into the majority of Stage 2 Groups. Due to the rare cases of Thrombosis and Thrombocytopenia Syndrome (TTS) associated with the approved AstraZeneca and EUA Johnson & Johnson/Janssen adenovirus-vectored COVID-19 vaccines in patients primarily <50 years old, we will focus on boosting subjects >60 years old with ChAd-S-TCE. In addition, ChAd-S-TCE vaccine may be a stronger T cell response inducer than the SAM-S-TCE vaccine, particularly in the elderly, which further supports boosting of subjects >60 years old.

Because the EUA/licensed COVID-19 vaccines encode only the Spike protein, a single boost with ChAd-S-TCE or SAM-S-TCE will boost spike-specific T cell immunity yet may only prime a TCE-specific response in previously vaccinated subjects. Ongoing studies suggest increased receipt of additional doses of mRNA COVID-19 vaccines may increase reactogenicity in persons previously vaccinated with mRNA COVID-19 vaccines. Therefore, subjects who previously received two EUA/licensed mRNA COVID-19 vaccines will receive one boost of SAM-S-TCE, whereas subjects previously given at least one dose of the Johnson & Johnson/Janssen Ad26 COVID-19 EUA plus one booster dose of EUA/licensed mRNA COVID-19 vaccine will receive two boosts of SAM-S-TCE to determine whether the TCE-specific response can be enhanced.

The vector, antigenic cassette, schedule and dose that generates the strongest T and B cell responses to SARS-CoV-2 will be identified during this phase 1 clinical trial for subsequent phase 2/3 testing and will also provide proof-of-concept that we can mix and match genetic and viral vector platforms, which will provide much needed information with the limited available doses of mRNA and adenoviral-vectored vaccines.

2.2.5 Study Population

The study population will include healthy adults aged 18 years and older, who are naïve or previously vaccinated with an EUA/licensed COVID-19 primary vaccination series with or without receipt of an approved/licensed COVID-19 booster vaccination. In addition, subjects that have experienced prior infection with SARS-CoV-2 or those not previously infected will be studied. However, subjects with recent (within the last 4 months of enrollment) or acute infection (PCR positive) will be excluded.

The full list of inclusion/exclusion criteria is provided in Section 5.1.

The study will enroll subjects from at least 4 US-based IDCRC sites.

2.3 Potential Risks and Benefits

The benefit/risk assessment for a ChAd and SAM directed to target SARS-CoV-2 is unknown given that this is a first-in-human study. Based on prior clinical experience with adenovirus and SAM vectors, the vaccinations are expected to result in mild to moderate local injection site reactions as well as systemic reactions such as mild flu-like symptoms. Based on preclinical data in non-human primates, on clinical data in patients with cancer and on data from other SARS-CoV-2 vaccines, the reactogenicity to the ChAd- and SAM-based vectors is expected to be lower in older adult subjects compared to younger ones. Despite this expectation, because this study involves first-in-human evaluations, a sentinel approach is planned as described in more details in Section 3. We further anticipate that T cell responses will be less robust in older adult subjects due to T cell senescence. The overall goal of this approach is to ensure safety in the older adult population without compromising the ability of the trial to rapidly identify the optimal dose to ensure a robust T cell activation in older subjects.

Although no thromboses with thrombocytopenia have been associated with the Gritstone ChAd COVID-19 vaccine, only limited vaccinations have been given to date. Cases of VITT have been rare (<1/100,000) with other COVID-19 adenovirus-vectored vaccines, and the CDC Advisory Committee on Immunization Practices (ACIP) recommended on April 23, 2021 that the benefits of the Johnson & Johnson/Janssen Ad26 COVID-19 vaccine under EUA outweigh the risks in persons 18 years and older. However, ACIP also recommended increased education of the public, individual vaccine recipients and physicians regarding the recognition and treatment of these rare risks of VITT. Similarly, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency concluded on 18 March, 2021 that there may be a risk of rare thrombotic events accompanied by thrombocytopenia following receipt of AstraZeneca's COVID-19 vaccine, but has allowed resuming utilization of vaccine, with adequate information to be added to its product information (79). Subsequently, the FDA determined that the

syndrome of blood clots and low platelets observed after the Johnson and Johnson (J&J)/Janssen COVID-19 vaccine warranted limiting the authorized use of the J&J COVID-19 vaccine. On May 5, 2022, the FDA limited the authorization of the J&J COVID-19 vaccine to adults for whom other authorized COVID-19 vaccines are not accessible, clinically appropriate, or for those who elect to receive the J&J vaccine because they would otherwise not receive a COVID-19 vaccine.

2.3.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, having nasal swabs collected, IM injection, leukapheresis (only for those subjects consented for leukapheresis), possible reactions to the study products (GRT-C907, GRT-R908, GRT-C909 and GRT-R910), and breach of confidentiality.

As described above, increased risks of VITT have been associated with other COVID-19 adenovirus-vectored vaccines and may occur with the use of the GRT-C907 and GRT-C909 vaccines (expected at <1/100,000). However, the Gritstone ChAd platform uses a different serotype of adenovirus and a different formulation compared with the other COVID-19 adenovirus-vectored vaccines that have been associated with VITT, so the true risks of VITT with GRT-C907 and GRT-C909 are not known. More details on these risks with other COVID-19 adenovirus-vectored vaccines are provided below in Section 2.3.3.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IM injection may also cause transient discomfort and fainting. Drawing blood and IM injection may cause infection. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or where the vaccination will be given extremely unlikely.

The nasal swabbing procedure is momentarily uncomfortable but is not otherwise associated with risk. It may cause brief pain, itchy nose, eye watering or sneezing.

2.3.2 Risks of Leukapheresis (only for those subjects consented for leukapheresis)

Leukapheresis risks are similar to those involved in whole blood or platelet donation and may be associated with pain, bruising, hematoma, and discomfort in the arms at the site of needle placement. Vasovagal episodes, characterized by transient hypotension, dizziness, nausea, vomiting, and syncope, are seen in less than 5% of procedures. Additional risks include increased pulse, seizures, infection, and blood loss. Anticoagulants added to prevent the blood from clotting may lead to a sour taste in the mouth, mild muscle cramps and/or tingling sensation

around the mouth, feet or hands. These reactions may be seen to a mild degree in 30-50% of leukapheresis procedures and can usually be relieved by slowing or temporarily interrupting the procedure or administering calcium carbonate tablets.

A temporary decrease (1-2 days) in red blood cell count is common. Rarely, machine malfunction or if the procedure needs to be stopped before completion may result in the loss of a half pint to a pint of blood. Leukapheresis does not affect the blood's ability to form clots in the event of subsequent cuts or injuries.

2.3.3 Risks of GRT-C907, GRT-R908, GRT-C909 and GRT-R910

Gritstone's preclinical pharmacology and toxicology data have shown an acceptable nonclinical safety profile. No dose-limiting safety signals have been identified in these studies. A toxicology study resulted in minimal safety findings with the most common event in non-human primates being temperature elevation that was transient and self-resolved. As of April 29, 2021, 56 doses of ChAd encoding for cancer-associated neoantigens have been administered to 48 cancer patients in ongoing phase 1-2 clinical trials. Eight patients have received up to two doses of ChAd (prime + 6-month boost).

Adenovirus as a vaccine vector has been used in many clinical studies including infectious disease and oncology settings. In all these studies, administration of an adenovirus has been well-tolerated. With respect to the infectious disease setting, adenoviral vectors have demonstrated safety in large numbers of gene therapy and vaccine clinical studies. Millions of military recruits have been vaccinated orally with adenovirus type 4 and type 7 attenuated, replication competent vaccines, and these vaccines demonstrated exemplary safety (80). Of note, adenovirus type 4 is closely related to ChAd68 (both belong to adenovirus clade E). Additional vaccine studies have employed human adenovirus serotype 5 (hAd5) for HIV vaccine studies and ChAd for Ebola and hepatitis C virus specific vaccines with all studies reporting good tolerability. Adverse events (AEs) primarily consisted of transient (24 to 48 hours) mild to moderate injection site reactions (pain, swelling, erythema) and mild to moderate fever, myalgia, arthralgia, headaches, fatigue, chills, and leukopenia, typically not requiring intervention other than acetaminophen. Cases of neurologic system disorders (Guillain-Barré Syndrome (GBS) and transverse myelitis) have been reported in subjects vaccinated using live-attenuated vaccines as well as adenoviral-vectored vaccines (81), and recently in one of the ChAd SARS-CoV-2 vaccines now in phase 3 (82). While causality with the vaccine has been difficult to ascertain in these rare and often transient cases, close monitoring of adverse drug reactions will be implemented in the current trial.

Post-marketing pharmacovigilance of the ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen) vaccines has revealed a very rare risk for serious possible vaccine-related TTS.

In the US, the background rates of central venous sinus thrombosis (CVST) associated with thrombocytopenia have been estimated to be 0.6-1.7 per million population (83).

The rates of this syndrome after these EUA/licensed adenovirus-vectored COVID-19 vaccinations vary by reporting region. In Norway 5 cases of CVST with thrombocytopenia were reported within 10 days after ChAdOx1 nCoV-19 receipt among 132,686 vaccine recipients (84). As of April 4, 2021, there were 169 cases of CVST and 53 cases of splanchnic vein thrombosis reported to EudraVigilance among the approximately 34 million people who had received ChAdOx1 nCoV-19 vaccine in the European Economic Area (EEA) and United Kingdom (UK). The estimated rate in the European Union of TTS after ChAdOx1 nCoV-19 vaccine was estimated at 10 cases per million (1 case per 100,000) vaccinated, with the majority of cases occurring in women less than 60 years of age, and within 6 to 24 days after the first vaccine dose. The European Medicines Agency (EMA) concluded benefit/risk ratio still favorable to use the vaccine. The EMA noted the causal association between ChAdOx1 vaccine as plausible and noted they were unable to identify a definitive cause but speculated the mechanism may be similar to HIT (85). The EMA recommended adding unusual blood clots with low platelets to the label as a very rare side effect (79).

Meanwhile, data from the UK pharmacovigilance through April 14, 2021 captured 168 reports of blood clotting with low platelets: 77 cases of CVST with thrombocytopenia and 91 cases of thrombosis in other major veins with thrombocytopenia. Overall, 55% of these cases occurred in women 18-93 years old, most cases occurring after the first vaccine dose, and 19% of the cases resulting in death. The estimated rate of Thrombosis with Thrombocytopenia Syndrome (TTS) among recipients of ChAdOx1 nCoV-19 vaccine from the UK data is 7.9 per million (among 21.2 million vaccine recipients). The UK concluded that the benefits of the vaccine continue to outweigh the risks, recommended that careful consideration be given to those at higher risk for blood clots due to medical conditions or pregnancy, and recommended that those aged 18-29 years who are at low risk of serious complications from COVID-19 be offered alternative vaccines (86).

As of May 7, 2021, the CDC reported that among 8.73 million recipients of the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine, there were 28 confirmed cases of TTS (overall rate of 3.2 cases/million vaccine doses) with the highest rates of 12.4 and 9.4 cases per million females among those 30-39 and 40-49 years of age, respectively. The rates in males less than 60 years old ranged from 1.3-2.8 cases/million vaccinated. Importantly, the rates for both men and women were 0 cases/million vaccinated in those ≥ 65 years old. Most of these cases occurred among women (22 of 28 cases of TTS) (87). After a 10-day pause in the administration of this vaccine in the US, on April 23, 2021, the US FDA and ACIP recommended vaccination with Ad26.COV2.S proceed and noted the benefits of the vaccine outweigh the risks. FDA and ACIP

advised that healthcare providers administering the vaccine and vaccine recipients should review the Johnson & Johnson/Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering the Vaccine and the Fact Sheet for Recipients and Caregivers respectively, which have been revised to include information about the risk of TTS (88). After updated analysis of the risk for VITT following administration of Johnson & Johnson/Janssen COVID-19 vaccine, on May 5, 2022, the FDA limited the authorization of the J&J COVID-19 vaccine to adults for whom other authorized COVID-19 vaccines are not accessible, clinically appropriate, or for those who elect to receive the J&J vaccine because they would otherwise not receive a COVID-19 vaccine.

On July 13, 2021, the FDA announced revisions to the vaccine recipient and vaccination provider fact sheets for the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine to include information pertaining to an observed increased risk of GBS following vaccination (89). As of July 13, 2021, there were 100 preliminary reports of GBS following Ad26.COV2.S vaccination reported to the Vaccine Adverse Event Reporting System (VAERS) after approximately 12.5 million doses administered. FDA noted that the available evidence suggests an association between Ad26.COV2.S, but there is insufficient evidence to establish a causal relationship (89). The EMA also recommended including a warning on the product information for the ChAdOx1 nCoV-19 vaccine to raise awareness among healthcare providers and vaccine recipients of cases of GBS following vaccination (90). GRT-C907 and GRT-C909 utilize an adenoviral vector platform that differs significantly structurally and from a manufacturing standpoint compared to the Johnson & Johnson/Janssen and AstraZeneca adenovirus-vectored COVID-19 EUA vaccines. As stated earlier, no similar complications of thrombosis with thrombocytopenia nor GBS have been seen in Gritstone's cancer vaccine programs using the same ChAd vaccine platform which has been adapted for this study, although the number of persons immunized has been small.

Out of an abundance of caution, we note the potential risks for thrombosis with thrombocytopenia and GBS should be considered with GRT-C907 and GRT-C909 vaccines, and potential subjects should be informed of these potential risks during the informed consent process. Through the informed consent process, subjects who receive an adenovirus-vectored vaccine in this study will be counseled to be aware of the symptoms of the potential events that have been observed with other viral-vectored COVID-19 vaccines, and what to do if they experience these symptoms. Because the clots have occurred in the brain and abdominal viscera, the following symptoms could occur: headache, fainting/loss of consciousness, blurred vision, seizures, other new neurologic symptoms, rashes, new or easy bruising, abdominal pain, back pain, leg pain or swelling, and/or shortness of breath. The clots have occurred most often in women less than 50 years old, and within 1-4 weeks of vaccination with an adenovirus-vectored vaccine. Similarly, subjects will be notified of potential symptoms of GBS which include

weakness or paresthesias, difficulty walking, difficulty with facial movements, double vision, or difficulty with bladder or bowel function. Subjects will be instructed to report to the study physician and their own healthcare provider immediately if they experience any of these symptoms during the course of this study. Additionally, thrombocytopenia will be monitored through safety labs at screening and Day 8 after each study vaccination. GBS and thrombotic events will be monitored as adverse events of special interest (AESIs).

Previously, mRNA-based vaccine vectors had not been evaluated as extensively as ChAd vaccines in clinical studies. However, two mRNA-based vaccines for SARS-CoV-2 have been evaluated in phase 3 clinical trials and have been authorized for emergency use in several countries, including the US (73-77). In addition, more than 300 million doses of these mRNA vaccines have now been given to persons in the US alone. In clinical trials of mRNA vaccines, AEs have been quite similar to those observed with adenovirus-based vectors, except for the absence of cases of VITT/TTS. Immune mediated thrombocytopenia has also been noted after mRNA vaccines without the clotting component. A small number of cases of anaphylactic reactions have been reported after administration of the authorized mRNA vaccines for SARS-CoV-2. These events are under investigation. It has been proposed that such reactions may be related to the polyethylene glycol in the LNP component of the vaccines. In addition, rare reports of myocarditis/pericarditis have been seen in persons given the EUA/licensed Moderna and Pfizer mRNA COVID-19 vaccines, and it is possible that they may occur with the Gritstone SAM vaccines (GRT-R908 and GRT-R910). Events of myocarditis/pericarditis will be monitored as AESIs.

Approximately, 52 million mRNA vaccines have been administered to persons 12–29 years old in the United States. From December 29, 2020–June 11, 2021, VAERS received 1,226 reports of myocarditis/pericarditis following mRNA vaccination (91). The median age was reported as 26 years old (range = 12–94 years), and median symptom onset occurred 3 days post-vaccination (range = 0–179 days). Of 1,194 reports, 687 persons were less than 30 years old and 507 were 30 years old or older. Of 1,212 cases, 923 identified as male, and 289 as female.

As of June 11, 2021, the CDC has confirmed 323 reports of myocarditis/pericarditis in persons (<30 years old) following EUA/licensed mRNA COVID-19 vaccination, reported to VAERS from May 1-June 11, 2021 (91, 92). Of the confirmed cases, 309 persons were hospitalized and 218 are known to have recovered. Between December 2020 and May 2021, the Israeli Ministry of Health reported 148 myocarditis cases occurring after Pfizer mRNA vaccine administration (93). Twenty-seven cases of a total of 5,401,150 vaccinated individuals occurred following the first vaccine dose and 121 cases out of a total of 5,049,424 vaccinated individuals occurred after the second vaccine dose. The majority of cases were reported among young men age 16-19 years old and were considered mild (95%). Most severe cases were hospitalized within 4 days. Several

case series have demonstrated similar epidemiologic findings. Following review of the myocarditis/ pericarditis cases in the United States, the FDA added a warning regarding the risk of myocarditis/pericarditis to the fact sheets for Moderna and Pfizer-BioNTech mRNA vaccines.

Cases of myocarditis and pericarditis have also been reported after Novavax COVID-19 vaccination. Among a total of 41,546 vaccine recipients in Novavax clinical trials aged ≥16 years, in the 2019nCoV-301, 2019nCoV-302, 2019nCoV-501, and 2019nCoV101 trials, six cases of myocarditis or pericarditis were detected. Five cases occurred within 20 days of vaccination, and in four of these cases, an alternative etiology was not found, suggesting a possible causal relationship with vaccine. Cases of myocarditis or pericarditis after Novavax COVID-19 vaccine have also been detected in global post-authorization surveillance. During a period in which 744,235 doses of Novavax COVID-19 vaccine were administered in Australia, Canada, the European Union, New Zealand, and South Korea, 35 reports of myocarditis/pericarditis/carditis were identified. These reports were among 20 male and 15 female vaccine recipients with a median age of 34 years (range = 23–62 years): 29 reports of pericarditis, including five in persons with a history of pericarditis after mRNA COVID-19 vaccine; four myocarditis cases; two myopericarditis cases; and one case of carditis, not otherwise specified.

Based on current data, myocarditis/pericarditis has occurred most often in adolescents and young men (<40 years old), several days to 1 week following COVID-19 vaccination, and more commonly after the second vaccine dose (94). Cases have been reported in older males and females, as well, and also following other doses. From available outcome data, persons with myocarditis/pericarditis have generally recovered. Long-term outcomes remain unknown.

During the informed consent process, subjects receiving a study vaccine will be informed of the potential risk of myocarditis/pericarditis with COVID-19 vaccines. Subjects will be advised to monitor for symptoms of myocarditis/pericarditis, including chest pain, shortness of breath, and/or palpitations. As part of the consenting process, subjects will be encouraged to immediately contact research staff and their medical provider if these symptoms occur following a study vaccination. Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 6 weeks after vaccination will have an unscheduled visit for assessment and will be referred to a cardiologist for evaluation and management. Additional details are provided in Section 8.1.5.

It is not known whether the risks of myocarditis or pericarditis are increased following repeated doses of mRNA vaccines. Since the Moderna and Pfizer mRNA COVID-19 vaccines have different LNP components and do not have the capacity for self-amplification, the reactogenicity profiles may differ for GRT-R908 and GRT-R910. Early experience in COVID-19 vaccine naïve subjects (18-60 yo) in this trial was associated with severe reactogenicity in the majority of

volunteers given either 30 µg of SAM-S or 10 µg of SAM-S-TCE as a prime vaccination. However, the reactogenicity profiles in older subjects with GRT-R908 and GRT-R910 have not been determined. Therefore, parallel dose escalations from 3 to 10 µg of SAM-S-TCE of booster vaccinations will occur in younger and older subjects, with the exception that the 10 µg dose will be given first in the older adult group. Enrollment in Group 7 will be dependent on the safety data generated from Group 11. After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

Gritstone's heterologous prime-boost vaccines are being developed for the treatment of patients with advanced solid tumors using a SAM vaccine GRT-R902 or GRT-R904 with up to 8 boosts, following a single administration of a ChAd-based prime using either GRT-C901 or GRT-C903. As of April 29, 2021, 48 patients with advanced cancers have been enrolled in phase 1-2 clinical trials and have received a ChAd-based prime vaccine consisting of either GRT-C901 or GRT-C903 at a fixed dose of 1×10^{12} vp followed by up to 8 SAM boosts of either GRT-R902 or GRT-R904 at doses ranging from 30 to 300 µg with at least 9 patients receiving the 300 µg dose as bilateral IM injections. All patients received concomitant doses of intravenous (IV) nivolumab at 480 mg flat dose. A majority of patients also received concomitant doses of ipilimumab subcutaneously at a 30 mg flat dose. No dose-limiting toxicities related to either the ChAd- or SAM-based vaccines in combination with nivolumab and ipilimumab have been observed at the time of this writing. One patient has experienced a serious adverse event (SAE) of treatment-related Grade 2 fever within approximately 12 hours after GRT-C901 and nivolumab, managed with anti-pyretics and fluids and resolved within 24 hours. Most patients reported transient episodes of low-grade fever, injection-site reactions, chills, nausea, fatigue and generally, flu-like symptoms, within 12 to 24 hours after vaccine administration with either the ChAd- or SAM-based vectors. Three patients presented with elevated serum creatine kinase with two patients developing transient signs and symptoms of myositis and rhabdomyolysis. Auto-immune myositis is a known toxicity of nivolumab and/or ipilimumab.

Overall, these symptoms were reversible and generally well tolerated, even in older adult patients with advanced solid tumors. The contribution of nivolumab and ipilimumab to these inflammatory-like responses cannot be excluded. These observations support the administration of the proposed ChAd-based vaccine and SAM-based vaccine encoding antigens of SARS-CoV-2 in healthy subjects at a dose of up to 5×10^{11} vp and 100 µg, respectively.

Risks to subjects receiving the study products are expected to primarily involve mild to moderate injection site reactions, which have been observed in animal studies and are generally observed and expected for other IM-administered vaccines. These local reactions may consist of transient and dose-dependent pain, swelling, and erythema. Possible systemic reactions, which are also

transient, may include fever, fatigue, chills, headache, myalgias, nausea, diarrhea, and arthralgias. Moderate to severe, short-term diarrhea has been observed in a minority of persons aged 18-60 years who received the investigational GRT-R908 and GRT-R910 vaccines. In addition, other AEs that have been generally associated with approved IM administered vaccines have included mild hematological and clinical chemistry abnormalities, which are usually reversible.

The investigational vaccines should not be administered to individuals with a known hypersensitivity to any component of the study product. There is also a potential risk of hypersensitivity reactions following the administration of any study product.

Several animal studies with experimental whole-virus inactivated and subunit vaccines of other coronaviruses have shown enhanced immunopathology in a greater number of vaccinated animals compared to controls upon subsequent virus infection. These experimental vaccines often exhibited Th2-biased immune responses or elicited antibodies that had poor neutralizing activity against the virus. In preclinical studies of the Gritstone ChAd-S/SAM-S, a predominant Th1-focused immune response was observed.

The relevance of these observations in humans is unknown. Notably, most people during their lifetimes have likely been infected with one or more of the 4 endemic strains of human coronaviruses (hCoV 229E, NL63, OC43, and HKU1) that circulate globally and are responsible for 10-30% of mild to moderate upper respiratory tract infections. Despite the likelihood of cross-reactive antibody responses with poor functional activity, no evidence of enhanced CoV disease in humans has ever been reported.

There is limited experience with administration of a boost dose(s) following EUA/licensed COVID-19 vaccine(s), and it is possible that the boost dose(s) may be associated with more frequent or more severe adverse events.

2.3.4 Risks to Privacy

Subjects will be asked to provide protected health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating site. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publications from this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance (QA) and data analysis include groups such as the IRB, NIAID and the FDA.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify subjects.

There may be other risks, discomforts or side effects that are unknown at this time.

2.3.5 Risks of Genetic Testing

Any genetic data generated will be kept private. There may be a risk that information resulting from research genetic testing could be misused for discriminatory purposes. However, state and federal laws provide protections against genetic discrimination. Researchers will need to maintain confidentiality in order to be granted access to genetic information.

2.3.6 Known Potential Benefits

There is no direct benefit to the subjects. There is potential benefit to society resulting from insights gained from participation in this study due to the on-going threat of the SARS-CoV-2 outbreak. Vaccination using Gritstone's investigational vaccines may or may not provide protection against infection by SARS-CoV-2. The duration of any such protection is currently unknown. The doses and vaccination strategies used in this trial may or may not alter protection by the EUA/licensed COVID-19 vaccines.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This is a multicenter, US-only, phase 1, open-label, dose escalation, non-randomized study of the safety, tolerability, and immunogenicity of investigational ChAd and SAM SARS-CoV-2 vaccines in healthy adult subjects. Homologous and heterologous prime-boost vaccination schedules (Stage 1), as well as boost(s) after receipt of EUA/licensed COVID-19 vaccines (Stage 2) will be examined. Subjects' willingness to receive ChAd vaccines will be assessed and documented at the time of informed consent and considered to determine group assignments.

This phase 1 study will enroll 17 Stage 1 and up to 118 Stage 2 subjects. Eligible subjects will be enrolled in different groups based on their age (18-60 years old and >60 years old) and their EUA/licensed COVID-19 vaccination status. A sentinel approach with 72-hour (Stage 1, and Stage 2, Groups 5, 6, 8*-10, 12, 13-15) or 7-day observation times (Groups 7* and 11) will be used, before recruiting the remainder of each dose escalation group. Decisions about dose escalation will be determined by the SSC with consultation with the DSMB as needed after all subjects in each group have been observed through Day 8 post first study vaccination. All subjects will be followed through 12 months after their last study vaccination. Vaccinated subjects will be carefully monitored for exposure and infection to SARS-CoV-2 throughout the study.

Escalation to the highest dose (10 µg) of SAM-S-TCE in younger subjects will proceed only following safety assessments of the 10 µg dose in older subjects for a period of 28 days post-vaccination.

In addition, the dosage of SAM-S-TCE given as a double boost to subjects previously vaccinated with the Johnson & Johnson/Janssen Ad26 COVID-19 EUA vaccine in Groups 8A, 8B, and 12A, 12B will be determined based on the dose escalation reactogenicity and immunogenicity results in Groups 5-7 and 9-11, respectively.

See Table 1, Figure 1, Table 3, and Section 10 for details on group assignments and study vaccines and doses to be administered.

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

3.2 Study Objectives and Endpoints

Table 2: Objectives and Endpoints (Outcome Measures)

Objectives	Endpoints (Outcome Measures)
Primary	
• To assess the safety and tolerability of different doses of ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE when administered as: o prime-boost in healthy naïve adult subjects o boost in healthy adult subjects previously vaccinated with an EUA/licensed mRNA or adenoviral-vectored COVID-19 vaccine	• Occurrence of solicited local reactogenicity signs and symptoms for 7 days following each study vaccination • Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following each study vaccination • Occurrence of unsolicited AEs for 28 days following each study vaccination • Change from baseline for clinical safety laboratory parameters 7 days after each study vaccination • Occurrence of SAEs and AESIs, including PIMMCs, MAAEs and NOCMCs, throughout the entire study following the first study vaccination
Secondary	
• To assess the humoral immunogenicity of ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization titers (including against emergent viral strains, e.g., B.1.1.7) in serum samples will be assessed via a range of assays measuring total Spike-specific IgG (ELISA-based), and function (neutralization, RBD binding, or similar) in serum on the following days:

Objectives	Endpoints (Outcome Measures)
	For Stage 1, Groups 1 and 3A: Days 1 and 29 post Dose 1; then Days 29, 181, and 366 post Dose 2 For Stage 1, Groups 3B and 4: Days 1, 29, 57, and 85-130 post Dose 1; then Days 15, 29, 85, 181, and 366 post Dose 2 For Stage 2, Groups 5-7A*, 7B*, 9, 10A, 10B, and 11A, 11B, and 13-15: Days 1, 15, 29, 85, 181, and 366 post study vaccination For Stage 2, Groups 8A*, 8B* and 12A, 12B: Days 1, 15, 29, and 57 post Dose 1; then Days 15, 29, 85, 181, and 366 post Dose 2
• To assess T cell responses to ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE	• Response rate, magnitude, and functional profiling of SARS-CoV-2 specific T cells stimulated with overlapping 15mers covering Spike and TCE regions from all subjects at pre- and post-treatment timepoints will be analyzed by IFN-γ ELISpot: For Stage 1, Groups 1 and 3A: Days 1 and 29 post Dose 1; then Days 29, 181, and 366 post Dose 2 For Stage 1, Groups 3B and 4: Days 1, 29, and 85-130 post Dose 1; then Days 15, 29, 85, 181, and 366 post Dose 2 For Stage 2, Groups 5-7A*, 7B*, 9, 10A, 10B, 11A, 11B, and 13-15: Days 1, 15, 29, 85, 181, and 366 post study vaccination For Stage 2, Groups 8A*, 8B*, and 12A, 12B: Days 1, 15, 29, and 57 post Dose 1;

Objectives	Endpoints (Outcome Measures)
	then Days 15, 29, 85, 181, and 366 post Dose 2 And by Intracellular Cytokine Staining (ICS): <u>For Stage 1, Groups 1 and 3A:</u> Days 1 and 29 post Dose 1; then Day 29 post Dose 2 <u>For Stage 1, Groups 3B and 4:</u> Days 1, 29, and 85-130 post Dose 1; then Day 15 post Dose 2 <u>For Stage 2, Groups 5-7A*, 7B*, 9, 10A, 10B, 11A, 11B, and 13-15:</u> Days 1 and 15 post study vaccination <u>For Stage 2, Groups 8A*, 8B*, and 12A, 12B:</u> Days 1, 15, and 57 post Dose 1; then Day 15 post Dose 2 • ELISpot supernatants from 4-week post-boost timepoints from a subset of subjects will be assessed for Th1/Th2 cytokine balance of T cell response by measuring IL-2, TNF-α, IL-4, IL-10, and IL-13
Exploratory	
• To assess memory B cell responses to ChAd-S or ChAd-S-TCE, and SAM-S or SAM-S-TCE	• Antigen-specificity of memory B cells at late timepoints (6- and/or 12-month follow-up) in a subset of subjects will be assessed by Spike multimer binding (flow cytometry-based assay) and/or IgG ELISpot
• To assess antibody responses to the ChAd68 vector	• Response rate and magnitude of ChAd68-specific neutralization titers in serum, pre- and post study vaccination, in subjects who

Objectives	Endpoints (Outcome Measures)
	receive the ChAd-S and ChAd-S-TCE vaccines, at the following timepoints: For Groups 1, 13, 14, and 15: Days 1 and 29 post Dose 1

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

This phase 1 study will assess the safety, immunogenicity, and reactogenicity of four (4) investigational products being developed as a SARS-CoV-2 vaccine. GRT-C907 and GRT-R908 are vaccine vectors containing a SARS-CoV-2 spike protein expression cassette. GRT-C909 and GRT-R910 are vaccine vectors containing a SARS-CoV-2 spike protein and T cell epitope expression cassette.

4.1.1 GRT-C907

GRT-C907 (ChAdV68) is a replication-defective, E1, E3 E4Orf2-4 deleted adenoviral vector based on chimpanzee adenovirus 68 (C68, 68/SadV-25, originally designated as Pan 9), which belongs to the sub-group E adenovirus family. The vector contains a spike expression cassette, introduced into the deleted viral E1 region, expressing SARS-CoV-2 spike protein (D614G variant) with a cytomegalovirus (CMV) promoter located at the 5′ end and the SV-40 polyadenylation signal at the 3′ end of the cassette sequence within the ChAdV vector. The vector was designed such that the CMV promoter sequence and SV-40 polyadenylation signal sequence remain part of the vector backbone. Therefore, the cassette is synthesized and inserted into the vector backbone to generate the GRT-C907 vaccine.

4.1.2 GRT-R908

GRT-R908 (SAM-LNP) is a SAM vector based on VEEV. In order to generate GRT-R908, sequences encoding the structural proteins of VEEV were deleted and replaced by an expression cassette encoding spike protein, the same spike protein as expressed in the GRT-C907 vaccine vector. The GRT-R908 vector encodes the VEEV proteins as well as the 5′ and 3′ RNA sequences required for RNA replication, but encodes no structural proteins, so no infectious viral particle is formed. The VEEV sub-genomic 26S promoter located 5′ of the inserted cassette drives expression of the spike cassette. The cassette is inserted into the SAM backbone vector to produce the GRT-R908 vaccine. The SAM is formulated in LNP composed of 4 lipids: an ionizable amino lipid, a phosphatidylcholine, cholesterol, and a polyethylene glycol (PEG)-based coat lipid to encapsulate the SAM and form LNPs.

4.1.3 GRT-C909

GRT-C909 (ChAdV68) is a replication-defective, E1, E3 E4Orf2-4 deleted adenoviral vector based on chimpanzee adenovirus 68 (C68, 68/SadV-25, originally designated as Pan 9), which

belongs to the sub-group E adenovirus family. The vector contains a modified spike protein and a separate TCE expression cassette, introduced into the deleted viral E1 region, expressing SARS-CoV-2 antigens with a CMV promoter located at the 5′ end and the SV-40 polyadenylation signal at the 3′ end of the spike cassette sequence within the ChAdV vector. The vector was designed such that the CMV promoter sequence and SV-40 polyadenylation signal sequence remains part of the vector backbone. Therefore, the spike cassette is synthesized and inserted into the vector backbone. The spike D614G protein is modified so that the furin cleavage site at amino acids position 682-685 (RRAR) is replaced with a non-cleavable amino acid sequence (GSAS). In addition, two proline amino acids are substituted at amino acid positions 896 and 897 (K896P, V897P). The TCE cassette is expressed using an additional CMV promoter and a BGH polyA driving expression of a TCE cassette and the CMV promoter. TCE5 cassette and BGH were cloned as a single DNA fragment downstream of the SV40 polyadenylation signal to generate the GRT-C909 vaccine.

4.1.4 GRT-R910

GRT-R910 (SAM-LNP) is a SAM vector based on VEEV. In order to generate GRT-R910, sequences encoding the structural proteins of VEEV were deleted and replaced by an expression cassette encoding a spike protein and T cell epitope, the same spike protein and T cell epitope as expressed in the GRT-C909 vaccine vector. The GRT-R910 vector encodes the VEEV proteins as well as the 5′ and 3′ RNA sequences required for RNA replication, but encodes no structural proteins, so no infectious viral particle is formed. The VEEV sub-genomic 26S promoter located 5′ of the inserted TCE cassette and this is followed by a second VEEV sub-genomic 26S promoter driving expression of the spike cassette. The spike cassettes and the second sub-genomic promoter driving the TCE expression are inserted into the SAM backbone vector to produce the GRT-R910 vaccine. The spike D614G protein is modified so that the furin cleavage site at amino acids position 682-685 (RRAR) is replaced with a non-cleavable amino acid sequence (GSAS). In addition, two proline amino acids are substituted at amino acid positions 896 and 897 (K896P, V897P). The SAM is formulated in LNPs composed of 4 lipids: an ionizable amino lipid, a phosphatidylcholine, cholesterol, and a PEG-based coat lipid to encapsulate the SAM and form LNPs.

4.1.5 Diluent: 0.9% Sodium Chloride, USP (Normal Saline)

The diluent used for this study will be 0.9% Sodium Chloride Injection, USP, and is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection. Each milliliter (mL) contains sodium chloride 9 mg. It contains no bacteriostat, antimicrobial agent or added buffer and is supplied only in single-dose containers to dilute or dissolve drugs for injection. 0.308 mOsmol/mL (calc.). 0.9% Sodium Chloride Injection, USP contains no preservatives. The

solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3 [4.5 to 7.0]).

4.1.6 Formulation, Packaging, and Labeling

4.1.6.1 GRT-C907

GRT-C907 will be supplied to clinical sites as a sterile vaccine for parenteral administration (IM), formulated as a suspension in an aqueous buffer containing 5 millimolar (mM) Tris, 5% sucrose, 75 mM NaCl, 1 mM $MgCl_2$, at pH 7.5 to 8.5. The product is formulated to achieve a nominal concentration of 5 x 10^{11} viral particles/mL. It will be supplied as a 1.2 mL fill volume in single-use 2 mL cycloolefin co-polymer vials stoppered with thermoplastic elastomer stoppers and capped with a red-colored high-density polyethylene seal, packaged as 2 vials per carton and labeled as required per local country requirements for investigational product. Upon receipt at the clinical site, GRT-C907 should be maintained in controlled-access storage at -60°C or colder.

4.1.6.2 GRT-R908

GRT-R908 will be supplied to clinical sites as a sterile vaccine for parenteral administration (IM), formulated as SAM in a suspension of LNPs in an aqueous buffer containing 5 mM Tris, 10% sucrose, 10% maltose, at pH 7.2 to 8.2. The product is formulated to deliver 0.2 mg of SAM per 1 mL of suspension. It will be supplied as a 0.7 mL fill volume in single-use 1 mL cycloolefin co-polymer vials stoppered with thermoplastic elastomer stoppers and capped with a white-colored high-density polyethylene seal, packaged as 4 vials per carton and labeled as required per local country requirements for investigational product. Upon receipt at the clinical site, GRT-R908 should be maintained in controlled-access storage at -60°C or colder.

4.1.6.3 GRT-C909

GRT-C909 will be supplied to clinical sites as a sterile vaccine for parenteral administration (IM), formulated as a suspension in an aqueous buffer containing 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM $MgCl_2$, at pH 7.5 to 8.5. The product is formulated to achieve a nominal concentration of 5 x 10^{11} viral particles/mL. It will be supplied as a 1.2 mL fill volume in single-use 2 mL cycloolefin co-polymer vials stoppered with thermoplastic elastomer stoppers and capped with a red-colored high-density polyethylene seal, packaged as 2 vials per carton and labeled as required per local country requirements for investigational product. Upon receipt at the clinical site, GRT-C909 should be maintained in controlled-access storage at -60°C or colder.

4.1.6.4 GRT-R910

GRT-R910 will be supplied to clinical sites as a sterile vaccine for parenteral administration (IM), formulated as SAM in a suspension of LNPs in an aqueous buffer containing 5 mM Tris, 10% sucrose, 10% maltose, at pH 7.2 to 8.2. The product is formulated to deliver 0.2 mg of SAM

per 1 mL of suspension. It will be supplied as a 0.7 mL fill volume in single-use 1 mL cycloolefin co-polymer vials stoppered with thermoplastic elastomer stoppers and capped with a white-colored high-density polyethylene seal, packaged as 4 vials per carton and labeled as required per local country requirements for investigational product. Upon receipt at the clinical site, GRT-R910 should be maintained in controlled-access storage at -60°C or colder.

4.1.6.5 Diluent: 0.9% Sodium Chloride, USP (Normal Saline)

Normal saline will be supplied to clinical research sites as a clear liquid in single-use 10 mL vials.

4.2 Acquisition/Distribution

Product 1 Name: GRT-C907

Product 2 Name: GRT-R908

Product 3 Name: GRT-C909

Product 4 Name: GRT-R910

Will be provided by Gritstone bio, Inc. (formerly known as Gritstone Oncology, Inc.) via the DMID Clinical Materials Services (CMS).

Upon request by DMID, GRT-C907, GRT-R908, GRT-C909, and GRT-R910 will be transferred to the following address:

DMID Clinical Materials Services Contract

Fisher BioServices

20439 Seneca Meadows Parkway

Germantown, MD 20876

Phone: 240-477-1350

Fax: 240-477-1360

Email: DMID.CMS@thermofisher.com

Product 5 Name: Diluent: 0.9% NaCl for injection, USP

Will be provided by DMID via the DMID CMS.

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 mixing vials will be provided by DMID via the DMID CMS.

All study products and sterile, empty mixing vials will be shipped to clinical research sites upon request and approval from DMID.

Visually inspect all study products upon receipt and prior to use. If the study product(s) appear(s) to have been damaged, contaminated or discolored, contain(s) visible particulate matter, or if there are any concerns regarding the integrity, do NOT use the affected study product(s). The affected study product(s) must be quarantined at appropriate storage temperature and labeled as 'Do Not Use' (until further notice). The participating site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and DMID Clinical Project Manager for further instructions before any additional vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If the affected study product(s) cannot be used, the participating site will receive specific instructions on how to return the affected study product(s) to the DMID Clinical Material Services (CMS) or destroy the affected study product(s) on-site. If the study product is unusable, study staff will use another vial from the study supply. Replacement vials may be requested by contacting DMID. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

4.3 Dosage/Regimen and Administration of Study Intervention/Investigational Product

Table 3: Dosing and Administration

Group	Product Name	Dose	Route	Volume	Frequency of Administration
Stage 1					
1	GRT-C907	$5x10^{10}$ vp	IM	0.5 mL	D1
	GRT-R908	30 µg	IM	0.5 mL	D29
3A	GRT-R908	30 µg	IM	0.5 mL	D1, D29
3B	GRT-R908	30 µg	IM	0.5 mL	D1
	GRT-R908	3 µg	IM	0.25 mL	D85-130
4	GRT-R910	10 µg	IM	0.5 mL	D1
	GRT-R910	3 µg	IM	0.25 mL	D85-130
Stage 2					

Group	Product Name	Dose	Route	Volume	Frequency of Administration
5	GRT-R910	3 µg	IM	0.25 mL	D1
6	GRT-R910	6 µg	IM	0.25 mL	D1
7A	GRT-R910	10 µg	IM	0.5 mL	D1
7B	GRT-R910	10 µg	IM	0.5 mL	D1
8A	GRT-R910	10 µg	IM	0.5 mL	D1, D57
8B	GRT-910	10 µg	IM	0.5mL	D1, D57
9	GRT-R910	3 µg	IM	0.25 mL	D1
10A	GRT-R910	6 µg	IM	0.25 mL	D1
10B	GRT-R910	6 µg	IM	0.25 mL	D1
11A	GRT-R910	10 µg	IM	0.5 mL	D1
11B	GRT-R910	10 µg	IM	0.5 mL	D1
12A	GRT-R910	10 µg	IM	0.5 mL	D1, D57
12B	GRT-910	10 µg	IM	0.5 mL	D1, D57
13	GRT-C909	$5x10^{10}$ vp	IM	0.5 mL	D1
14	GRT-C909	$1x10^{11}$ vp	IM	0.5 mL	D1
15	GRT-C909	$5x10^{11}$ vp	IM	1.0 mL	D1

4.4 Preparation of Study Intervention/Investigational Product

Refer to the protocol-specific Pharmacy Manual for details regarding study product preparation. Vaccine preparation will be performed by the participating site's research pharmacist on the same day of vaccine administration to the subject.

Aseptic technique will be used for the withdrawal and administration of all study products using a disposable, sterile needle appropriate in length and a disposable, sterile syringe appropriate in size.

Product 1 Name: GRT-C907

GRT-C907 should be thawed at ambient temperature (+20°C to +25°C) and mixed by gently inverting the vial 8-10 times. Once thawed, the product should appear as clear to opalescent, colorless to slightly blue-grey solution, and essentially free from particles.

Additional details regarding product preparation for administration (including dilution as applicable) are provided in the protocol-specific Pharmacy Manual.

A single 0.5 mL IM injection will be administered in the deltoid muscle. When possible, the prime vaccine and boost vaccine should be administered in different arms.

Once drawn up into the syringe (and diluted, if applicable), the vaccine may be stored at room temperature for up to 6 hours.

Product 2 Name: GRT-R908

GRT-R908 should be thawed at ambient temperature (+20° to +25°C) and mixed by gently swirling or inverting the vial 8-10 times. Do not vortex. Once thawed, the product should appear as a white to off-white, homogenous, opalescent liquid, and essentially free from particles.

Additional details regarding product preparation for administration (including dilution as applicable), are provided in the protocol-specific Pharmacy Manual.

A single 0.25 mL or 0.5 mL IM injection (depending on dose level) will be administered in the deltoid muscle. When possible, the prime vaccine and boost vaccine should be administered in different arms.

Once drawn up into the syringe (and diluted, if applicable), the vaccine may be stored at room temperature for up to 3 hours.

Product 3 Name: GRT-C909

GRT-C909 should be thawed at ambient temperature (+20°C to +25°C) and mixed by gently inverting the vial 8-10 times. Once thawed, the product should appear as clear to opalescent, colorless to slightly blue-grey solution, and essentially free from particles.

Additional details regarding product preparation for administration (including dilution as applicable), are provided in the protocol-specific Pharmacy Manual.

A single 0.5 mL or 1 mL IM injection (depending on dose level) will be administered in the deltoid muscle. When possible, the prime vaccine and boost vaccine should be administered in different arms.

Once drawn up into the syringe (and diluted, if applicable), the vaccine may be stored at room temperature for up to 6 hours.

Product 4 Name: GRT-R910

GRT-R910 should be thawed at ambient temperature (+20° to +25°C) and mixed by gently swirling or inverting the vial 8-10 times. Do not vortex. Once thawed, the product should appear as a white to off-white, homogenous, opalescent liquid, and essentially free from particles.

A single 0.25 mL or 0.5 mL IM injection (depending on dose level) will be administered in the deltoid muscle. When possible, the prime vaccine and boost vaccine should be administered in different arms.

Once drawn up into the syringe (and diluted, if applicable), the vaccine may be stored at room temperature for up to 3 hours.

Product 5 Name: Diluent: 0.9% NaCl for injection, USP

Normal saline is clear in appearance, and available in 10 mL vials.

4.5 Accountability Procedures for the Study Intervention/Investigational Product(s)

All study products will be stored and shipped from the DMID CMS to the clinical research sites. Once received, all study products will be stored in and dispensed by the clinical research site's Investigational Pharmacy.

The participating site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Study product accountability records and dispensing logs should include, but are not limited to the following: DMID protocol number; name, dosage form, strength of the study product; capture vial numbers assigned sequentially by the pharmacists as vials/syringes are used (number uniquely, do not start over at 1 or repeat numbers), manufacturer or other source; control, lot number or other identification number; expiration or retest date; date of receipt of the study product; quantity received from supplier; subject identification number; quantity dispensed as amount or dose per subject; balance of study product currently available; disposition of study product if not dispensed to a study subject (e.g., disposed/destroyed or retuned to supplier as per protocol or protocol-specific MOP or as directed by DMID); date of vaccine preparation/administration, time of vaccine preparation, expiration of vaccine preparation; and amount of vaccine withdrawn for administration. Time of vaccine administration to the subject will be recorded on the appropriate data collection form (DCF). All study product(s), including the amount of vaccine and diluent (0.9% NaCl for injection, USP), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the DMID-approved clinical monitoring plan (CMP).

All used vials of GRT-C907, GRT-R908, GRT-C909, and GRT-R910 should be disposed of at the clinical site immediately after use, according to standard institutional requirements for BSL-2 material (applicable to disposal of GRT-C907 and GRT-C909) and BSL-1 material (applicable to

disposal of GRT-R908 and GRT-R910). Used vials should not be retained. Vials may be destroyed in accordance with site-specific SOPs with a second staff member's observation and verification as documented in the pharmacy log. Investigational Product Accountability records must reflect dispensation of all used vials.

Any unused vials of GRT-C907, GRT-R908, GRT-C909, and GRT-R910 should be retained by the clinical research site until the end of the study. If for any reason unused vials of GRT-C907, GRT-R908, GRT-C909, and GRT-R910 must be disposed of at the clinical site, written authorization must be obtained from the DMID Clinical Project Manager prior to disposal. Vials may be destroyed in accordance with site-specific SOPs with a second staff member's observation and verification as documented in the pharmacy log. Disposal of unused vials must be clearly documented in the Investigational Product Accountability Log. Written authorizations from the DMID Clinical Project Manager should be retained with the investigational product accountability records.

Used syringes may be destroyed in accordance with site-specific SOPs.

4.5.1 Study Product Storage

The temperature of the storage unit must be manually recorded daily (excluding non-business days and holidays, as applicable) and continuously monitored and recorded during the course of this clinical trial per site-specific SOPs, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). The participating site's research pharmacist must alert the participating site PI and study coordinator, if the temperature fluctuates outside of the required range. In the event the temperature fluctuates outside of the required range, including accidental deep-freezing or disruption of the cold chain, the affected study product(s) must not be administered. The participating site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov for further instructions before any additional vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the participating site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy it on-site. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

All study products (except Normal Saline) should be maintained in controlled-access storage at -60°C or colder. The freezer should have an automated temperature recording and alert system. There must be an available back up freezer. The freezers must be connected to a back-up generator, or alternate plan in the event of a power failure. The pharmacy must have in place a

24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any study product that was not temperature controlled during shipment or during storage to the pharmacy staff. Such study product will be retained for inspection by the pharmacy staff and disposed of according to approved methods.

5 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL/DISCONTINUATION

Up to 135 men and non-pregnant women (17 for Stage 1 and up to 118 for Stage 2), aged 18 or older, who are in good health and meet all eligibility criteria will be enrolled at IDCRC sites participating in this trial. The target population should reflect the community at large at each of the participating IDCRC sites.

For Stages 1 and 2, recruitment of eligible participants will proceed if the candidate participant expresses no intention to seek an EUA/licensed COVID-19 vaccine at least until completion of the key follow-up timepoint (at least 1 month after the last study vaccination). The study investigator or staff will discuss with potential participants that de-identified antibody aggregate data will be shared with them during the conduct of the study. It will be explained to potential study participants that, in the absence of a clear immune correlate of protection, the aggregate data could be used to estimate how each study group is responding to the study products.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

Healthy adults will be recruited through IRB-approved advertising and screened through the participating institution's screening protocol to confirm eligibility requirements for participation. The following eligibility criteria will be used:

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

Subjects eligible to participate in this trial must meet all of the following inclusion criteria:

1. Provide written informed consent prior to initiation of any study procedures.
2. Able and willing (in the investigator's opinion) to comply with all study requirements.
3. Are men or non-pregnant women aged 18 years or older at enrollment.
4. Are in good health*.

As defined by absence of clinically significant medical conditions defined by the CDC as increasing risk for severe COVID-19 disease (see exclusion criteria), or other acute or chronic medical conditions determined by medical history, physical examination (PE), screening laboratory test results, and/or clinical assessment of the investigator that are either listed as exclusion criteria below or in the opinion of the investigator would increase risk for study participation or affect the assessment of the safety of subjects. Chronic medical conditions should be stable for the last 60 days (no hospitalizations, emergency room or urgent care for condition, or invasive medical procedures). Any prescription change that is due to change of health care provider, insurance company, etc., or done for financial reasons, and in the same class of medication, will not be considered a deviation of this inclusion criterion. Any change in prescription medication due to* ***improvement* *of a disease outcome, as determined by the participating site PI or appropriate sub- investigator, will not be considered a deviation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the participating site PI or appropriate sub-investigator, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity, and do not indicate a worsening of medical diagnosis/condition. Similarly, medication changes in the 60 days prior to enrollment as well as subsequent to enrollment and study vaccination are acceptable provided the change was not precipitated by deterioration in the chronic medical condition, and there is no anticipated additional risk to the subject or interference with the evaluation of responses to study vaccination.*

5. Agree to refrain from blood donation during the course of the study.
6. Plan to remain living in the area for the duration of the study.
7. Women of childbearing potential (WOCBP)* must plan to avoid pregnancy for at least 60 days after the last study vaccination and be willing to use an adequate method of contraception** consistently for 30 days prior to first study vaccine and for at least 60 days after the last study vaccine.

   **Not sterilized via bilateral oophorectomy, tubal ligation/salpingectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization with documented radiological confirmation test at least 90 days after the procedure); still menstruating; or < 1 year has passed since the last menses if menopausal.*

   ***Acceptable methods of birth control include the following: oral contraceptives, injection hormonal contraceptive, implant hormonal contraceptive, hormonal patch, intrauterine device, spermicidal products and barrier methods (such as cervical sponge,*

diaphragm, or condom with spermicide), abstinence, monogamous with a vasectomized partner, non-male sexual relationship.

8. Women of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to each study vaccination.
9. Vital signs within acceptable ranges:
   - Pulse >50 and ≤100 beats per minute
   - Systolic blood pressure (BP) ≤140 millimeters of mercury (mmHg)
   - Diastolic BP ≤90 mmHg
   - Oral temperature <37.8°C (100.0°F)
10. Clinical screening lab evaluations (white blood cell (WBC), hemoglobin (HgB), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (T Bili), creatine kinase (CK), serum creatinine (Cr) and prothrombin time (PT)/partial thromboplastin time (PTT)) are within acceptable normal reference ranges at the clinical lab being used*.

    **With the exception that ALT, AST, ALP, and creatinine values that are below the reference range will not be exclusionary as these values below reference range are clinically insignificant. Any other screening lab value outside the reference range that is thought to be clinically insignificant by a site investigator must be discussed with the DMID Medical Officer prior to enrollment.*
11. Must agree to genetic testing and storage of samples for secondary research.
12. Received at least 2 doses of EUA/licensed mRNA vaccines or at least 1 dose of Ad26 vaccine followed by an mRNA booster, with the last COVID-19 vaccine dose given at least 112 days prior to enrollment (Stage 2 only), as confirmed via CDC vaccination card or other appropriate documentation. Subjects may or may not have been previously infected with SARS-CoV-2.*

    *In version 7.0 of the protocol, we prioritize enrollments of subjects who have either received 3 EUA/licensed mRNA vaccinations (SAM-S-TCE single boosting Groups 7A, 7B, 10A, 10B, 11A, 11B, 12A and 12B, and ChAd-S-TCE single boosting Groups 13-15) or 1-2 doses of EUA/licensed Ad26 prior to 1 dose of EUA/licensed mRNA (SAM-S-TCE double boosting Groups 8A, 8B, 12A and 12B).

5.1.2 Leukapheresis Inclusion Criteria

A subject must meet all of the following criteria to be eligible for leukapheresis:

1. Written informed consent for leukapheresis is provided.
2. Weight ≥110 pounds.
3. Screening laboratory evaluations are within acceptable ranges at the site where the leukapheresis procedure will be performed.
4. Negative urine or serum pregnancy test at screening and on the day of the leukapheresis procedure for women of childbearing potential.
5. Adequate bilateral antecubital venous access.
6. No use of blood thinners, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs) at least 5 days before the leukapheresis procedure.

5.1.3 Subject Exclusion Criteria

Subjects eligible to participate in this trial must not meet any of the following exclusion criteria:

1. History of prior confirmed (PCR or antigen test positive) COVID-19 less than 112 days prior to enrollment.
2. Positive for anti-nucleoprotein SARS-CoV-2 specific antibody by enzyme-linked immunosorbent assay (ELISA) and had the history of upper respiratory illness (URI) compatible with COVID-19 during the 112 days prior to enrollment (seropositivity without a history of URI during the 112 days prior to enrollment will be considered remotely infected persons eligible for enrollment).
3. Positive nasal swab polymerase chain reaction (PCR) at screening.
4. Body mass index (BMI) > 30 kg/m^2 for Stage 1 participants and BMI > 35 kg/m^2 for Stage 2 participants.
5. Presence of medical comorbidities that would place the subject at increased risk for severe COVID-19*.

   **Chronic kidney disease, chronic lung disease (including moderate-to-severe asthma), chronic heart disease (heart failure, coronary artery disease or cardiomyopathies), cerebrovascular disease, diabetes mellitus, chronic liver disease, sickle cell disease.*

6. Increased risk of occupational exposure to SARS-CoV-2 (healthcare workers and emergency response personnel)*.

   **Applies to Stage 1 participants only.*

7. Prior receipt of an approved/licensed or investigational SARS-CoV-2 vaccine (including under EUA)*, approved or investigational adenovirus-vectored vaccines**, or any other approved or investigational vaccine likely to impact the interpretation of the trial data.

   **Exclusion of prior receipt of EUA/licensed COVID-19 vaccines applies to Stage 1 participants only.*

   ***With the exception of prior receipt of EUA Johnson & Johnson/Janssen Ad 26 COVID-19 vaccine which is permitted for Groups 8 and 12.*

8. On current treatment or prevention agents with activity against SARS-CoV-2.
9. Current smoking or vaping or history of smoking or vaping in prior year*.

   **Applies to Stage 1 participants only.*

10. Breastfeeding, pregnant, or planning to become pregnant during the course of the study.
11. Participation in another research study involving receipt of an investigational product in the 60 days preceding enrolment or planned use during the study period.
12. Receipt or planned receipt of any live, attenuated vaccine within 28 days before or after study vaccination.
13. Receipt or planned receipt of any subunit or killed vaccine within 14 days before or after vaccination.
14. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of first study vaccination or at any time during the study.
15. Any confirmed or suspected immunosuppressive or immunodeficient state, including human immunodeficiency virus (HIV) infection, asplenia, recurrent, severe infections and chronic (more than 14 continuous days) immunosuppressant medication within the past 6 months (inhaled, ophthalmic, and topical steroids are allowed).
16. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine, including urticaria, respiratory difficulty or abdominal pain (or any immediate

allergic reaction of any severity to polysorbate due to potential cross-reactive hypersensitivity with the polyethylene glycol component of the vaccine).

17. Any history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
18. Any history of anaphylaxis, including but not limited to reaction to vaccination.
19. Any history of severe allergic drug reaction.
20. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
21. History of serious ongoing, unstable psychiatric condition that in the opinion of the investigator would interfere with study participation.
22. Seizure in the past 3 years or treatment for seizure disorder in the past 3 years.
23. Bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture or family history of bleeding disorder.
24. Recent (within the past 3 months) surgery, immobility, chronic infection, or head trauma that could increase the risks of thrombosis.
25. Suspected or known current alcohol abuse. Suspected or known drug abuse in the 5 years preceding enrollment.
26. Seropositive for HIV, hepatitis B surface antigen (HBsAg), or seropositive for hepatitis C virus (antibodies to HCV).
27. Have an acute illness* within 72 hours prior to study vaccination.

    **An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the site PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.*
28. History of venous or arterial thrombosis or any known thrombophilic condition including heparin-induced thrombocytopenia (HIT) or family history of thrombosis.
29. History of myocarditis or pericarditis.
30. History of Guillain-Barré Syndrome (GBS).
31. Receiving heparin treatment or on medications associated with increased risk of bleeding or thrombosis.

32. Any other condition that in the opinion of the investigator would pose a health risk to the participant if enrolled or could interfere with evaluation of the trial vaccine or interpretation of study results.

5.2 Delay of Study Vaccination, Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

5.2.1 Delay of Study Vaccination

The following events constitute contraindications to administration of vaccine. If any of these events occur at the time scheduled for vaccination, then the subject may be vaccinated at a later date, within the window specified in the Schedule of Activities, or withdrawn from dosing at the discretion of the Investigator.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. Vaccination can occur in persons with a minor illness, such as diarrhea, mild upper respiratory infection with or without low-grade fever.
    - Fever is defined as oral temperature of >37.8°C (100.0°F) at the time of vaccination.
- If the subject received a non-study inactivated vaccine within 14 days or a live vaccine within 28 days of the scheduled study vaccine, then the study vaccine may be delayed to be given at least 15 days after the inactivated vaccine or 29 days after the live vaccine.

5.2.2 Withdrawal from the Study or Discontinuation of the Study Product and Replacement

Subjects are free to withdraw from participation in the study at any time upon request, without any consequence.

A study subject will be discontinued from participation in the study if any of the following reasons occur prior to initial dosing:

- Request by the subject to terminate participation.
- Study non-compliance to protocol requirements that in the opinion of the participating site PI or appropriate sub-investigator poses an increased risk (e.g., missing safety labs) or compromises the validity of the data.
- Request of primary care provider or NIAID.

A subject may be removed from the study for the following reasons post initial dosing; however, whenever possible the subject should be followed for safety and immunogenicity evaluations per protocol:

- Subject becomes pregnant before receiving the second dose of vaccine.
- Study non-compliance to protocol requirements that in the opinion of the participating site PI or appropriate sub-investigator poses an increased risk (e.g., missing safety labs) or compromises the validity of the data.
- Lost to follow-up.
- If the subject met an exclusion criterion for participation in the study (either newly developed or not previously recognized) that precludes further vaccination.
- Request of primary care provider, the IRB, FDA, or NIAID.
- Medical disease or condition, or new clinical finding(s) for which further vaccination, in the opinion of the participating site PI or appropriate sub-investigator, might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses.
- If any AE, clinical laboratory abnormality or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The occurrence of a related SAE.

If the subject agrees, every attempt will be made to follow all AEs through resolution or stabilization.

The reason for subject discontinuation or withdrawal from the study will be recorded on the appropriate data collection form.

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product will not be replaced if they are withdrawn for safety reasons.

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF but before administration of the study product may be replaced. If 2 or more subjects in a single group are withdrawn after the first study vaccination and before the second study vaccination for reasons other than safety issues (e.g., are found to be newly infected with SARS-CoV-2 by COVID-19 PCR and/or serology at the time of the second vaccination), the protocol team will discuss and determine whether replacement subjects should be enrolled.

5.2.3 Withdrawal Criteria for Second Study Vaccination

Prior to receiving the second vaccination, subjects will be reassessed. If any of these events occur during the study, the subject must not receive the second vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after the last study vaccination.

The study intervention will be discontinued in a subject for any of the following reasons:

1. Withdrawal of consent.
2. As deemed necessary by the participating site PI or appropriate sub-investigator for non-compliance or other reasons. This may include previously undisclosed or new conditions that meet the exclusion criteria.
3. Any clinically significant medical condition that, in the opinion of the participating site PI or appropriate sub-investigator, poses an additional risk to the subject if he/she continues to participate in the study.
4. Anaphylaxis or unexpected systemic hypersensitivity reaction following the administration of the first study vaccination.
5. Any SAE judged to be related to study vaccine.
6. Pregnancy.
7. Subject is lost to follow-up.
8. New information becomes available that makes further participation unsafe.
9. Termination of the trial.
10. Myocarditis or pericarditis that occurs after the first study vaccination.

5.2.4 Follow-up for Subjects that Discontinued Study Intervention

Discontinuation of study intervention does not require discontinuation from the study, and the remaining study procedures should be completed as indicated by the Schedule of Activities. If a clinically significant finding is identified, including, but not limited to, changes from baseline, after enrollment, the participating site PI or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE.

If the participant is enrolled and seeks vaccination with an EUA/licensed COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and research team and will be able to receive the authorized vaccine at least

one month after the last study vaccination. An unscheduled visit will occur, if possible, prior to the receipt of an EUA/licensed COVID-19 vaccine. The remaining study procedures should be completed as indicated by the Schedule of Activities or the participant will only be followed for safety.

The data to be collected at the time of study intervention discontinuation should include the following:

- Clinical safety laboratory evaluations.
- Complete physical examination (PE).
- Vital signs (BP, pulse, and oral temperature).
- Immunogenicity evaluations.

5.2.5 Study Termination

This study may be prematurely terminated if there is sufficient reasonable cause, including, but not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Results of interim analysis.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or not evaluable.
- Regulatory authorities.

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and the IRB, as applicable. Study subjects will be contacted, and appropriate follow-up will be conducted, as necessary.

The sponsor will notify regulatory authorities as applicable.

5.2.6 Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-mails, etc., made on separate occasions) will be made to locate or recall the subject, or at least to determine the subject's health status. These efforts will be documented in the subject's study file.

6 STUDY PROCEDURES

At some participating sites, subjects will be given the option for in-person non-vaccination visits to be conducted in clinic or at home.

6.1 Screening

Screening for this study will be completed through the participating institution's screening protocol or this study's informed consent. Testing will be done according to eligibility criteria and clinical assessment at screening. Screening evaluations for specific eligibility criteria must be completed within 30 days prior to enrollment for the given parameter but may be repeated as needed to confirm eligibility. If consent is obtained, the screening procedures indicated in the Schedule of Activities (see Table 6, Table 7, Table 8, and Table 9) will be undertaken. To avoid unnecessary additional venipuncture, if the appropriate blood test results for screening are available for the same subject (e.g., recent doctor's visit), these results may be used for assessing eligibility provided the results date is within the 30 days preceding enrolment to this trial.

Abnormal clinical findings from the medical history, physical examination or blood tests at screening will be assessed. Abnormal blood tests following enrollment will be assessed according to the FDA guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". If a test is deemed clinically significant it may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant, the subject will be informed and referred for appropriate medical care with the permission of the subject. Decisions to exclude the subject from enrolling in the trial or to withdraw a subject from the trial will be at the discretion of the Investigator.

Any study subject who has not yet received the current year influenza vaccination may receive this, if available, during the screening period but not within 14 days before or after study treatment start.

6.1.1 Visit 00, Screening, Day -30 to -1, Clinic Visit

- Subjects will be provided with a description of this trial (purpose and study procedures) and asked to read and sign the ICF prior to performing any study procedures.
- Demographic information will be obtained by interview of subjects.
- Eligibility criteria will be reviewed with subjects to ensure eligibility.
- Complete medical history will be obtained by interview of subjects to ensure eligibility.

- All concomitant medications taken within 30 days prior to signing the ICF will be reviewed with subjects to determine stability of chronic diseases and eligibility.
- Vital signs, including oral temperature, pulse, and BP, will be obtained to ensure eligibility. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- Height and weight will be collected for the calculation of BMI.
- A physical examination will be performed on all subjects by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- A urine or serum pregnancy test will be performed locally by the site for all women of childbearing potential within 24 hours of vaccination. Results must be negative to ensure eligibility.
- Nasal swab will be collected for SARS-CoV-2 PCR.
- Approximately 17 mL of venous blood will be collected for baseline screening labs including WBC, HgB, PLT, ALT, AST, ALP, T Bili, Cr, CK and PT/PTT.
- Approximately 14 mL of venous blood will be collected for HBsAg, Anti-HCV, SARS-CoV-2 serology (N-specific), and HIV.

6.2 Enrollment

6.2.1 Visit 01, Day 1, Clinic Visit, 1st Study Vaccination (Dose 1)

- Subject's willingness to participate will be reconfirmed and documented in the subject's study records prior to performing any further study procedures, including administration of the first study vaccination.
- Eligibility criteria, including results of the screening labs, will be reviewed with subjects prior to the first study vaccination to ensure eligibility. Subjects who have received approved COVID-19 booster vaccinations are no longer excluded. In addition, subjects with evidence of previous non-acute COVID-19 (serologically positive, but PCR negative) are also no longer excluded.
- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, will be obtained by interview of subjects prior to the first study

vaccination. Any changes in medical history since the screening visit will be reviewed with subjects prior to the first study vaccination to ensure continued eligibility.

- All concomitant medications (including solicitation for receipt of any non-study vaccines) will be reviewed with subjects prior to the first study vaccination for accuracy and completeness. Any new concomitant medications taken since the screening visit will be reviewed with subjects prior to the first study vaccination to ensure continued eligibility.
- Vital signs, including oral temperature, pulse, and BP, will be obtained prior to the first study vaccination to ensure continued eligibility. Vital signs assessed on Day 1 prior to the first study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed prior to the first study vaccination, if indicated based on review of complete medical history and any updates obtained by interview of subjects since the screening visit, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- A urine or serum pregnancy test will be performed locally by the site within 24 hours prior to the first study vaccination for all women of childbearing potential. Results must be negative and known prior to enrollment and the first study vaccination.
- A saliva sample will be collected to check for antibodies.
- Approximately 72-80 mL of venous blood will be collected immediately prior to the first study vaccination for baseline cellular immunology assays.
- Approximately 20 mL of venous blood will be collected immediately prior to the first study vaccination for baseline antibody assays. An aliquot may be used as needed to determine pre-vaccination levels of troponins.
- Approximately 32 mL of venous blood will be collected immediately prior to the first study vaccination for peripheral blood mononuclear cell (PBMC) and plasma storage for secondary research.
- Groups 5-15 Only: Approximately 2.5 mL of venous blood will be collected immediately prior to the first study vaccination for baseline transcriptomal analysis and comparisons with post study vaccination transcriptomal signature changes associated with study vaccine reactogenicity and immunogenicity.
- Groups 5-15 Only: Approximately 4 mL of blood will be collected for cytokines.

- Subjects will be enrolled in Advantage *eClinical* and assigned to a treatment arm prior to the first study vaccination.
- Subjects will then receive one 0.25, 0.5, or 1.0 mL dose of study vaccine (depending on treatment assignment) via a single IM injection into the deltoid muscle of the subject's preferred arm. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 45 minutes after the first study vaccination. The first study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF prior to discharge from the clinic.
- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the first study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

6.3 Planned Study Visits for Groups 1 and 3A

At all clinic visits for Groups 1 and 3A, the following study procedures will be performed:

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases will be obtained by interview of subjects and any changes since the previous clinic visit, phone call, or other form of contact will be noted.
- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed, if indicated, based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

6.3.1 Visits 02 and 03, Days 2 and 4, Telephone, Email, or Text Contact

(Windows: Day 2+1 day and Day 4+2 days post 1st study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AE), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.3.2 Visit 04, Day 8, Clinic Visit

(Window: Day 8+2 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- A saliva sample will be collected to check for antibodies.
- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili.
- Approximately 24 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including potentially immune-mediated medical conditions (PIMMCs), medically attended adverse events (MAAEs), and new onset chronic medical conditions (NOCMCs) will be recorded on the appropriate DCF.

6.3.3 Visit 05, Day 29, Clinic Visit, 2nd Study Vaccination (Dose 2)

(Window: Day 29±3 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- Eligibility criteria will be reviewed with subjects prior to the second study vaccination to ensure continued eligibility.
- A urine or serum pregnancy test will be performed locally by the site within 24 hours prior to the second study vaccination for all women of childbearing potential. Results must be negative and known prior to the second study vaccination.
- Nasal swab will be collected for SARS-CoV-2 PCR prior to the second vaccination.

- Approximately 2 mL of venous blood will be collected for SARS-CoV-2 serology (N-specific).
- Approximately 14 mL of venous blood will be collected immediately prior to the second study vaccination for baseline clinical safety labs (WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr) to be performed by the local (clinical) laboratory. The results from these evaluations will not be available or reviewed prior to the second study vaccination.
- Approximately 80 mL of venous blood will be collected immediately prior to the second study vaccination for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected immediately prior to the second study vaccination for antibody assays.
- Approximately 32 mL of venous blood will be collected immediately prior to the second study vaccination for PBMC and plasma storage for secondary research.
- Subjects will then receive one- 0.5 mL dose of study vaccine (depending on treatment assignment) via a single IM injection into the deltoid muscle. If possible, administer study vaccine in the opposite arm used for the first study vaccination. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 45 minutes after the second study vaccination. The second study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF prior to discharge from the clinic.
- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the second study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

6.3.4 Visits 06 and 07, Days 30 and 32, Telephone, Email, or Text Contact (Windows: Day 2+1 and Day 4+2 days post 2nd study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.3.5 Visit 08, Day 36, Clinic Visit

(Window: Day 8+2 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- A saliva sample will be collected to check for antibodies.
- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili.
- Approximately 24 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- Memory Aid information will be reviewed with subjects.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.3.6 Visit 08A, Day 15, Optional Leukapheresis

(Window: Day 15+4 weeks post 2nd study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- Subjects will be provided with a description of the Leukapheresis substudy (purpose and study procedures) and asked to read and sign the ICF prior to performing the procedure. A Leukapheresis specific informed consent may be needed prior to performing the procedure based on institutional requirements.
- Review eligibility criteria for leukapheresis procedure.
- Blood collection for safety labs required prior to the procedure.
- Urine or serum pregnancy test prior to the procedure.
- Only SAEs that occur during or within 24 hours after the leukapheresis study visit will be recorded on the appropriate DCF.

6.3.7 Visit 09, Day 57, Clinic Visit

(Window: Day 29±3 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.3.8 Visit 10, Day 209, Clinic Visit

(Window: Day 181±14 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF

6.3.9 Visit 11, Day 394, Clinic Visit, Final Study Visit

(Window: Day 366±14 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.3, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.

- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4 Planned Study Visits for Groups 3B and 4

At all clinic visits for Groups 3B and 4, the following study procedures will be performed:

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases will be obtained by interview of subjects and any changes since the previous clinic visit, phone call, or other form of contact will be noted.
- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed, if indicated, based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

6.4.1 Visits 02 and 03, Days 2 and 4, Telephone, Email, or Text Contact

(Window: Day 2+1 day and Day 4+2 days post 1st study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.4.2 Visit 04, Day 8, Clinic Visit

(Window: Day 8+2 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- A saliva sample will be collected to check for antibodies.
- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili.

- Approximately 24 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- Memory Aid information will be reviewed with subjects.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.3 Visit 05, Day 29, Clinic Visit

(Window: Day 29±3 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.4 Visit 06, Day 57, Clinic Visit

(Window: Day 57±3 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.5 Visit 07, Day 85, Clinic Visit, 2nd Study Vaccination (Dose 2)

(Window: Day 85+45 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Eligibility criteria will be reviewed with subjects prior to the second study vaccination to ensure continued eligibility.
- A urine or serum pregnancy test will be performed locally by the site within 24 hours prior to the second study vaccination for all women of childbearing potential. Results must be negative and known prior to the second study vaccination.
- Nasal swab will be collected for SARS-CoV-2 PCR prior to the second vaccination.
- Approximately 2 mL of venous blood will be collected for SARS-CoV-2 serology (N-specific).
- Approximately 14 mL of venous blood will be collected immediately prior to the second study vaccination for baseline clinical safety labs (WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr) to be performed by the local (clinical) laboratory. The results from these evaluations will not be available or reviewed prior to the second study vaccination.
- Approximately 80 mL of venous blood will be collected immediately prior to the second study vaccination for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected immediately prior to the second study vaccination for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- Subjects will then receive one- 0.25 or 0.5 mL dose of study vaccine (depending on treatment assignment) via a single IM injection into the deltoid muscle. If possible, administer study vaccine in the opposite arm used for the first study vaccination. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 45 minutes after the second study vaccination. The second study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any

AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF prior to discharge from the clinic.

- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the second study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

6.4.6 Visit 08, Day 86, Clinic Visit

(Window: Day 2+1 day post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.7 Visit 09, Day 88, Telephone, Email, or Text Contact

(Window: Day 4+2 days post 2nd study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.4.8 Visit 10, Day 92, Clinic Visit

(Window: Day 8+2 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- A saliva sample will be collected to check for antibodies.
- Memory Aid information will be reviewed with subjects.
- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.9 Visit 11, Day 99, Clinic Visit

(Window: Day 15+2 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.10 Visit 11A, Day 15, Optional Leukapheresis

(Window: Day 15+4 weeks post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Subjects will be provided with a description of the Leukapheresis substudy (purpose and study procedures) and asked to read and sign the ICF prior to performing the procedure.

A Leukapheresis specific informed consent may be needed prior to performing the procedure based on institutional requirements.

- Review eligibility criteria for leukapheresis procedure.
- Blood collection for safety labs required prior to the procedure.
- Urine or serum pregnancy test prior to the procedure.
- Only SAEs that occur during or within 24 hours after the leukapheresis study visit will be recorded on the appropriate DCF.

6.4.11 Visit 12, Day 113, Clinic Visit

(Window: Day 29±3 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.12 Visit 13, Day 169, Clinic Visit

(Window: Day 85±3 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.13 Visit 14, Day 265, Clinic Visit

(Window: Day 181±14 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.4.14 Visit 15, Day 450, Clinic Visit, Final Study Visit

(Window: Day 366±14 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.4, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5 Planned Study Visits for Groups 5-7A, 7B, 9, 10A, 10B, 11A, 11B, and 13-15

At all clinic visits for Groups 5-7A, 7B, 9, 10A, 10B, 11A, 11B, and 13-15, the following study procedures will be performed:

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases will be obtained by interview of subjects and any changes since the previous clinic visit, phone call, or other form of contact will be noted.

- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed, if indicated, based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

6.5.1 Visit 02, Day 2, Clinic Visit

(Window: Day 2+1 post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5.2 Visit 03, Day 4, Telephone, Email, or Text Contact

(Window: Day 4+2 days post study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.5.3 Visit 04, Day 8, Clinic Visit

(Window: Day 8+2 days post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- A saliva sample will be collected to check for antibodies.

- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5.4 Visit 05, Day 15, Clinic Visit

(Window: Day 15+2 days post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5.5 Visit 05A, Day 15, Optional Leukapheresis

(Window: Day 15+4 weeks post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Subjects will be provided with a description of the Leukapheresis substudy (purpose and study procedures) and asked to read and sign the ICF prior to performing the procedure. A Leukapheresis specific informed consent may be needed prior to performing the procedure based on institutional requirements.
- Review eligibility criteria for leukapheresis procedure.
- Blood collection for safety labs required prior to the procedure.
- Urine or serum pregnancy test prior to the procedure.

- Only SAEs that occur during or within 24 hours after the leukapheresis study visit will be recorded on the appropriate DCF.

6.5.6 Visit 06, Day 29, Clinic Visit

(Window: Day 29±3 days post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5.7 Visit 07, Day 85, Clinic Visit

(Window: Day 85±3 days post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5.8 Visit 08, Day 181, Clinic Visit

(Window: Day 181±14 days post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.

- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.5.9 Visit 09, Day 366, Clinic Visit, Final Study Visit

(Window: Day 366±14 days post study vaccination)

In addition to the study procedures listed in Section 6.5, the following study procedures will also be performed:

- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6 Planned Study Visits for Groups 8A, 8B and 12A, 12B

At all clinic visits for Groups 8A, 8B, and 12A, 12B, the following study procedures will be performed:

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases will be obtained by interview of subjects and any changes since the previous clinic visit, phone call or other form of contact will be noted.
- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed, if indicated, based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

6.6.1 Visit 02, Day 2, Clinic Visit,

(Window: Day 2+1 day 1st post study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.2 Visit 03, Day 4, Telephone, Email, or Text Contact

(Window: Day 4+2 days post 1st study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.6.3 Visit 04, Day 8, Clinic Visit

(Window: Day 8+2 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- A saliva sample will be collected to check for antibodies.
- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.

- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.4 Visit 05, Day 15, Clinic Visit

(Window: Day 15+2 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 24 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.5 Visit 06, Day 29, Clinic Visit

(Window: Day 29±3 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.6 Visit 07, Day 57, Clinic Visit, 2nd Study Vaccination (Dose 2)

(Window: Day 57±3 days post 1st study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Eligibility criteria will be reviewed with subjects prior to the second study vaccination to ensure continued eligibility.

- A urine or serum pregnancy test will be performed locally by the site within 24 hours prior to the second study vaccination for all women of childbearing potential. Results must be negative and known prior to the second study vaccination.
- Nasal swab will be collected for SARS-CoV-2 PCR prior to the second vaccination.
- Approximately 2 mL of venous blood will be collected for SARS-CoV-2 serology (N-specific).
- Approximately 14 mL of venous blood will be collected immediately prior to the second study vaccination for baseline clinical safety labs (WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr) to be performed by the local (clinical) laboratory. The results from these evaluations will not be available or reviewed prior to the second study vaccination.
- Approximately 72 mL of venous blood will be collected immediately prior to the second study vaccination for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected immediately prior to the second study vaccination for antibody assays.
- Approximately 24 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- Subjects will then receive one- 0.25 or 0.5 mL dose of study vaccine (depending on treatment assignment) via a single IM injection into the deltoid muscle. If possible, administer study vaccine in the opposite arm used for the first study vaccination. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 45 minutes after the second study vaccination. The second study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF prior to discharge from the clinic.
- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold within

10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the second study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

6.6.7 Visit 08, Day 58, Clinic Visit

(Window: Day 2+1 day post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Memory Aid information will be reviewed with subjects.
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.8 Visit 09, Day 60, Telephone, Email, or Text Contact

(Window: Day 4+2 days post 2nd study vaccination)

- Memory Aids will be reviewed with the subjects via telephone, email, or text for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications. Based on the information collected, subjects may be asked to return to the clinic for an evaluation.

6.6.9 Visit 10, Day 64, Clinic Visit

(Window: Day 8+2 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- A saliva sample will be collected to check for antibodies.
- Memory Aid information will be reviewed with subjects.

- Approximately 14 mL of venous blood will be collected for safety labs including WBC, HgB, PLT, ALT, AST, ALP, Cr, CK and T Bili
- Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity.
- Approximately 4 mL of blood will be collected for cytokines.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.10 Visit 11, Day 71, Clinic Visit

(Window: Day 15+2 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected immediately prior to the second study vaccination for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected immediately prior to the second study vaccination for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.11 Visit 11A, Day 15, Optional Leukapheresis

(Window: Day 15+4 weeks after 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Subjects will be provided with a description of the Leukapheresis substudy (purpose and study procedures) and asked to read and sign the ICF prior to performing the procedure. A Leukapheresis specific informed consent may be needed prior to performing the procedure based on institutional requirements.
- Review eligibility criteria for leukapheresis procedure.
- Blood collection for safety labs required prior to the procedure.

- Urine or serum pregnancy test prior to the procedure.
- Only SAEs that occur during or within 24 hours after the leukapheresis study visit will be recorded on the appropriate DCF.

6.6.12 Visit 12, Day 85, Clinic Visit

(Window: Day 29±3 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.13 Visit 13, Day 141, Clinic Visit

(Window: Day 85±3 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.14 Visit 14, Day 237, Clinic Visit

(Window: Day 181±14 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.6.15 Visit 15, Day 422, Clinic Visit, Final Study Visit

(Window: Day 366±14 days post 2nd study vaccination)

In addition to the study procedures listed in Section 6.6, the following study procedures will also be performed:

- Approximately 72 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.7 Early Termination Visit

- Interim medical history, including an assessment for new medical conditions will be obtained by interview of subjects and any changes since the previous clinic visit, phone call, or other form of contact will be noted.
- All concomitant medications will be recorded on the appropriate DCF.
- All AEs will be recorded on the appropriate DCF (if prior to Visit 09 for Stage 1, Groups 1 and 3A, Visit 12 for Stage 1, Groups 3B and 4, Visit 06 for Stage 2, Groups 5-7, 9-11, and 13-15, and Visit 12 for Stage 2, Groups 8 and 12).
- Memory Aid information will be reviewed with subjects (if within 7 days after the last study vaccination).

- Vital signs, including oral temperature, pulse, and BP, may be obtained if indicated. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed, if indicated, based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- Approximately 14 mL of venous blood will be collected for clinical safety labs (WBC, HgB, PLT, ALT, AST, ALP, Cr, CK, and T Bili) to be performed by the local clinical laboratory (if within 7 days after the last study vaccination).
- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- STAGE 1, Groups 3B and 4 and STAGE 2, Groups 5, 6, 7A, 7B, 8A, 8B, 9, 10A, 10B, 11A, 11B, 12A, 12B, and 13-15: Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity (if on or prior to Day 8 of either vaccination).
- STAGE 1, Groups 3B and 4 and STAGE 2, Groups 5, 6, 7A, 7B, 8A, 8B, 9, 10A, 10B, 11A, 11B, 12A, 12B, and 13-15: Approximately 4 mL of venous blood will be collected for cytokines (if on or prior to Day 8 of either vaccination).
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.8 Unscheduled Study Visits

An Unscheduled Visit may occur at any time during this trial and will be conducted in clinic or at home, based on participating site and subject preference. Any of the following activities may be performed:

- Interim medical history, including an assessment for new medical conditions will be obtained by interview of subjects and any changes since the previous clinic visit, phone call, or other form of contact will be noted (if indicated).
- All concomitant medications will be recorded on the appropriate DCF.

- All AEs will be recorded on the appropriate DCF (if prior to Visit 09 for Stage 1, Groups 1 and 3A, Visit 12 for Stage 1, Groups 3B and 4, Visit 06 for Stage 2, Groups 5-7A, 7B, 9, 10A, 10B, 11A, 11B, and 13-15, and Visit 12 for Stage 2, Groups 8A, 8B and 12A, 12B).
- Memory Aid information will be reviewed with subjects (if within 7 days after the last study vaccination).
- Vital signs, including oral temperature, pulse, and BP, may be obtained if indicated. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed, if indicated, based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- Approximately 14 mL of venous blood will be collected for clinical safety labs (WBC, HgB, PLT, ALT, AST, ALP, Cr, CK, and T Bili) will be performed by the central (clinical) laboratory (if indicated).
- If a participant presents with signs or symptoms suggestive of pericarditis or myocarditis within 6 weeks post vaccination, blood will be collected for troponin-I or troponin-T testing and an electrocardiogram (ECG) will be performed.
- Approximately 80 mL of venous blood will be collected for cellular immunology assays.
- Approximately 20 mL of venous blood will be collected for antibody assays.
- Approximately 32 mL of venous blood will be collected for PBMC and plasma storage for secondary research.
- STAGE 1, Groups 3B and 4 and STAGE 2, Groups 5, 6, 7A, 7B, 8A, 8B, 9, 10A, 10B, 11A, 11B, 12A, 12B, and 13-15: Approximately 2.5 mL of venous blood will be collected for identification of transcriptomal signatures associated with vaccine reactogenicity and immunogenicity (if on or prior to Day 8 of either vaccination).
- STAGE 1, Groups 3B and 4 and STAGE 2, Groups 5, 6, 7A, 7B, 8A, 8B, 9, 10A, 10B, 11A, 11B, 12A, 12B, and 13-15: Approximately 4 mL of venous blood will be collected for cytokines (if on or prior to Day 8 of either vaccination).
- All SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be recorded on the appropriate DCF.

6.9 Leukapheresis Substudy

To support development of diagnostics, therapeutics and vaccines, a subset of subjects enrolled in any of the Stage 1 or Stage 2 groups may undergo leukapheresis to collect additional samples for secondary research.

6.9.1 Screening Procedures for Leukapheresis (only for those subjects consented for leukapheresis)

- For those subjects consented for leukapheresis, screening procedures, including screening laboratory evaluations, will be performed locally prior to the leukapheresis procedure.

6.9.2 Leukapheresis Procedure (only for those subjects consented for leukapheresis)

- Leukapheresis is an outpatient procedure during which leukocytes will be selectively harvested; red cells and other blood components will be returned to the subject. In a typical leukapheresis procedure, approximately 1-3 $x10^9$cells can be isolated with only minimal loss of red blood cells. No sedation is required. The procedure will be done by trained site staff and will be done using devices and procedures that conform to standard guidelines and SOPs.
- Refer to the protocol-specific MOP for details on the leukapheresis procedure.

6.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific MOP or GCP requirements, or any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

The non-compliance may be either on the part of the subject, the participating site PI or the study staff. Following a deviation(s), corrective actions should be developed by the participating site and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of the site PI and study staff to use continuous vigilance to identify and report protocol deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations must be sent to the IRB per their guidelines. The participating site PI and study staff are responsible for knowing and adhering to the IRB requirements. A completed copy of the DMID

Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

7.1 Clinical Evaluations

Complete medical history will be obtained by interviewing the subjects at the first study visit. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, clotting or other abnormality of the coagulation system, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited. At follow-up visits after the first study visit, an interim medical history will be obtained by interview of the subjects noting any changes since the previous clinic visit, phone call, or other form of contact. The interim medical history should include an assessment for new medical conditions and symptoms suggestive of an autoimmune disorder.

Concomitant medications will be collected as described in Section 7.1.1.

At the screening visit (Visit 00), a physical examination will be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. On Day 1 (Visit 01) prior to the first study vaccination and at follow-up visits after the first study vaccination, a targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator, if indicated based on subject's interim medical history.

Vital signs (oral temperature, pulse, and BP) will be collected at each study visit. Vital signs assessed on Day 1 prior to the first study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.

Height and weight will be collected on the screening visit to determine BMI.

Pre-administration reactogenicity assessments will be performed prior to each study vaccination to establish baseline, then the study vaccination will be given.

Subjects will be observed in the clinic for at least 45 minutes after each study vaccination. The study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs/AESIs will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.

All subjects will complete a Memory Aid from Day 1 through Day 8 after each study vaccination. Memory Aids will be reviewed with subjects for AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs, AESIs, and concomitant medications occurring after each study vaccination. Memory Aid reviews will take place during telephone calls, e-mails, text contacts, or clinic visits on Days 2 and 4 after each study vaccination as well as during clinic visits on Day 8 after each study vaccination.

Reactogenicity assessments will include an assessment of solicited AEs occurring from the time of each study vaccination on Day 1 through Day 8 after each study vaccination, which includes an assessment of injection site reactions including erythema (redness), induration (hardness)/edema (swelling), pain, and tenderness as well as systemic reactions including fever, chills (feverishness), fatigue (tiredness), malaise (general unwell feeling), myalgia (body aches/muscular pain exclusive of the injection site), arthralgia (joint pain exclusive of the injection site), headache, nausea, and diarrhea.

7.1.1 Assessment of Concomitant Medications/Treatments other than Study Product

Administration of any medications, therapies or vaccines will be recorded on the appropriate DCF. Concomitant medications will include all current medications and medications taken in the 30 days prior to signing the ICF for the duration of the study. Medications reported in the electronic case report form (eCRF) are limited to those taken within 30 days prior to the first study vaccination and for 12 months after the last study vaccination. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements. In addition, receipt of any non-study vaccines will be solicited for the entire duration of the study and reported in the eCRF. Use of a new medication should prompt evaluation for the occurrence of any medication associated adverse effects, including a new diagnosis of chronic medical disease or condition.

Medications that might interfere with the evaluation of the investigational product(s) should not be used during the trial-reporting period (until approximately 12 months after the last study vaccination) unless clinically indicated as part of the subject's health care. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (see Section 5.1.3). In addition, the site PI or appropriate sub-investigator may identify other medications that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity.

7.1.2 Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

Subjects will be directly observed at the time of dosing by a member of the clinical research team who is licensed to administer the study product. Administration will be documented on the appropriate data collection form and entered into the eCRF.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

Urine or serum pregnancy tests will be performed by the site laboratory at the screening visit (Visit 00) and within 24 hours prior to each study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to enrollment on Day 1 (Visit 01) and administration of each study vaccination to be eligible for participation in the study and receipt of each dose of study product, respectively.

Subjects will be screened for HIV, hepatitis B surface antigen, antibody to hepatitis C virus, and SARS-CoV-2. Results will be discussed with the subject. If a positive result occurs, the subject will be referred for appropriate follow-up and results will be reported as required by state law. These screening tests must be negative for the subject to be eligible to participate.

In order to be eligible for participation in the study and receipt of the study product, the subject's clinical screening laboratory evaluations prior to each study vaccination must be confirmed to meet the eligibility criteria as outlined in the Subject Inclusion Criteria (see Section 5.1.1).

WBC, HgB, and PLT; ALT, AST, ALP, T Bili, CK, and Cr; PT/PTT; serum or urine pregnancy test; HIV, Hepatitis B surface antigen, and Hepatitis C virus antibody tests; SARS-CoV-2 serology; and a nasal swab for SARS-CoV-2 PCR will be performed by the local laboratory. Venous blood samples (approximately 17 mL) will be collected from each subject at the Screening Visit (Visit 00).

Clinical safety laboratory parameters evaluated after receipt of study product will include WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK and Cr. For participants enrolled under version 10.0 of the protocol with clinical suspicion of myocarditis or pericarditis, an aliquot of serum collected pre-vaccination and a new sample collected at an unscheduled visit will be assessed for troponin-I or troponin T. These evaluations will be performed by the local laboratory and will be done approximately 7 days after each study vaccination.

7.2.2 Research Assays

Serum samples collected for Immunogenicity assays prior to and post administration of prime and boost vaccines per the Schedule of Activities (Table 6, Table 7, Table 8, and Table 9) will be assessed for SARS-CoV-2 antibody binding. Neutralizing antibody titers will be assessed against live virus in an assay which uses recombinant SARS-CoV-2 expressing the fluorescent reporter gene mNeonGreen (Live-FRNT-mNG assay) and against SARS-CoV-2 pseudoviruses. PBMCs will be isolated from acid citrate dextrose (ACD) blood according to IDCRC PBMC processing standard operating procedure (SOP) at processing laboratories identified for each clinical site. Antigen-specific $CD8^+$ and $CD4^+$ T cell responses will be assessed via ICS and flow cytometry.

In addition, multiple timepoints will be assessed via *ex vivo* IFN-gamma ELISpot using smaller minimal epitope and overlapping 15mer peptide pools covering Spike and TCE regions to assess breadth and kinetics, and ELISpot supernatants will be assessed for Th1/Th2 cytokine balance of T cell response by measuring IL-2, TNF-alpha, IL-4, IL-10, and IL-13.

Exploratory assays may be performed to measure memory B cell responses in a subset of subjects by ICS and flow cytometry. Neutralizing antibody responses to the ChAd68 vector in subjects who receive the ChAd-S or ChAd-S-TCE vaccines may be performed.

The volume of venous blood to be collected for immunogenicity evaluations is presented in Table 10, Table 11, Table 12, and Table 13.

7.2.3 Samples for Genetic/Genomic Analysis

7.2.3.1 Genetic/Genomic Analysis

Stored PBMCs, including leukocyte samples obtained by leukapheresis, may be used in secondary research for sequencing of DNA from B cells to characterize B cell receptors and monoclonal antibodies. The DNA data may be used to synthesize antigen-specific antibodies to characterize antibody binding. Secondary research samples may also be used for other genomic analysis, including, but not limited to, single nucleotide polymorphisms (SNP) arrays, human leukocyte antigen (HLA) typing, transcriptomic analysis, evaluation of the immune response to the vaccine, and/or evaluation of any AE from the vaccine.

7.2.3.2 Genetic Privacy and Confidentiality

Any genetic data generated will be kept private. Informed consent permitting data sharing will be part of the consent process. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified. No data that may identify specific subjects will be kept with the genetic data.

7.2.3.3 Management of Results

All genetic testing in this protocol will be performed for research only and is not performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. Therefore, results will not be shared with the subjects.

7.2.3.4 Laboratory Specimen Preparation, Handling, and Storage

Instructions for specimen preparation, handling, and storage are included in protocol-specific MOP.

7.2.3.5 Laboratory Specimen Shipping

Instructions for specimen shipment are included in the protocol-specific MOP.

Specimen shipment will occur at intervals during the course of this study following all applicable International Air Transport Association (IATA) requirements and according to the specifics for storage temperature and documentation as detailed in the protocol-specific MOP.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

Safety will be assessed by the frequency and severity of:

- SAEs occurring from the time of the first study vaccination throughout the entire study.
- Solicited AEs – reactogenicity events occurring from the time of the first study vaccination through 7 days after each study vaccination.
    - Reactogenicity local reactions including erythema, induration/edema, pain, and tenderness.
    - Reactogenicity systemic reactions including fever, chills, fatigue, malaise, myalgia, arthralgia, headache, nausea, and diarrhea.
- Clinical safety laboratory AEs occurring from the time of the first study vaccination through approximately 7 days after the last study vaccination. Parameters to be evaluated include WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK and Cr. For participants enrolled under version 10.0 of the protocol, with clinical suspicion of myocarditis or pericarditis, troponin-I or troponin-T will be evaluated.
- Unsolicited AEs –non-serious AEs occurring from the time of the first study vaccination through approximately 28 days after each study vaccination.
- AESIs, including serologically or virologically confirmed SARS-CoV-2 infection and severity of COVID-19, myocarditis/pericarditis, GBS, and TTS/VITT, PIMMCs, MAAEs, and NOCMCs occurring from the time of the first study vaccination throughout the entire study.

8.1.1 Adverse Events (AEs)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). In a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. The FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study

visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor. AEs, including solicited injection site and systemic (subjective and quantitative) reactions, not meeting the protocol-defined criteria for SAEs will be recorded on the appropriate DCF and entered into the eCRF. Information to be collected for unsolicited non-serious AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product or alternate etiology (if not related to study product) (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site PI or sub-investigator), date of resolution, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship to study product. AEs will be followed through resolution.

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 should be recorded as an AE.

If an event meets both the criteria of a study endpoint and an AE, the event will be reported either as a study endpoint or as an AE (not both).

8.1.1.1 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 post each study vaccination.

Solicited AEs (i.e., reactogenicity) will be collected using a Memory Aid and recorded on the appropriate DCF from the time of each study vaccination through 7 days post each study vaccination.

For this study, solicited AEs will be:

- Injection site Pain
- Injection site Tenderness
- Injection site Erythema
- Injection site Edema/Induration
- Headache
- Fatigue
- Malaise

- Myalgia
- Arthralgia
- Nausea
- Fever
- Chills
- Diarrhea

8.1.1.2 Unsolicited Adverse Events

Unsolicited non-serious AEs will be captured for 28 days following each study vaccination.

In addition, AESIs, including PIMMCs, MAAEs, and NOCMCs, will be captured throughout the entire study following the first study vaccination.

8.1.1.3 Possible Adverse Events Associated with Leukapheresis

For those subjects consented for leukapheresis, the possible AEs associated with the leukapheresis procedure are:

- Site of needle placement: pain, bruising, and discomfort in the arms.
- Vasovagal episodes, characterized by transient hypotension, dizziness, nausea, and rarely syncope.
- Temporary decrease (1-2 days) in red blood cell count.
- Blood loss secondary to machine malfunction.
- Toxicity-associated anticoagulant resulting in a sour taste in the mouth, mild muscle cramps, and/or tingling sensation around the mouth, feet, or hands.

The risks of the leukapheresis procedure are minimal and are generally confined to the period of the actual study visit itself. For this procedure, AEs that are non-serious will not be routinely recorded in the study database. Only SAEs that occur during or within 24 hours after the leukapheresis study visit will be recorded in the study database.

8.1.2 Definition of Serious Adverse Event (SAE)

An SAE is defined in 21 CFR 312.32 as follows: An AE or suspected adverse reaction is considered serious if, in the view of either the participating site PI or appropriate sub-investigator or the sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening AE,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered an SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the appropriate SAE DCF.

All SAEs will be followed through resolution or stabilization by a study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator.

All SAEs will be reviewed and evaluated by DMID and will be sent to the DSMB (for periodic review, unless related) and IRB/IEC.

8.1.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the IBs, Package Insert, and/or Summary of Product Characteristics.

8.1.4 Classification of an Adverse Event

The determination of seriousness, severity and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs and

classify AEs based upon medical judgment. This includes, but is not limited to, physicians, physician assistants and nurse practitioners.

8.1.4.1 Severity of Adverse Events

All AEs or SAEs will be assessed for severity, according to the toxicity grading scales in the FDA guidance document entitled "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.

Moderate (Grade 2): Events that are usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate DCF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

All SAEs will be reviewed and evaluated by DMID and will be sent to the DSMB (for periodic review unless related) and IRB/IEC.

8.1.4.2 Relationship to Study Product

For each reported adverse reaction, the participating site PI or qualified designee must assess the relationship of the event to the study product using the following guidelines:

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event, there is no temporal relationship between the study product and event onset, or an alternate etiology has been established.

8.1.5 Adverse Events of Special Interest (AESIs)

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. For this study, protocol specified AESIs are serologically or virologically confirmed SARS-CoV-2 infection, severe COVID-19 to evaluate for potential episodes of vaccine-induced immune disease enhancement, myocarditis/pericarditis, GBS, and TTS/VITT. Protocol-specified AESIs also include Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms (PTs) and text strings as proposed by the Centers for Disease Control and Prevention (CDC) for surveillance of TTS events (87). In addition, specified AESIs include any PTs included in the Standard MedDRA® Query (SMQ) "embolic and thrombotic events", including the PTs listed under the following SMQs, active as of 15JUL2021 in MedDRA® dictionary 24.0: Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; and Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. These AESIs also include PTs incorporated into Section 4.6 of the CDC Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (95), and the Brighton Collaboration AESIs relevant to vaccination that are listed below:

- NOCMCs – defined as any new ICD diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that is applied to the subject during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.
- MAAEs – defined as hospitalization, an emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason.
- PIMMCs – These constitute a group of AEs that includes diseases which are clearly autoimmune in etiology and other inflammatory and/or neurologic disorders which may or may not have autoimmune etiology. PIMMCs that are of special interest for this study are Brighton Collaboration AESIs relevant to vaccination that include: seizures, GBS, acute disseminated encephalomyelitis, vasculitides, anaphylaxis, vaccine-associated

enhanced respiratory disease, myocarditis/pericarditis, thrombocytopenia, and thrombotic events.

Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 6 weeks after vaccination will have an unscheduled visit for assessment. After investigator review and physical exam, if there is concern for myocarditis/pericarditis, an ECG will be performed, a troponin laboratory test will be done, and referral will be made to a cardiologist for evaluation and management.

Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Medical records and test results from cardiology evaluation will be requested.

The definitions below [https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm] are intended to serve as a guide to help in the reporting of suspected cases of myocarditis and/or pericarditis; however, the diagnosis of suspected cases is left to the investigator's clinical judgement.

Probable Case of Acute Myocarditis

Presence of ≥ 1 new or worsening of the following clinical symptoms:

• Chest pain/pressure/discomfort

• Dyspnea/shortness of breath/pain with breathing

• Palpitations

• Syncope

AND

Presence of ≥ 1 new finding of the following:

• Troponin level above upper limit of normal (any type of troponin)

• Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis which includes at least one of the following:

▪ ST segment or T-wave abnormalities

▪ Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias

▪ AV nodal conduction delays or intraventricular conduction defects

• Abnormal cardiac function or wall motion abnormalities on echocardiogram

• Cardiac magnetic resonance imaging (cMRI) finding consistent with myocarditis52

AND

• No other identifiable cause of the symptoms and findings

Confirmed Case of Acute Myocarditis

Meets the case definition for a probable case

AND

• Histopathologic confirmation of myocarditis (using Dallas criteria) (96)

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

AND

• No other identifiable cause of the symptoms and findings

Acute Pericarditis Case Definition

Presence of ≥ 2 new or worsening of the following clinical features54:

• 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)

• Pericardial rub on examination

• New ST-elevation or PR-depression on EKG

• 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.

All AESIs are assessed, recorded, and followed as described above under AEs.

8.1.6 Dose Escalation Criteria

As this is a first-in-human study, a sentinel approach will be used for enrollment into dose escalation groups in Stage 1 and 2, consisting of the first three subjects in each group who will be observed for 72 hours (Stage 1, and Stage 2, Groups 5, 6, 8-10, 12, 13-15) or 7-day observation times (Groups 7 and 11) after the first study vaccination before enrolling the remaining subjects to the same group. Determinations of when to move from sentinels to the rest of the group will be made by the protocol team as described in Section 8.6.1.

Prior to moving to the next dose group, the aggregate AE data through Day 8 post first study vaccination for at least 7 subjects/group, including the Day 8 post first study vaccination safety labs, reactogenicity, and any SAEs/AESIs including PIMMCs/MAAEs/NOCMCs, will be reviewed by the SSC.

The SSC will be responsible for overseeing the dose escalation of the trial by reviewing and interpreting the data. This will be achieved through conference calls once a potential dose escalation halt is warranted. The SSC will have the authority to halt or continue the dose escalation and to seek recommendations from the DSMB.

The SSC will be comprised of five members:

- DMID Medical Monitor
- DMID Medical Officer
- Protocol Chair
- One PI to be selected by the Protocol Chair
- Gritstone Medical Monitor/Representative

Dose escalation decisions will be guided by the following criteria:

- If three or more subjects in a study group experience a Grade 3 related AE (unsolicited and/or clinical laboratory abnormality) within the same system organ class (SOC), then the SSC will review the safety data to confirm whether a potential safety signal has occurred suggesting that subject safety is compromised within a study group.
- If three or more subjects in a study group experience a Grade 3 solicited AE within the same category (see Section 8.1.1.1), then the SSC will review the safety data to confirm

whether a potential safety signal has occurred suggesting that subject safety is compromised within a study group.

- The SSC will decide whether to resume the dose escalation or request formal DSMB review.

Dose escalation dependencies:

- Enrollment into Group 6 is dependent on observation of all subjects in Group 5 through Day 8 post first study vaccination.
- Enrollment into Group 10 is dependent on observation of at least 8 subjects in Group 9 through Day 8 post first study vaccination, enrollment into Group 11 is dependent on observation of at least 10 subjects in Group 10 through Day 8 post first study vaccination.
- Enrollment into Group 7 is dependent on observation of at least 10 subjects in Group 11 through Day 29 post first study vaccination.
- Enrollment of Group 8 is dependent on observation of at least 10 subjects enrolled into the dose escalation Groups 5, 6 and 7 which will be used to determine the tolerable dose of SAM-S-TCE for double boosting of subjects previously given at least 1 EUA Johnson & Johnson/Janssen Ad26 COVID-19 vaccination and 1 approved mRNA booster vaccination.
- Enrollment into Group 12 is dependent on observation of at least 8 subjects enrolled into the dose escalation Groups 9, 10 and 11 which will be used to determine the tolerable dose of SAM-S-TCE for double boosting in subjects previously given at least 1 EUA Johnson & Johnson/Janssen Ad26 COVID-19 vaccination and 1 approved mRNA booster vaccination.
- Enrollment into Group 14 is dependent on observation of at least 7 subjects in Group 13 through Day 8 post first study vaccination, and enrollment into Group 15 is dependent on observation of at least 7 subjects in Group 14 through Day 8 post first study vaccination.

Groups 1, 3A and 3B were enrolled prior to protocol version 4.0. There is no dose escalation for Groups 8 and 12.

8.2 Reporting Procedures

Solicited injection site and systemic reactogenicity events will be documented and reported from the time of the first study vaccination through 7 days after each study vaccination.

Clinical safety laboratory AEs will be documented and reported before each study vaccination and 7 days after each study vaccination.

Unsolicited non-serious AEs will be documented and reported from the time of the first study vaccination through 28 days after each study vaccination.

SAEs/AESIs including PIMMCs/MAAEs/NOCMCs will be documented and reported from the time of the first study vaccination throughout the entire study.

8.2.1 Reporting Serious Adverse Events and AESIs

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AESIs of myocarditis or pericarditis, even if these do not qualify as SAEs, and any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group

Clinical Research Operations and Management Support (CROMS)

6500 Rock Spring Dr. Suite 650

Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)

SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the data coordinating center (DCC) system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site principal investigator or appropriate sub-investigator licensed to make medical diagnoses and listed on the Form FDA 1572 becomes aware of an SAE that is suspected to be related to study product, the site principal investigator or appropriate sub-investigator licensed to make medical diagnoses and listed on the Form FDA 1572 will report the event to the DMID Pharmacovigilance Group.

All AESIs (serious or non-serious) will be reported on a SAE form. AESIs that do not meet SAE criteria, other than myocarditis and pericarditis, will be reported as an AE to the DMID Pharmacovigilance Group; however, the narrative will indicate that the AESI did not meet SAE criteria.

8.2.2 Regulatory Reporting for Studies Conducted Under DMID Sponsored IND

Following notification from the participating site PI or appropriate sub-investigator, DMID, as the IND sponsor, will report any SUSAR in an IND safety report and will notify all participating PIs [i.e., all PIs to whom the sponsor is providing study product under its IND(s)] of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the Sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

8.2.3 Reporting of Pregnancy

Pregnancies occurring in study subjects will be reported via Advantage electronic data capture system (Advantage *eClinical*) on the Pregnancy Report form. No further study product will be administered to pregnant subjects, but with the subject's permission a venous blood sample for serological assays will be collected per protocol, however large volume blood samples for cellular immunological assays will be discontinued, and the subject will continue to be followed for safety for the duration of this study. Efforts will be made to follow all pregnancies reported during the course of this study to pregnancy outcome with the subject's permission.

8.3 Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be collected, assessed, and followed from initial recognition of the AE through 28 days after the last study vaccination.

SAEs will be collected, assessed, and followed through resolution even if duration of follow-up goes beyond the protocol-defined the follow-up period.

Resolution of AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Specifically for VITT/TTS, we will follow guidelines for diagnosis (e.g., https://brightoncollaboration.us/wp-content/uploads/2021/05/TTS-Interim-Case-Definition-v10.16.3-May-23-2021.pdf (97) and any future updates) and management of suspected events, including hematology consult, and a list of laboratory tests including but not limited to CBC with manual count as indicated, PF4 antibody ELISA, PT/INR, aPTT, fibrinogen, and D-dimer.

Follow-up procedures, evaluations, and outcomes will be recorded on appropriate DCF and entered into the eCRF.

8.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The site PI or appropriate sub-investigator is responsible for recording all AE/SAEs that are observed or reported during this trial, regardless of relationship to study product. AE/SAEs, abnormal laboratory test values or abnormal clinical findings will be collected, assessed, documented, reported, and followed appropriately, using a local laboratory as necessary. In determining eligibility, refer to Section 5.1 and the protocol-specific MOP.

8.5 Halting Rules

In the event a halting rule is met:

- An unscheduled safety analysis of the DSMB will be required for approval of further enrollment, and
- Further administration of study vaccines, including a second dose, is suspended for ALL subjects in the same study group until an assessment by the DSMB takes place.

8.5.1 Halting Rules for Sentinel Subjects

If any of the following events occur to the sentinel subjects, the study will be paused:

- Any subject experiences ulceration, abscess, or necrosis at the injection site.
- Any subject experiences laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study vaccine.
- Any subject experiences generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of study vaccine.
- Any subject experiences a SAE (except for accident or trauma) after administration of study vaccine that is considered related to study vaccine.
- Any 2 subjects in the same study group experience the same Grade 3 Solicited Local AE or Systemic AE (excluding measured grades of erythema and edema/induration alone) that lasted at least 24 hours within 7 days after administration of study vaccine.
- Any 2 subjects experience the same Grade 3 AE (unsolicited and/or clinical laboratory abnormality) in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities coding, that lasted at least 24 hours after administration of the same study vaccine and is considered related to the study vaccine. Clinical laboratory abnormalities are not subject to the time window.

8.5.2 Study Group Halting Rules

1. Any subject experiences a SAE after administration of study vaccine that is considered related to study vaccine.
2. Any subject experiences laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study vaccine that is considered related to study vaccine.
3. Any subject experiences ulceration, abscess, or necrosis at the injection site that is considered related to study vaccine administration.
4. Two (2) or more subjects experience an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of study vaccine that is considered related to study vaccine.
5. Three (3) or more subjects experience a Grade 3 AE (unsolicited and/or clinical laboratory abnormality) in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities coding, that lasted at least 24 hours after administration of study

vaccine and is considered related to study vaccine. Clinical laboratory abnormalities are not subject to the same time window.

6. One (1) or more subjects with myocarditis and/or pericarditis meeting the CDC case definition, considered related to study vaccine.

Study product administration and enrollment may resume only after review of the AEs that caused the pause results in recommendation to permit further study product administration and enrollments.

8.6 Safety Oversight

8.6.1 Protocol Team Oversight

The protocol team will meet to review AE data and to ensure no halting rules have been met.

For Groups 1, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14, 15:

- After 3 sentinel subjects in each group (irrespective of subgroup) have been observed for at least 72 hours.
- After all subjects in each study group have been enrolled and observed through Day 8 post first study vaccination.

For Groups 7 and 11:

- After 3 sentinel subjects in each group (irrespective of subgroup) have been enrolled and observed for at least 7 days.
- After all subjects in Groups 11A and 11B have been observed through Day 28 (before considering dose escalation to 10 µg SAM-S-TCE in the younger Groups 7A and 7B).

8.6.2 Data and Safety Monitoring Board (DSMB)

The DSMB is an independent group of at least 3 experts that monitors subject safety and advises DMID. DSMB members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. DSMBs must consist of at least three voting members, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise. A quorum will consist of a simple majority.

The DSMB will hold an organizational meeting prior to enrollment. At this meeting, the DSMB will review the charter, protocol, ICF, IB, and safety report templates.

The DSMB will review cumulative AE data as stated in Section 10.4.1.

Ad hoc reviews will occur when trial halting rules are met, or as requested by the sponsor or PI.

Ad hoc reviews will also occur when VITT/TTS or myocarditis/pericarditis AESIs are reported.

The DSMB will have a final review meeting at the end of the study.

Procedures for DSMB reviews/meetings will be defined in the DSMB charter. The DSMB will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the DSMB charter.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study product administration, and whether to continue, modify, or terminate this trial.

Per the DSMB's request in their recommendations following the ad hoc meeting on 01 February 2022 to discuss Groups 5 and 6 (3µg and 6µg SAM-S-TCE respectively, 18-60 yo) safety and immunogenicity data, the following electronic safety summary reports will be provided to the DSMB:

- Sentinel data from Group 11 (10µg SAM-S-TCE, >60 yo) through Day 8 post vaccination.
- Sentinel data from Group 7 (10µg SAM-S-TCE, 18-60 yo) through Day 8 post vaccination.

9 HUMAN SUBJECTS PROTECTION

9.1 Institutional Review Board/Independent Ethics Committee

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; April 18, 1979), and the federal policy for the Protection of Human Subjects codified in 45 CFR Part 46, 21 CFR Part 50 (Protection of Human Subjects), and the ICH E6(R2).

An OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment materials, and handouts or surveys intended for the subjects, prior to the recruitment, screening and enrollment of subjects. The IRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), and other federal, state, and local regulations and policies, as applicable.

Each institution engaged in this research will hold an OHRP-approved FWA.

Any amendments to the protocol or informed consent documents will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the study. The participating site PI will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy.

DMID must receive the documentation that verifies IRB approval for this protocol, informed consent documents and associated documents, prior to the recruitment, screening and enrollment of subjects, and any IRB approvals for continuing review or amendments as required by DMID.

A single IRB of record, Vanderbilt University IRB, will be accountable for compliance with regulatory requirements for this multi-centered study, at participating sites. Written agreements between the single IRB and participating sites will be required. The agreements will set forth the specific responsibilities of the IRB and each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the DMID or regulatory authorities upon request.

9.2 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Subjects will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

At the first study visit, informed consent will be obtained and documented before any study procedures are performed. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study interventions/products, risks and discomforts, the expected duration of the subject's participation in the trial, any expected benefits to the subject, and alternative treatments and procedures that may be available to the subject. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the participating site PI) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. Subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed, even if identifiers are removed, that information collected from this research and/or specimens may be used for secondary research, including the sharing of de-identified data.

Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the subject is authorizing such access.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject for their records.

New information, including interim aggregate antibody results, will be communicated by the participating site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated if new risks or additional procedures are indicated, and subjects will be re-consented per IRB requirements, if necessary.

Once signed, a copy of the informed consent form will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.2.1 Other Informed Consent Procedures

Subjects' willingness to receive ChAd (GRT-C907, GRT-C909) vaccines will be assessed and documented on the ICF for participants >60 years old.

The rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times. The consent process, including relevant language in the ICF, will provide an explanation of the potential risks to the individual study subjects and their families. Clinical metadata, genomic, or other datasets or a subset of the clinical and other metadata that may potentially identify human subjects will not be released in unrestricted databases. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified.

Subjects will be asked for consent to collect additional blood as well as saliva specimens, the use of residual specimens, and the sharing of genetic information and samples for secondary research. This extra/residual blood and corresponding serum, plasma, PBMCs, and saliva will be used as back-up specimens for PP defined assays or designated for secondary research use and stored indefinitely at a designated storage facility.

Subjects will be asked to consent specifically to HLA typing. HLA typing data will be kept private. HLA typing data may be used to produce commercial antibody-based therapeutics. Subjects will not share in profits or commercial rights to those products.

To support development of diagnostics, therapeutics and vaccines, a subset of subjects enrolled will also be asked to consent for leukapheresis to collect additional samples for secondary research, which will be stored indefinitely at a designated storage facility.

If subjects choose not to provide permission for extra blood and secondary research use, they will not be eligible for enrollment into the study. However, consent for leukapheresis is not required for study participation.

Collection of extra/residual samples during the course of the study will help facilitate rapid follow-on analyses, if warranted, to provide more comprehensive scientific insights into the impact (safety and immunological) of the vaccine on the host response to vaccination. To maintain statistical power in follow-on analyses it is important that extra blood collection and secondary research use be included in as many subjects as possible, due to the limited sample size per treatment arm, with the exception of leukapheresis.

The stored samples will be labeled with barcodes to maintain confidentiality. Research with identifiable samples and data may occur as needed, however, subject confidentiality will be maintained as described for this protocol and with IRB approval.

Samples designated for secondary research use may be used for additional immunological assessments that may include but are not limited to evaluation of immune responses associated with concomitant SARS-CoV-2 infection in individuals that become seropositive while on study, assessment of mucosal antibody responses in saliva, further characterization of vaccine-induced serum antibodies, and the ability of vaccine-induced antibodies and T cells to cross-react to endemic and other coronaviruses, PBMC signatures linked with T cell responses and cytokine profiles, and transcriptomic and biomarker signatures that may be associated with study vaccine reactogenicity or immunogenicity. These samples might be used in new or different immunological laboratory tests, to conduct additional immunologic, microbiologic and ‘omics’ analyses to facilitate further development of new SARS-CoV-2 vaccines, diagnostics or therapeutics. Secondary research using HLA typing may also be warranted to understand genetic factors involved in vaccination failures.

Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, subjects will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the subject for extra specimens collected or from secondary research. No results from secondary research will be entered into the subject’s medical record. Incidental findings will not be shared with the subject, including medically actionable incidental findings, unless required by law.

Risks are associated with the volume of blood collected, such as anemia. Risks for loss of privacy and confidentiality are described below.

Subjects may withdraw permission to use samples for secondary use at any time. They will need to contact the participating site and the samples will be removed from the study repository after this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples. Subjects who withdraw consent before the last visit will not have the extra blood drawn for secondary use.

9.2.2 Human Genetic Testing

The research staff will seek the subjects' consent for extra and residual specimens to be stored and used for secondary research, including genetic research, evaluating human genomic and phenotypic markers. The rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times.

The consent process will include an explanation of the potential risks to the individual subjects and their families associated with data submitted to an NIH data repository and subsequent sharing. Data that may potentially identify human subjects will not be released in unrestricted databases. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified. The consent will include whether individual subject data will be shared through a NIH controlled access data repository. Data for genomic or phenotypic research will be submitted to a controlled access data repository, therefore, informed consent permitting the data sharing must be documented, even if the specimens are de-identified.

9.3 Consent for Secondary Research of Stored Specimens and Data

9.3.1 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ‘‘primary’’ or ‘‘initial’’ activity, such as the data and samples collected in this protocol. This section will detail the samples and data available for secondary research, which will include blood collected in PAXgene tubes for RNA extractions and transcriptomics, and serum samples for serum cytokines or other biomarkers, on Days 1, 2 and 8 in relation to each study vaccination. Depending on the results from our main trial, these samples may be very important for understanding the mechanisms responsible for study vaccine reactogenicity. Any use of the sample or data, however, will be presented in a separate protocol and require separate IRB approval.

9.3.1.1 Samples for Secondary Research

The following types of samples will be stored and used for secondary research:

- Residual Research Sample: Any leftover Primary Research Sample after the laboratory testing specified in this protocol is completed will be stored for future studies with the subject's consent.
- Repository Research Sample: Samples will be collected with the subject's consent in this protocol with the intent to store for additional research (i.e., samples collected beyond those needed for primary research) and will be used in future studies. Amendments to this protocol with additional assays may use repository research samples.

Samples will be stored indefinitely at a designated storage facility. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may occur, however, subject confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

Residual/Repository Research Samples, upon written request and approval from DMID and any approvals required by the site or network, may be shared for secondary research with investigators at the participating site, with researchers at other IDCRC sites or other institutions, or company-designated research laboratories. The recipients of specimens will be informed that these specimens have a NIH Certificate of Confidentiality. The samples will not be sold or used directly for production of any commercial product. DMID will authorize shipment from the DMID CMS.

Reports from secondary research will not be kept in the subjects' health records or shared with subjects, unless required by law. Reports will not be sent to the specimen repository.

The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. To participate in this study, subjects must consent for storage of samples for secondary use. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

9.3.1.2 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All of the individual subject data collected during this study will be made available after de-identification. The statistical analysis plan (SAP) and Analytic Code will also be made available. Data will be available immediately following publication, with no end date. Upon written request, with provision of a methodologically sound proposal, and approval from DMID and any approvals required by the

site or network, data may be shared for secondary research with investigators/researchers. The data will be available for only the purpose outlined in the approved proposal.

For access to genomic data in the NIH designated controlled access database, an investigator (or data requestor) must submit a Data Access Request which certifies adherence to the NIH Security Best Practices for Controlled-Access data subject to the NIH Genomic Data Sharing (GDS) Policy.

The participating site PI may request removal of data on individual study subjects from NIH data repositories in the event that a research subject withdraws or changes his or her consent. However, some data that have been distributed for approved research use cannot be retrieved

9.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study will be inclusive of all healthy adults who meet the inclusion/exclusion criteria, regardless of religion, sex, or ethnic background. Children and pregnant women will be excluded from this trial to protect these more vulnerable subjects because this is a first-in-human trial.

9.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. The SARS-CoV-2 serology test results may be disclosed to subjects. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked, and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number. Subjects who agree to home visits have an increased potential for loss of confidentiality due to the presence of study staff. Records will be coded and transported using secure transport containers. Study staff will ensure the subject is interviewed in a private location.

9.6 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the FDA.

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

9.7 Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH to the subject, or by the participating site for any injury suffered due to participation in this trial.

10 STATISTICAL ANALYSES

10.1 Study Hypotheses

This is a phase 1, open-label, dose escalation, non-randomized study of homologous and heterologous prime-boost vaccination schedules, as well as boost(s) in subjects previously given EUA/licensed COVID-19 vaccines, and it is not designed to formally test a specific hypothesis. The study aim is to characterize and obtain preliminary estimates of the safety, reactogenicity, and immunogenicity of different doses of homologous prime-boost (SAM-S x 2 and SAM-S-TCE x 2), heterologous prime-boost (ChAd-S + SAM-S) regimens in COVID-19 infection and vaccination naïve individuals, as well as single and double boosting subjects previously given EUA/licensed COVID-19 vaccination(s), in healthy adults 18-60 years old and >60 years old. No hypothesis testing comparing the different vaccine schedule and dose groups will be performed.

10.2 Sample Size Considerations

The targeted sample size for each of the study groups was determined based on previous phase 1 studies. The study is targeted to enroll up to 135 subjects, with up to 12 subjects in each group.

Sample size calculations for safety

The goal of the safety evaluation for this study is to identify safety concerns associated with product administration. The ability of the study to detect serious adverse events (SAEs) (see Section 8.1.2) can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed in each of the groups.

Specifically, in each sentinel group of 3 subjects, there is a 48.8% chance of observing at least 1 event if the true rate of such event is 20% or higher; and there is at least a 72.9% chance of observing no events if the true event rate is 10% or less. For each group of 7 subjects, there is a 79% chance of observing at least 1 event if the true rate is 20% or higher, and there is at least 47.8% chance of observing no events if the true event is 10% or less. For each group of 10 subjects, there is an 89.3% chance of observing at least 1 event if the true rate is 20% or higher, and there is at least 34.9% chance of observing no events if the true event is 10% or less. For each group of 12 subjects, there is a 93.1% chance of observing at least 1 event if the true rate is 20% or higher, and there is at least 28.2% chance of observing no events if the true event is 10% or less.

Binomial probabilities of observing 0, 1 or more, and 2 or more events among groups of size 3, 7, 10 or 12 are presented in Table 4 for a range of possible true adverse event rates. These calculations provide a more complete picture of the sensitivity of the study design to identify potential safety problems with the vaccine.

Table 4: Probability of observing 0 events, 1 or more events, and 2 or more events, among groups of size 3, 10, for different true event rates

True Event Rate (%)	Group Size (N)	Pr(0 Events)	Pr(1+ Events)	Pr(2+ Events)
1	3	97	3	<0.1
	7	93.2	6.8	0.2
	10	90.4	9.6	0.4
	12	88.6	11.4	0.6
4	3	88.5	11.5	0.5
	7	75.1	24.9	2.9
	10	66.5	33.5	5.8
	12	61.3	38.7	8.1
10	3	72.9	27.1	2.8
	7	47.8	52.2	15
	10	34.9	65.1	26.4
	12	28.2	71.8	34.1
20	3	51.2	48.8	10.4
	7	21.0	79.0	42.3
	10	10.7	89.3	62.4
	12	6.9	93.1	72.5

Sample size calculations for SARS-CoV-2-specific antibody binding and neutralization titer in serum

A Secondary Objective of this study is to evaluate the magnitude of SARS-CoV-2-specific antibody binding and neutralization titers in serum samples. This objective is descriptive in nature and will be accomplished by estimating the geometric mean titer (GMT) at each timepoint when samples are collected.

The precision with which a true GMT can be estimated from observed data depends on the standard deviation (SD) of the measurements, in the logarithmic scale, and the sample size. Table 5 displays two-sided 95% confidence intervals for the GMT for several values of the observed antibody titer.

Table 5: Two-sided 95% confidence intervals based on observing a particular average $\log_e$-antibody titer in subjects' groups, taking 0% or 20% attrition into consideration (n = 12, 10, 8, 7)

Observed average $\log_e$ antibody titer	SD of $\log_e$ antibody titer	95% confidence interval			
		n=12	n = 10	n = 8	n=7
$\log_e(5)$	0.5	(3.6, 6.9)	(3.5, 7.2)	(3.3, 7.6)	(3.1,7.9)
$\log_e(20)$		(14.6, 27.5)	(14, 28.6)	(13.2, 30.4)	(12.6,31.8)
$\log_e(50)$		(36.4, 68.7)	(35, 71.5)	(32.9, 75.9)	(31.5,79.4)
$\log_e(100)$		(72.8, 137.4)	(69.9, 143)	(65.8, 151.9)	(63,158.8)
$\log_e(250)$		(182, 343.5)	(174.8, 357.5)	(164.6, 379.7)	(157.4,397)
$\log_e(500)$		(363.9, 687)	(349.6, 715)	(329.2, 759.5)	(314.9,794)
$\log_e(1000)$		(727.8, 1373.9)	(699.3, 1430)	(658.4, 1518.9)	(629.8,1587.9)
$\log_e(5)$	1.0	(2.6, 9.4)	(2.4, 10.2)	(2.2, 11.5)	(2,12.6)
$\log_e(20)$		(10.6, 37.8)	(9.8, 40.9)	(8.7, 46.1)	(7.9,50.4)
$\log_e(50)$		(26.5, 94.4)	(24.5, 102.2)	(21.7, 115.4)	(19.8,126.1)
$\log_e(100)$		(53, 188.8)	(48.9, 204.5)	(43.3, 230.7)	(39.7,252.1)
$\log_e(250)$		(132.4, 471.9)	(122.3, 511.2)	(108.4, 576.8)	(99.1,630.4)
$\log_e(500)$		(264.9, 943.9)	(244.5, 1022.5)	(216.7, 1153.6)	(198.3,1260.7)
$\log_e(1000)$		(529.7, 1887.7)	(489, 2044.9)	(433.4, 2307.2)	(396.6,2521.5)

10.3 Treatment Assignment Procedures

10.3.1 Group Assignment Procedures

Prior to version 3.0 of the protocol, subjects 18-60 years old were randomized in a 1:1 ratio to Groups 1 and 3A. After protocol version 3.0, no random assignment to groups is planned or will be conducted. As of the writing of protocol version 5.0, Groups 1, 3A, 3B and 4 will not enroll any additional subjects, and no further enrollments are planned for Stage 1. After protocol version 9.0 was implemented, it was decided Groups 7A, 7B, 8A and 8B in Stage 2 will not be opened to enroll subjects.

Subjects enrolled into Stage 2 may elect not to receive ChAd-S-TCE, in which case the subject will only be considered for enrollment into SAM-S-TCE single or double boosted vaccination groups. Subjects that consent to receiving a ChAd vaccine may enroll into groups that do not provide ChAd vaccine, but enrollment into groups providing a ChAd vaccine will be prioritized.

As of the writing of protocol version 5.0, subjects will be enrolled into the different groups according to 1) age (see Table 1), 2) whether the subject consented to ChAd vaccine, and 3) dose escalation dependencies (as specified in Section 8.1.6). In protocol version 8.0 Stage 2 Groups 7-8 and 10-12 will enroll 8-12 subjects that are vaccinated, with either no prior infection history or evidence of infection at least 4 months previously into A & B subgroups, respectively. Groups 13-15 will allow sample sizes of 7-10 subjects total with no prespecified ratio for infected vs noninfected.

See Figure 1. Stage 1 does not need to be completed prior to enrollment of subjects in Stage 2.

If replacements are needed, each replacement subject will receive the same treatment as the originally enrolled subject.

Treatment allocation schedules will be generated by a statistician at Emmes, the statistical and data coordinating center (SDCC) for this study. Subjects will be registered using a web-based application developed by Emmes.

After informed consent has been obtained and study eligibility has been established at the Screening Visit, subjects will return to the clinical site for their Enrollment Visit, when the first dose of study product will be administered (see Section 6.2). Group assignment will occur following confirmation of their eligibility and their willingness to participate.

Per ICH guideline E6: GCP, screening records will be kept at the participating site to document the reason why an individual was screened but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the SDCC Advantage *eClinical* (electronic data capture system).

Enrollment of subjects will be done online using the registration module of Advantage *eClinical*. The assignment code will be prepared by statisticians at the SDCC and included in the registration module for this trial. Advantage *eClinical* will assign each subject to a treatment arm after the demographic and eligibility data have been entered into the system.

Instructions for use of the registration module are included in the Advantage *eClinical* User's Guide.

10.3.2 Masking Procedures

Subjects and site staff will be unblinded as to subjects' group assignments in Stage 1 and Stage 2.

10.4 Planned Interim and Early Analyses

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community. Early analyses will include safety and immunogenicity as described in Sections 10.4.1 and 10.4.2. Further, the protocol team will review data periodically to confirm that no halting rules have been met as described in Section 8.6.1.

Cumulative safety information, study status, and endpoint results may be published, presented at a public forum, or presented as summaries aggregated by study arm at the discretion of the sponsor while the primary study is ongoing. Any ad hoc analyses, jointly developed by the protocol team, SDCC and/or Gritstone bio, Inc. (formerly known as Gritstone Oncology, Inc.), will be executed by the SDCC as needed. None of the interim analyses will include any formal statistical hypothesis testing; therefore, p value adjustment will not be made to any analyses.

10.4.1 Interim Safety Review

Given the need for rapid review and dissemination of study data for public health reasons, AEs and SAEs may be reviewed as necessary outside of DSMB reviews. The DSMB will not need to meet unless halting rules are met, or as requested by the sponsor or PI, and materials will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

Safety reviews for sentinel halting rules by the protocol team and for dose escalation criteria by the SSC are described in Sections 8.5.1 and 8.1.6. Additional safety reviews may be conducted as necessary.

Safety Reviews by the DSMB

Given the frequency and urgency to review data, the DSMB will not need to meet to assess sentinel halting rules or dose escalation criteria unless halting rules are met or as requested by the SSC.

If any of the halting rules listed in Sections 8.5.1 and 8.5.2 are met, cumulative safety data from all enrolled subjects will be summarized for DSMB review.

If no halting rules are met, or in addition to unscheduled DSMB reviews, the DSMB will review cumulative AE data as follows:

- After all subjects in Groups 1, 3A, 3B, and 4 have completed Day 8 post first study vaccination visit.

- After all subjects in Groups 1, 3A, 3B and 4 have completed Day 8 post second study vaccination visit.
- After all subjects in Groups 5-7, 9, 10, 11, and 13-15 have completed Day 8 post study vaccination visit.
- After all subjects in Groups 8 and 12 have completed Day 8 post first study vaccination visit.

The DSMB reviews listed above do not have to occur in a sequential manner and may be combined if milestones are reached on dates that are close together.

In addition, the DSMB will meet to review available safety data after all subjects in all groups enrolled in Stages 1 and 2 have completed the visit that occurs 28 days after their last study vaccination.

Ad hoc safety reports may also be prepared for DSMB review as deemed necessary and appropriate by DMID.

Materials for all DSMB reviews will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

10.4.2 Interim Immunogenicity Review

Interim data review of immunogenicity may be performed to inform public health decisions.

Statistical analyses of secondary immunogenicity endpoints, by vaccine schedule group, may be performed when subjects have completed key immunogenicity visits. Immunogenicity reviews may be shared with the DSMB, as determined by DMID. Immunogenicity reports may be combined with safety reports if projected milestones for reports will occur close enough to each other where, in the opinion of the protocol team, producing one report, as opposed to two separate reports, is more informative regarding the safety of subjects and more beneficial to the overall needs of the protocol team.

Data may be disseminated to public health officials and partners as needed. In addition, subjects will be informed regarding interim aggregate antibody results after the 4-week timepoint after the last study vaccination.

10.5 Final Analysis Plan

This section describes the final study analyses. All safety data from enrolled subjects will be analyzed according to vaccination group for those subjects who received at least one dose of

study vaccine. Group 3A and Group 3B safety and immunogenicity data collected prior to the second study vaccination may be combined for analysis. In the rare instance that a participant receives the wrong treatment at a specific study product administration time, the Statistical Analysis Plan (SAP) will address how to analyze the participant's safety data. The Safety Analysis Population will include all subjects who received at least one dose of study product.

The Clinical Study Report (CSR) will be completed when all primary and secondary safety, clinical, and immunological endpoint data are available. Any available data from the exploratory endpoints may also be included. Additional exploratory endpoint data may be included in an addendum to the CSR, publication of manuscript(s), or other report. The primary analysis of immunogenicity (secondary) endpoints will use the modified intent-to-treat (mITT) analysis population, defined as individuals who received at least one dose of vaccine and contributed both pre- and at least one post-vaccination venous blood sample for immunogenicity testing for which valid results were reported. In the final analysis, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis. The per protocol (PP) population will then be defined – and this includes all subjects in the mITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits subsequent to the protocol deviations that are considered to affect the science.
- Data from any visit that occurs substantially out of window.

Analyses for primary endpoints will be performed using SAS v9.4.

No formal multiple comparison adjustments will be employed for multiple primary or secondary endpoints. However, multiplicity adjustments will be made for certain primary or secondary endpoint assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (e.g., testing multiple pseudo-viruses to determine a positive antiviral functional activity response). Unless otherwise noted, 95% confidence intervals will be calculated. Any statistical tests will be 2-sided and will be considered statistically significant if the p-value is below 0.05.

An SAP will be developed by the SDCC and finalized prior to data lock. Unless specified otherwise in the SAP, missing data will not be imputed.

General Approach

Unless otherwise noted in the SAP, continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of

observed levels will be reported for all categorical measures. Unless otherwise specified in the SAP, geometric means of relevant continuous endpoints will be computed as Williams means.

Analysis of the Primary Endpoint(s)

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

Solicited reactogenicity signs and symptoms (local and systemic) will be summarized by severity for each day post study vaccination (Days 1-8) and as the maximum severity over all 7 days. Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals (CI), to summarize the proportion of subjects reporting each symptom, any application site symptom, and any systemic symptom.

Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after each study vaccination. Unsolicited AEs will be coded by MedDRA® for Preferred Term and SOC. All SAEs will be collected from the time of first vaccination through the end of the study. SAEs will be described by detailed listings showing the event description, MedDRA® Preferred Term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA® Preferred Term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA® categories will be computed.

Clinical laboratory data will be summarized as change from baseline and by severity for each visit, and as the maximum over all post study vaccination visits.

Analysis of the Secondary Endpoint(s)

Antibody titers (binding and neutralizing antibody) will be described by group and timepoint using geometric mean titer (GMT) and geometric fold-rise (GMFR), including 95% confidence intervals based on the t-distribution. Undetectable titers will be imputed as one-half of the lower limit of quantitation and the number and proportion of subjects with undetectable titers at each timepoint will be reported. Plots such as reverse cumulative distributions or longitudinal presentations of GMTs will be presented.

Analysis of ICS endpoints will present the percent of cells expressing various cytokines or combinations of cytokines, including 95% confidence intervals, tabularly and graphically by group, peptide pool/stimulant, and timepoint. ELISpot results will be summarized by cytokine,

group, peptide pool/stimulant, and timepoint using summary statistics and 95% confidence intervals.

Baseline Descriptive Statistics

Summaries of demographic variables such as age, sex, ethnicity, and race will be presented by cohort and overall. Summaries of baseline clinical laboratory values will be presented by cohort and overall.

Tabulation of Individual Subject Data

In general, all data will be listed, sorted by cohort and subject, and when appropriate by visit number within subject.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

11.1 Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, Memory Aids, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, each participating site(s) and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and current documentations are maintained on site.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data collection forms will be derived from the eCRF and will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

13.2 Data Coordinating Center/Biostatistician Responsibilities

All data collection forms, and laboratory reports must be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. Adverse events must be recorded on the appropriate data collection form, assessed for severity and relationship, and reviewed by the site principal investigator or appropriate sub-investigator.

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study.

The data coordinating center for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

13.3 Data Capture Methods

Clinical (including, but not limited to, AEs/SAEs/AESIs including PIMMCs/MAAEs/NOCMCs, concomitant medications, medical history, physical assessments, and clinical laboratory values) and reactogenicity will be collected on data collection forms by study personnel then entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the study data coordinating center. The data system includes password protection and internal quality checks,

such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

13.4 Types of Data

Data for this trial will include clinical, safety, and outcome measures (e.g., clinical laboratory values, reactogenicity, and immunogenicity data).

13.5 Study Records Retention

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, laboratory test results, and study drug disposition records will be retained for 2 years after a marketing application is approved for the study product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the study product, until 2 years after the investigation is discontinued and the FDA has been notified. These documents will be retained for a longer period, however, if required by local regulations. ICFs for future use will be maintained as long as the sample/specimen exists.

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the site principal investigator when these documents no longer need to be retained. The participating IDCRC sites must contact DMID for authorization prior to the destruction of any study records.

14 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial complies with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study staff and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with all participating site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

15 PUBLICATION POLICY

15.1.1 Publication and Data Sharing Policy

Analyses will be conducted as data become available while the study is ongoing at the discretion of the sponsor. Analyses of data will be available for publication to inform the scientific community. Data will be available immediately following publication, with no end date, with data sharing at the discretion of the PI. Publication of manuscripts may occur at the discretion of the sponsor in accordance with DMID's Expanded Distribution of Clinical Research Endpoint Data Policy.

15.1.2 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

15.1.3 Genomic Data Sharing (GDS) Plan

This study will comply with the NIH GDS Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), SNP arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

15.1.4 Publication

At intervals throughout the study at the discretion of the sponsor and following completion of the study, the lead PI is expected to publish the results of this research in a scientific journal. This study will adhere to the following publication and data sharing policies and regulations:

- NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. As such, the final peer-reviewed journal manuscripts will be accessible to the public on PubMed Central no later than 12 months after publication.

15.1.5 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed

and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all protocol team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

15.1.6 Human and Genomic Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication

This study will comply with the NIH GDS Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), SNP arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

16 LITERATURE REFERENCES

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17 APPENDICES

Appendix A. SCHEDULE OF ACTIVITIES – STAGE 1, GROUPS 1 AND 3A

Table 6: Stage 1 (Groups 1 and 3A) Schedule

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V08A**	**V09**	**V10**	**V11**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D29 ±3d**	**D30+1d**	**D32+2d**	**D36+2d**	**D43 +4wk**	**D57±3d**	**D209±14d**	**D394±14d**		
Study Day post 2nd Study Vaccination						**D1**	**D2+1d**	**D4+2d**	**D8+2d**	**D15 +4wk**	**D29±3d**	**D181±14d**	**D366±14d**		
Obtain Written Informed Consent	X									X					
Review Eligibility Criteria	X	X				X				X					
Medical History	X														
Review Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (Oral Temp, Pulse, BP)	X	X			X	X			X	X	X	X	X	X	X
Physical Examination including Height and Weight	X														
Targeted PE, if indicated		X			X	X			X	X	X	X	X	X	X
Serum or Urine Pregnancy Test	X	X				X				X					
Nasal Swab Collection for SARS-CoV-2 PCR	X					X									
Blood Collection for Safety Labs	X[1]				X[2]	X[2]			X[2]	X[3]				X[2,4]	X[2,5]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 serology, HIV	X					X[6]									
Blood Collection for ELISpot		X				X					X	X	X	X	X
Blood Collection for ICS Assays		X				X					X			X	X

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V08A**	**V09**	**V10**	**V11**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D29 ±3d**	**D30+1d**	**D32+2d**	**D36+2d**	**D43 +4wk**	**D57±3d**	**D209±14d**	**D394±14d**		
Study Day post 2nd Study Vaccination						**D1**	**D2+1d**	**D4+2d**	**D8+2d**	**D15 +4wk**	**D29±3d**	**D181±14d**	**D366±14d**		
Blood Collection for Antibody Assays		X				X					X	X	X	X	X
Blood Collection for PBMC and Plasma Storage		X			X	X			X		X	X	X	X	X
Enroll in Advantage *eClinical*		X													
Study Vaccination		X				X									
45 Minute Evaluation After Study Vaccination		X				X									
Distribute Memory Aid and Study Related Materials		X				X									
Review Memory Aid			X	X	X		X	X	X					X[5]	X[5]
Adverse Events		X	X	X	X	X	X	X	X		X			X[7]	X[7]
SAEs/AESIs including PIMMCs/MAAEs/NOCMCs		X	X	X	X	X	X	X	X	X[8]	X	X	X	X	X
Optional Leukapheresis[9]										X					
Saliva Collection for Antibodies		X			X				X						
Phone Call[10]			X	X			X	X							

[1] Includes WBC. HgB. PLT, ALT. AST, ALP, T Bili, CK, Cr and PT/PTT
[2] Includes WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr
[3] Safety lab per local Leukapheresis procedure
[4] If clinically indicated
[5] If within 7 days after study vaccination
[6] Includes SARS-CoV-2 serology (N-specific) only
[7] If prior to Study Visit 09
[8] SAEs only
[9] Extra screening visit may be needed prior to Leukapheresis procedure
[10] Can be phone, text, or email contact

Appendix B. SCHEDULE OF ACTIVITIES – STAGE 1, GROUPS 3B AND 4

Table 7: Stage 1 (Groups 3B and 4) Schedule

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V11A**	**V12**	**V13**	**V14**	**V15**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D29 ±3d**	**D57 ±3d**	**D85 +45d**	**D86 +1d**	**D88 +2d**	**D92 +2d**	**D99 +2d**	**D99 +4wk**	**D113 ±3d**	**D169 ±3d**	**D265 ±14d**	**D450 ±14d**		
Study Day post 2nd Study Vaccination								**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D15 +4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Obtain Written Informed Consent	X												X						
Review Eligibility Criteria	X	X						X					X						
Medical History	X																		
Review Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (Oral Temp, Pulse, BP)	X	X			X	X	X	X	X		X	X	X	X	X	X	X	X	X
Physical Examination including Height and Weight	X																		
Targeted PE, if indicated		X			X	X	X	X	X		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test	X	X						X					X						
Nasal Swab Collection for SARS-CoV-2 PCR	X							X											
Blood Collection for Safety Labs	X[1]				X[2]			X[2]			X[2]		X[3]					X[2,4]	X[2,5]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 serology, HIV	X							X[6]											

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V11A**	**V12**	**V13**	**V14**	**V15**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D29 ±3d**	**D57 ±3d**	**D85 +45d**	**D86 +1d**	**D88 +2d**	**D92 +2d**	**D99 +2d**	**D99 +4wk**	**D113 ±3d**	**D169 ±3d**	**D265 ±14d**	**D450 ±14d**		
Study Day post 2nd Study Vaccination								**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D15 +4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Blood Collection for ELISpot		X				X		X				X		X	X	X	X	X	X
Blood Collection for ICS Assays		X				X		X				X						X	X
Blood Collection for Antibody Assays		X				X	X	X				X		X	X	X	X	X	X
Blood Collection for PBMC and Plasma Storage		X			X	X	X	X				X		X	X	X	X	X	X
Blood Collection for Transcriptomal Signatures								X	X		X							X	X[5]
Blood Collection for Cytokines								X	X		X							X	X
Enroll in Advantage *eClinical*		X																	
Study Vaccination		X						X											
45 Minute Evaluation After Study Vaccination		X						X											
Distribute Memory Aid and Study Related Materials		X						X											
Review Memory Aid			X	X	X				X	X	X							X[5]	X[5]
Adverse Events		X	X	X	X	X	X	X	X	X	X	X		X				X[7]	X[7]
SAEs/AESIs including PIMMCs/MAAEs/ NOCMCs		X	X	X	X	X	X	X	X	X	X	X	X[8]	X	X	X	X	X	X
Optional Leukapheresis[9]													X						

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V11A**	**V12**	**V13**	**V14**	**V15**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D29 ±3d**	**D57 ±3d**	**D85 +45d**	**D86 +1d**	**D88 +2d**	**D92 +2d**	**D99 +2d**	**D99 +4wk**	**D113 ±3d**	**D169 ±3d**	**D265 ±14d**	**D450 ±14d**		
Study Day post 2nd Study Vaccination								**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D15 +4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Saliva Collection for Antibodies		X			X						X								
Phone Call[10]			X	X						X									

[1] Includes WBC, HgB. PLT, ALT, AST, ALP, T Bili, CK, Cr and PT/PTT
[2] Includes WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr
[3] Safety lab per local Leukapheresis procedure
[4] If clinically indicated
[5] If within 7 days after study vaccination
[6] Includes SARS-CoV-2 serology (N-specific) only
[7] If prior to Study Visit 12
[8] SAEs only
[9] Extra screening visit may be needed prior to Leukapheresis procedure
[10] Can be phone, text, or email contact

Appendix C. SCHEDULE OF ACTIVITIES – STAGE 2, GROUPS 5, 6, 7A, 7B, 9, 10A, 10B, 11A, 11B, AND 13-15

Table 8: Stage 2 (Groups 5-7A*, 7B*, 9, 10A, 10B, 11A, 11B, and 13-15) Schedule

Study Visit	V00	V01	V02	V03	V04	V05	V05A	V06	V07	V08	V09	Unsc	Early Term
Study Day post Study Vaccination	**Scr -30 to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8+2d**	**D15+2d**	**D15+4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Obtain Written Informed Consent	X						X						
Review Eligibility Criteria	X	X					X						
Medical History	X												
Review Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (Oral Temp, Pulse, BP)	X	X	X		X	X	X	X	X	X	X	X	X
Physical Examination including Height and Weight	X												
Targeted PE, if indicated		X	X		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test	X	X					X						
Nasal Swab Collection for SARS-CoV-2 PCR	X												
Blood Collection for Safety Labs	X[1]				X[2]		X[3]					X[2,4]	X[2,5]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 serology, HIV	X												
Blood Collection for ELISpot		X				X		X	X	X	X	X	X
Blood for ICS Assays		X				X						X	X
Blood Collection for Antibody Assays		X				X		X	X	X	X	X	X

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V05A**	**V06**	**V07**	**V08**	**V09**	**Unsc**	**Early Term**
Study Day post Study Vaccination	**Scr -30 to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8+2d**	**D15+2d**	**D15+4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Blood Collection for PBMC and Plasma Storage		X				X		X	X	X	X	X	X
Blood Collection for Transcriptomal Signatures		X	X		X							X	X[5]
Blood Collection for Cytokines		X	X		X							X	X
Enroll in Advantage *eClinical*		X											
Study Vaccination		X											
45 Minute Evaluation After Study Vaccination		X											
Distribute Memory Aid and Study Related Materials		X											
Review Memory Aid			X	X	X							X[5]	X[5]
Adverse Events		X	X	X	X	X		X				X[6]	X[6]
SAEs/AESIs including PIMMCs/MAAEs/NOCMCs		X	X	X	X	X	X[7]	X	X	X	X	X	X
Optional Leukapheresis[8]							X						
Saliva Collection for Antibodies		X			X								
Phone Call[9]				X									

[1] Includes WBC, HgB. PLT, ALT, AST, ALP, T Bili, CK, Cr and PT/PTT
[2] Includes WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr, [3] Safety lab per local Leukapheresis procedure
[4] If clinically indicated
[5] If within 7 days after study vaccination
[6] If prior to Study Visit 06
[7] SAEs only
[8] Extra screening visit may be needed prior to Leukapheresis procedure
[9] Can be phone, text, or email contact

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

Appendix D. SCHEDULE OF ACTIVITIES – STAGE 2, GROUPS 8A, 8B AND 12A, 12B

Table 9: Stage 2 (Groups 8A*, 8B*, 12A and 12B) Schedule

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V11A**	**V12**	**V13**	**V14**	**V15**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D29 ±3d**	**D57 ±3d**	**D58 +1d**	**D60 +2d**	**D64 +2d**	**D71 +2d**	**D71 +4wk**	**D85 ±3d**	**D141 ±3d**	**D237 ±14d**	**D422 ±14d**		
Study Day post 2nd Study Vaccination								**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D15 +4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Obtain Written Informed Consent	X												X						
Review Eligibility Criteria	X	X						X					X						
Medical History	X																		
Review Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (Oral Temp, Pulse, BP)	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X
Physical Examination including Height and Weight	X																		
Targeted PE, if indicated		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test	X	X						X					X						
Nasal Swab Collection for SARS-CoV-2 PCR	X							X											
Blood Collection for Safety Labs	X[1]				X[2]			X[2]			X[2]		X[3]					X[2,4]	X[2,5]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 serology, HIV	X							X[6]											

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V11A**	**V12**	**V13**	**V14**	**V15**	**Unsc**	**Early Term**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D29 ±3d**	**D57 ±3d**	**D58 +1d**	**D60 +2d**	**D64 +2d**	**D71 +2d**	**D71 +4wk**	**D85 ±3d**	**D141 ±3d**	**D237 ±14d**	**D422 ±14d**		
Study Day post 2nd Study Vaccination								**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D15 +4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Blood Collection for ELISpot		X				X	X	X				X		X	X	X	X	X	X
Blood Collection for ICS Assays		X				X		X				X						X	X
Blood Collection for Antibody Assays		X				X	X	X				X		X	X	X	X	X	X
Blood Collection for PBMC and Plasma Storage		X				X		X				X		X	X	X	X	X	X
Blood Collection for Transcriptomal Signatures		X	X		X			X	X		X							X	X[5]
Blood Collection for Cytokines		X	X		X			X	X		X							X	X
Enroll in Advantage *eClinical*		X																	
Study Vaccination		X						X											
45 Minute Evaluation After Study Vaccination		X						X											
Distribute Memory Aid and Study Related Materials		X						X											
Review Memory Aid			X	X	X				X	X	X							X[5]	X[5]
Adverse Events		X	X	X	X	X	X	X	X	X	X	X		X				X[7]	X[7]
SAEs/AESIs including PIMMCs/MAAEs/ NOCMCs		X	X	X	X	X	X	X	X	X	X	X	X[8]	X	X	X	X	X	X
Optional Leukapheresis[9]													X						

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V11A	V12	V13	V14	V15	Unsc	Early Term
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D29 ±3d**	**D57 ±3d**	**D58 +1d**	**D60 +2d**	**D64 +2d**	**D71 +2d**	**D71 +4wk**	**D85 ±3d**	**D141 ±3d**	**D237 ±14d**	**D422 ±14d**		
Study Day post 2nd Study Vaccination								**D1**	**D2 +1d**	**D4 +2d**	**D8 +2d**	**D15 +2d**	**D15 +4wk**	**D29 ±3d**	**D85 ±3d**	**D181 ±14d**	**D366 ±14d**		
Saliva Collection for Antibodies		X			X						X								
Phone Call[10]				X						X									

[1] Includes WBC, HgB. PLT, ALT, AST, ALP, T Bili, CK, Cr, and PT/PTT
[2] Includes WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, and Cr,[3] Safety lab per local Leukapheresis procedure
[4] If clinically indicated
[5] If within 7 days after study vaccination
[6] Includes SARS-CoV-2 serology (N-specific) only
[7] If prior to Study Visit 12
[8] SAEs only
[9] Extra screening visit may be needed prior to Leukapheresis procedure
[10] Can be phone, text, or email contact

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

Appendix E. VENIPUNCTURE VOLUMES – STAGE 1, GROUPS 1 AND 3A

Table 10: Stage 1 (Groups 1 and 3A) Blood Volumes (mL)

Study Visit	**V00**	**V01**	**V04**	**V05**	**V08**	**V09**	**V10**	**V11**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D8+2d**	**D29±3d**	**D36+2d**	**D57±3d**	**D209±14d**	**D394±14d**
Study Day post 2nd Study Vaccination				**D1**	**D8+2d**	**D29±3d**	**D181±14d**	**D366±14d**
Safety Labs including WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, Cr, PT/PTT, Serum Pregnancy[2]	16.7		14[1]	14[1]	14[1]			
HIV, HBsAg, Anti-HCV	12							
SARS-CoV-2 Serology (N-specific)	2			2				
PBMCs for Immunology (T and B cell Assays)		80		80		80	80	80
Serum for Immunology (Antibody Assays)		20		20		20	20	20
PBMC and Plasma Storage for Secondary Research		32	24	32	24	32	32	32
Per Visit Blood Volume Total (mL)	30.7	132	38	148	38	132	132	132
Cumulative Blood Volume (mL) (prior 56 days)	30.7	162.7	200.7	348.7	386.7	518.7	132	132
Running Blood Volume Total (mL)	30.7	162.7	200.7	348.7	386.7	518.7	650.7	782.7

Blood volume limit is 550 mL over an 8-week period. If the volunteer agrees to the optional leukapheresis visit, then up to 10-20 mL of additional safety bloods may be drawn before/during the procedure.

[1] PT/PTT and Serum Pregnancy will not be done at these visits.

[2] WOCBP only

Appendix F. VENIPUNCTURE VOLUMES – STAGE 1, GROUPS 3B AND 4

Table 11: Stage 1 (Groups 3B and 4) Blood Volumes (mL)

Study Visit	**V00**	**V01**	**V04**	**V05**	**V06**	**V07**	**V08**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D8+2d**	**D29±3d**	**D57±3d**	**D85+45d**	**D86+1d**	**D92+2d**	**D99+2d**	**D113±3d**	**D169±3d**	**D265±14d**	**D450±14d**
Study Day post 2nd Study Vaccination						**D1**	**D2+1d**	**D8+2d**	**D15+2d**	**D29±3d**	**D85±3d**	**D181±14d**	**D366±14d**
Safety Labs including WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, Cr, PT/PTT, Serum Pregnancy[2]	16.7		14[1]			14[1]		14[1]					
HIV, HBsAg, Anti-HCV	12												
SARS-CoV-2 Serology (N-specific)	2					2							
PBMCs for Immunology (T and B cell Assays)		80		80	80	80			80	80	80	80	80
Serum for Immunology (Antibody Assays)		20		20	20	20			20	20	20	20	20
PBMC and Plasma Storage for Secondary Research		32	24	32	32	32			32	32	32	32	32
Transcriptomal Signatures						2.5	2.5	2.5					
Cytokines						4	4	4					
Per Visit Blood Volume Total (mL)	30.7	132	38	132	132	154.5	6.5	20.5	132	132	132	132	132
Cumulative Blood Volume (mL) (prior 56 days)	30.7	162.7	200.7	332.7	464.7	418.5	425	313.5	445.5	445.5	264	132	132
Running Blood Volume Total (mL)	30.7	162.7	200.7	332.7	464.7	619.2	625.7	646.2	778.2	910.2	1042.2	1174.2	1306.2

Blood volume limit is 550 mL over an 8-week period. If the volunteer agrees to the optional leukapheresis visit, then up to 10-20 mL of additional safety bloods may be drawn before/during the procedure.

[1] PT/PTT and Serum Pregnancy will not be done at these visits.

[2] WOCBP only

Appendix G. VENIPUNCTURE VOLUMES – STAGE 2, GROUPS 5-7, 9-11, AND 13-15

Table 12: Stage 2 (Groups 5-7A*, 7B*, 9, 10A, 10B, 11A, 11B, and 13-15) Blood Volumes (mL)

Study Visit	V00	V01	V02	V04	V05	V06	V07	V08	V09
Study Day post Study Vaccination	Scr -30d to -1d	D1	D2+1d	D8+2d	D15+2d	D29±3d	D85±3d	D181±14d	D366±14d
Safety Labs including WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, Cr, PT/PTT, Serum Pregnancy[2]	16.7			14[1]					
HIV, HBsAg, Anti-HCV	12								
SARS-CoV-2 Serology (N-specific)	2								
PBMCs for Immunology (T and B cell Assays)		80			80	80	80	80	80
Serum for Immunology (Antibody Assays)		20			20	20	20	20	20
PBMC and Plasma Storage for Secondary Research		32			32	32	32	32	32
Transcriptomal Signatures		2.5	2.5	2.5					
Cytokines		4	4	4					
Per Visit Blood Volume Total (mL)	30.7	138.5	6.5	20.5	132	132	132	132	132
Cumulative Blood Volume (mL) (prior 56 days)	30.7	169.2	175.7	196.2	328.2	460.2	264	132	132
Running Blood Volume Total (mL)	30.7	169.2	175.7	196.2	328.2	460.2	592.2	724.2	856.2

Blood volume limit is 550 mL over an 8-week period. If the volunteer agrees to the optional leukapheresis visit, then up to 10-20 mL of additional safety bloods may be drawn before/during the procedure.

[1] PT/PTT and Serum Pregnancy will not be done at these visits.

[2] WOCBP only

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.

Appendix H. VENIPUNCTURE VOLUMES – STAGE 2, GROUPS 8 AND 12

Table 13: Stage 2 (Groups 8A*, 8B*, 12A and 12B) Blood Volumes (mL)

Study Visit	V00	V01	V02	V04	V05	V06	V07	V08	V10	V11	V12	V13	V14	V15
Study Day post 1st Study Vaccination	**Scr -30d to -1d**	**D1**	**D2+1**	**D8+2d**	**D15+2d**	**D29±3d**	**D57±3d**	**D58+1d**	**D64+2d**	**D71+2d**	**D85±3d**	**D141±3d**	**D237±14d**	**D422±14d**
Study Day post 2nd Study Vaccination							**D1**	**D2+1d**	**D8+2d**	**D15+2d**	**D29±3d**	**D85±3d**	**D181±14d**	**D366±14d**
Safety Labs including WBC, HgB, PLT, ALT, AST, ALP, T Bili, CK, Cr, PT/PTT, Serum Pregnancy[2]	16.7			14[1]			14[1]		14[1]					
HIV, HBsAg, Anti-HCV	12													
SARS-CoV-2 Serology (N-specific)	2						2							
PBMCs for Immunology (T and B cell Assays)		72			72	72	72			72	72	72	72	72
Serum for Immunology (Antibody Assays)		20			20	20	20			20	20	20	20	20
PBMC and Plasma Storage for Secondary Research		32			24		24			32	32	32	32	32
Transcriptomal Signatures		2.5	2.5	2.5			2.5	2.5	2.5					
Cytokines		4	4	4			4	4	4					
Per Visit Blood Volume Total (mL)	30.7	130.5	6.5	20.5	116	92	138.5	6.5	20.5	124	124	124	124	124
Cumulative Blood Volume (mL) (prior 56 days)	30.7	161.2	167.7	188.2	304.2	396.2	534.7	541.2	394	497.5	505.5	124	124	124
Running Blood Volume Total (mL)	30.7	161.2	167.7	188.2	304.2	396.2	534.7	541.2	561.7	685.7	809.7	933.7	1057.7	1181.7

Blood volume limit is 550 mL over an 8-week period. If the volunteer agrees to the optional leukapheresis visit, then up to 10-20 mL of additional safety bloods may be drawn before/during the procedure.

[1] PT/PTT and Serum Pregnancy will not be done at these visits.

[2] WOCBP only

* After protocol version 9.0 was implemented, it was decided not to enroll subjects into Groups 7 and 8 because of competing priorities and predicted difficulties enrolling into these two groups.