Protocol Version 5.0

Official Title: A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of a Self-Amplifying mRNA Prophylactic Vaccine Boost Against SARS-CoV-2 in Previously Vaccinated Healthy Adults 18 Years and Older

NCT ID: NCT05148962

Document Date: 09 Feb 2023

CLINICAL TRIAL PROTOCOL

Protocol Title:	**A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of a Self-Amplifying mRNA Prophylactic Vaccine Boost Against SARS-CoV-2 in Previously Vaccinated Healthy Adults 18 Years and Older**
Protocol Number:	GO-009
Sponsor:	Gritstone bio, Inc. 5959 Horton Street, Suite 300 Emeryville, CA 94608 U.S.A.
Clinical Study Director:	[redacted]
Study Drug Name(s):	GRT-R910
EudraCT Number:	2020-004138-39
Development Phase:	Phase 1
Approval Date:	09 February 2023
Version:	5.0

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

CONFIDENTIALITY NOTE:

The information contained in this document is confidential and proprietary to Gritstone bio, Inc. Any distribution, copying, or disclosure is strictly prohibited unless such disclosure is required by federal regulations or state law. Persons to whom the information is disclosed must know that it is confidential and that it may not be further disclosed by them.

1 SPONSOR SIGNATURE PAGE

Protocol Title	**A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of a Self-Amplifying mRNA Prophylactic Vaccine Boost Against SARS-CoV-2 in Previously Vaccinated Healthy Adults 18 Years and Older**
Date	**09 February 2023**

This clinical study was reviewed and approved by the Sponsor. This protocol contains all the information necessary to conduct the study consistent with the principles governing clinical research according to the Declaration of Helsinki, International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

[redacted]

02/09/2023

[redacted]

Date

[redacted]

Gritstone bio, Inc.

2 INVESTIGATOR SIGNATURE PAGE

Protocol Title **A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of a Self-Amplifying mRNA Prophylactic Vaccine Boost Against SARS-CoV-2 in Previously Vaccinated Healthy Adults 18 Years and Older**

I have carefully read this protocol and appendices and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study in accordance with the protocol and according to the Declaration of Helsinki, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements. All study site personnel involved in the study will be under my direction and informed about the contents of this study protocol and will receive all necessary instructions for conducting the study in accordance with the study protocol.

_____ _____

Investigator's Signature Date

_____

Name (printed)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE-2	Angiotensin-Converting Enzyme 2
ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
ChAd	Chimpanzee Adenovirus
CI	Confidence Interval
CK	Creatine Kinase
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
DCC	Data Coordinating Center
DCF	Data Collection Form
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
E	Envelope (Protein)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISpot	Enzyme-Linked Immunospot
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
GCP	Good Clinical Practice
GMFR	Geometric Fold-Rise
GMT	Geometric Mean Titer
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
[redacted]	[redacted]
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational New Drug Application
INR	International Normalized Ratio
IV	Intravenous
LNP	Lipid Nanoparticle
M	Membrane (Protein)
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MHRA	Medicines and Healthcare Products Regulatory Agency
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
N	Nucleocapsid (Protein) or Number of Subjects
NHP	Non-Human Primate
NOCMCs	New Onset Chronic Medical Conditions
PBMCs	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PI	Principal Investigator
PIMMCs	Potentially Immune-Mediated Medical Conditions
PLT	Platelets
PT	Prothrombin Time
QA	Quality Assurance
QC	Quality Control
RBD	Receptor-Binding Domain
RNA	Ribonucleic Acid
S	Spike
SAE	Serious Adverse Event
SAM	Self-Amplifying mRNA
SAP	Statistical Analysis Plan

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SGP	Subgenomic Promoter
SIV	Simian Immunodeficiency Virus
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCE	T-cell Epitope(s)
Th1	T Helper Cell Type 1
Th2	T Helper Cell Type 2
UK	United Kingdom
US	United States
UTR	Untranslated Regions
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VEEV	Venezuelan Equine Encephalitis Virus
Vp	Viral Particle(s)
WBC	White Blood Cell

3 PROTOCOL SUMMARY

3.1 Synopsis

Protocol Title	A Phase 1 Trial to Evaluate the Safety, Immunogenicity, and Reactogenicity of a Self-Amplifying mRNA Boost Prophylactic Vaccine Against SARS-CoV-2 in Previously Vaccinated Healthy Adults 18 Years and Older
Trial Centers	Multi-center trial in the United Kingdom
Clinical Phase	Phase 1
Study Design	Open-label, multiple cohort, dose-escalation vaccine study
Study Population	Healthy adults 18 years and older
Sample Size	This study will enroll 50 volunteers as follows: • Cohort 1 (N=10, including 2 sentinels): 10 mcg GRT-R910 (after AstraZeneca) 2 doses, homologous prime-boost, booster dose will be 113 days (16 weeks) after the prime for adults ≥60 years of age. • Cohort 2 (N=10, including 2 sentinels): 30 mcg GRT-R910 (after AstraZeneca) 2 doses, homologous prime-boost, booster dose will be 113 days (16 weeks) after the prime for adults ≥60 years of age. • Cohort 3 (N=10): 10 mcg GRT-R910 (dose selected from Cohorts 1 and 2) after adenovirus-based vector vaccine, homologous prime-boost, booster dose will be 28 days after the prime for adults ≥60 years of age. • Cohort 4 (N=10): 10 mcg GRT-R910 (dose selected from Cohorts 1 and 2) after messenger ribonucleic acid (mRNA) vaccine, homologous prime-boost, booster dose will be 28 days after the prime for adults ≥60 years of age. • Cohort 6 (N=10): 10 mcg GRT-R910 (dose selected from Cohorts 1 and 2) after mRNA vaccine, homologous prime-boost, booster dose will be 28 days after the prime for adults ≥18 to ≤59 years of age. Sentinel dosing in Cohorts 1 and 2 will consist of 2 volunteers in each cohort dosed 72 hours ahead of the remainder of each cohort, with the remainder of the volunteers dosed at the same dose level only if no halting rules are met. Enrollment in Cohort 2 will only proceed if safety data from all volunteers in Cohort 1 meet the dose-escalation rules. Injection will be given intramuscularly as a prime-boost at least 2 months after the last administration of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine either approved for emergency supply or approved for use by the Medicines and Healthcare Products Regulatory Agency (MHRA) for prevention of SARS-CoV-2. Subjects should refrain from a subsequent boost with an emergency supply or approved SARS-CoV-2 vaccine for a minimum of 4 months after the second dose of study vaccine.
Follow-up Duration	For Cohorts 1 and 2 (NOT receiving booster dose): 12 months For Cohorts 1 and 2 (receiving booster dose): 16 months For Cohorts 3 and 4: up to 13 months For Cohort 6: 7 months
Primary Objectives	• To assess the safety and tolerability of 2 different doses (10 or 30 mcg) of GRT-R910 when administered to healthy adults (≥60 years of age) who were previously vaccinated with a first-generation Coronavirus Disease 2019 (COVID-19) vaccine (Cohorts 1 and 2; AstraZeneca) • To assess the safety and tolerability of a 10 mcg dose of GRT-R910 when administered to healthy adults (≥18 years of age) who were previously vaccinated with an mRNA-based COVID-19 vaccine (Pfizer/BioNTech, Moderna)

Primary Outcome Measures	• Occurrence of solicited local reactogenicity signs and symptoms for 7 days after GRT-R910 vaccination • Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days after GRT-R910 vaccination • Occurrence of unsolicited adverse events (AEs) for 28 days after last study-administered GRT-R910 vaccination • Change from baseline for clinical safety laboratory parameters 7 days after last study-administered GRT-R910 vaccination • Occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs), including potentially immune-mediated medical conditions (PIMMCs), medically attended adverse events (MAAEs), and new onset chronic medical conditions (NOCMCs), throughout the entire study after GRT-R910 vaccination
Secondary Objective	• To assess the cellular and humoral immunogenicity of GRT-R910 when administered to volunteers (≥60 years of age for Cohorts 1, 2, 3, and 4 and ≥18 to ≤59 years of age for Cohort 6) who were previously vaccinated with either an adenoviral COVID-19 vaccine (AstraZeneca, Janssen) or an mRNA-based COVID-19 vaccine (Pfizer/BioNTech, Moderna)
Secondary Outcome Measures	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization in serum samples • Response rate, magnitude, and breadth of SARS-CoV-2 specific T-cells as assessed by interferon (IFN)-γ enzyme-linked immunospot (ELISpot) in 10 subjects per cohort
[redacted]	[redacted]

Rationale

This Phase 1 clinical trial will explore, in vaccinated subjects 18 years and older, the ability of a self-amplifying mRNA (SAM; GRT-R910) vaccine to boost and expand, beyond Spike, the immunogenicity of AstraZeneca's AZD1222 (Covishield®, Vaxzevria®; referred to as AstraZeneca vaccine), JNJ-78436735 (the Janssen COVID-19 Vaccine; referred to as the Janssen vaccine), Moderna (Spikevax®; referred to as the Moderna vaccine), and Pfizer/BioNTech (Comirnaty®; referred to as the Pfizer vaccine) COVID-19 antigenic vaccines. GRT-R910 uses a novel codon optimized Spike cassette with additional T-cell epitopes (cassette S-TCE) to safely drive strong, broad, and durable B- and T-cell immune responses to SARS-CoV-2.

Overall Design

This is a multi-center, open-label, dose-escalation design study to examine dose, safety, tolerability, and immunogenicity of GRT-R910, an investigational SAM SARS-CoV-2 vaccine when administered to healthy adults 18 years and older who were previously vaccinated with a first-generation COVID-19 vaccine (Cohorts 1 and 2; AstraZeneca), an adenoviral COVID-19

vaccine (Cohort 3; AstraZeneca, Janssen), or an mRNA-based COVID-19 vaccine (Cohorts 4 and 6; Pfizer/BioNTech, Moderna).

In Cohorts 1 and 2, healthy adults ≥60 years of age (N=10, including 2 sentinels per cohort) will receive 2 doses of GRT-R910 (homologous prime-boost) at 1 of 2 dose levels (10 mcg or 30 mcg) at least 2 months after receiving AstraZeneca's COVID-19 prime and boost vaccine. The GRT-R910 booster dose will be administered 113 days (16 weeks) after the prime. In Cohorts 3 and 4, healthy adults ≥60 years of age (N=10) will receive 2 doses of GRT-R910 (homologous prime-boost) 10 mcg (dose selected from Cohorts 1 and 2) at least 2 months after receiving an adenoviral COVID-19 vaccine (Cohort 3; AstraZeneca, Janssen), or an mRNA-based COVID-19 vaccine (Cohort 4; Pfizer/BioNTech, Moderna). In Cohort 6, healthy adults ≥18 to ≤59 years of age (N=10) will receive 2 doses of GRT-R910 (homologous prime-boost) 10 mcg (dose selected from Cohorts 1 and 2) at least 2 months after receiving an mRNA-based COVID-19 vaccine (Pfizer/BioNTech, Moderna). The GRT-R910 booster dose will be administered 28 days after the prime.

Sentinel dosing in Cohorts 1 and 2 will consist of 2 volunteers in each cohort dosed 72 hours ahead of the remainder of each cohort, with the remainder of the volunteers dosed at the same dose level only if no halting rules are met. Enrollment in Cohort 2 will only proceed if safety data from all volunteers in Cohort 1 meet the dose-escalation rules. There will be no sentinel dosing in Cohorts 3, 4, and 6. The dose for Cohorts 3, 4, and 6 was selected from Cohorts 1 and 2 after evaluation of reactogenicity, safety, and initial immunogenicity. Dose selection will be determined by the Gritstone clinical team in consultation with the Principal Investigator(s).

The reactogenicity and immunogenicity data assessed after the first dose of GRT-R910 will inform selection of the GRT-R910 dose to be tested in future studies. The 10 mcg dose of GRT-R910 was selected for use in Cohorts 3, 4, and 6 by evaluating the balance of immunogenicity and reactogenicity of a single dose of GRT-R910 in Cohorts 1 and 2.

3.2 Schedules of Assessments

Table 1 Schedule of Assessments: Cohorts 1 and 2 – Subjects NOT Receiving Booster Dose

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	Unsch Visit	Early Term Visit
Study Day(s)	SCR -30 to -1	Day 1	Day 2 +1d	Day 4 +2d	Day 8 +2d	Day 29 ±3d	Day 57 ±3d	Day 180 ±3d	Day 365 ±7d		
Obtain Written Informed Consent	X										
Review Eligibility Criteria	X	X									
Medical History	X										
Review of Interim Medical History		X	X	X	X	X	X	X	X	X	X
Concomitant Medications	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
Physical Examination Including Height and Weight	X										
Targeted Physical Examination, if Indicated		X			X	X	X	X	X	X	X
Nasal Swab Collection for SARS-CoV-2 PCR	X									X[7]	
Blood Collection for Safety Labs	X[1]				X[2]		X[2]	X[2]		X[2]	X[2]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 Serology[3], HIV	X						X[3]				
Blood Collection for Cellular Immune Assays		X			X	X		X	X	X	X
Blood Collection for Antibody Assays		X				X	X	X	X	X	X
Vaccination		X									
45 Minute Evaluation After Study Vaccination		X									
Distribute Memory Aid and Study-Related Materials		X									
Review Memory Aid			X	X	X					X[4]	X[4]

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**Unsch Visit**	**Early Term Visit**
Study Day(s)	**SCR -30 to -1**	**Day 1**	**Day 2 +1d**	**Day 4 +2d**	**Day 8 +2d**	**Day 29 ±3d**	**Day 57 ±3d**	**Day 180 ±3d**	**Day 365 ±7d**		
Adverse Events		X	X	X	X	X				X[5]	X[5]
SAEs/AESIs Including PIMMCs/MAAEs/NOCMCs[8]		X[9]	X	X	X	X	X	X	X	X	X
Phone Visit[6]			X	X							
Saliva Collection for Antibodies		X			X			X			

Abbreviations: AESI, adverse event of special interest; BP, blood pressure; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MAAE, Medically Attended Adverse Event; NOCMC, New Onset Chronic Medical Condition; SAE, serious adverse event; PCR, polymerase chain reaction; PIMMC, Potentially Immune-Mediated Medical Condition; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, screening; Unsch, unscheduled

1 Includes white blood cells (WBCs), hemoglobin (Hb), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatine kinase (CK), serum creatinine, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
2 Includes WBCs, Hb, PLT, ALT, AST, ALP, total bilirubin, CK, and serum creatinine
3 Includes SARS-CoV-2 serology (N-specific) only
4 If within 7 days after vaccination
5 If prior to Visit 05
6 Can be phone, text, or e-mail contact
7 A nasal swab for SARS-CoV-2 should be performed within 3 days of COVID-19 symptoms and repeated after 7 days.
8 AESIs, including serologically or virologically confirmed SARS-CoV-2 infection and severity of COVID-19, PIMMCs, MAAEs, and NOCMCs will be collected from the time of first vaccination throughout the entire study.
9 SAEs occurring after signing of the informed consent form (ICF) will be recorded and reported to the sponsor or designee by the investigator within 24 hours of becoming aware of the SAE.

Table 2 Schedule of Assessments: Cohorts 1 and 2 – Subjects Receiving Booster Dose

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	V13	V14	Unsch Visit	Early Term Visit
Study Day(s)	**SCR -30 to -1**	**Day 1**	**Day 2 +1d**	**Day 4 +2d**	**Day 8 +2d**	**Day 29 ±3d**	**Day 57 ±3d**	**Day 113[12] -3d/+21d**	**Day 114 +1d**	**Day 116 +2d**	**Day 120 +2d**	**Day 142 ±3d**	**Day 170 ±3d**	**Day 293 ±3d**	**Day 478 ±7d**		
Obtain Written Informed Consent	X																
Review Eligibility Criteria	X	X						X									
Medical History	X																
Review of Interim Medical History		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
Vital Signs (Oral Temp, Pulse, BP)	X	X			X	X	X	X			X	X	X	X	X	X	X
Physical Examination Including Height and Weight	X																
Targeted Physical Examination, if Indicated		X			X	X	X	X			X	X	X	X	X	X	X
ECG[8]		X[9]			X	X	X	X[9]			X	X	X	X	X		
Cardiac Biomarkers (Troponin T, CRP, ESR)[10]		X[11]			X	X	X	X[11]			X	X	X	X	X		
Nasal Swab Collection for SARS-CoV-2 PCR	X															X[7]	
Blood Collection for Safety Labs	X[1]				X[2]		X[2]				X[2]		X[2]	X[2]		X[2]	X[2]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 Serology[3], HIV	X						X[3]						X[3]				

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V12**	**V13**	**V14**	**Unsch Visit**	**Early Term Visit**
Study Day(s)	**SCR -30 to -1**	**Day 1**	**Day 2 +1d**	**Day 4 +2d**	**Day 8 +2d**	**Day 29 ±3d**	**Day 57 ±3d**	**Day 113[12] -3d/+21d**	**Day 114 +1d**	**Day 116 +2d**	**Day 120 +2d**	**Day 142 ±3d**	**Day 170 ±3d**	**Day 293 ±3d**	**Day 478 ±7d**		
Blood Collection for Cellular Immune Assays		X			X	X		X				X		X	X	X	X
Blood Collection for Antibody Assays		X				X	X	X				X		X	X	X	X
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[4]	X[4]
Adverse Events		X	X	X	X	X		X	X	X	X	X				X[5]	X[5]
SAEs/AESIs Including PIMMCs/MAAEs/NOCMCs[13]	X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Visit[6]			X	X					X	X							
Saliva Collection for Antibodies		X			X			X			X			X			

Abbreviations: AESI, adverse event of special interest; BP, blood pressure; d, day(s); ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MAAE, Medically Attended Adverse Event; NOCMC, New Onset Chronic Medical Condition; SAE, serious adverse event; PCR, polymerase chain reaction; PIMMC, Potentially Immune-Mediated Medical Condition; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, screening; Unsch, unscheduled

1 Includes white blood cells (WBCs), hemoglobin (Hb), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatine kinase (CK), serum creatinine, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
2 Includes WBC, Hb, PLT, ALT, AST, ALP, total bilirubin, CK, and creatinine
3 Includes SARS-CoV-2 serology (N-specific) only
4 If within 7 days after each vaccination (prime or boost dose)

5 If prior to Visit 11
6 Can be phone, text, or e-mail contact
7 A nasal swab for SARS-CoV-2 should be performed within 3 days of COVID-19 symptoms and repeated after 7 days.
8 ECG will be performed for subjects receiving booster dose in Cohorts 1 and 2. ECG data will include heart rate and RR, PR, QT, and QRS durations.
9 ECG will be performed before 1st and 2nd doses of vaccination.
10 Cardiac biomarker assessment will be performed for subjects receiving booster dose in Cohorts 1 and 2. Cardiac biomarker assessments will include troponin T, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).
11 Cardiac biomarker assessment will be performed before 1st and 2nd doses of vaccination.
12 In case of second dose delay (allowed -3 days/+21 days), all safety visits (Visit 08 to Visit 12) will be scheduled based on the day of the second dose (e.g., Visit 08 will occur 1 day after delayed second dose and not on Day 114). All visits will shift based on the second dose without changing the time interval between 2 consecutive visits.
13 AESIs, including serologically or virologically confirmed SARS-CoV-2 infection and severity of COVID-19, PIMMCs, MAAEs, and NOCMCs will be collected from the time of first vaccination throughout the entire study.
14 SAEs occurring after signing of the informed consent form (ICF) will be recorded and reported to the sponsor or designee by the investigator within 24 hours of becoming aware of the SAE.

Table 3 Schedule of Assessments: Cohorts 3, 4, and 6

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	V13	Unsch Visit	Early Term Visit
Study Day(s)	SCR -30 to -1	Day 1	Day 2 +1d	Day 4 +2d	Day 8 +2d	Day 15 ±2d	Day 29 ±3d	Day 30 +1d	Day 32 +2d	Day 37 +2d	Day 58 ±3d	Day 86 ±3d	Day 209 ±3d	Day 394[16] ±7d		
Obtain Written Informed Consent	X															
Review Eligibility Criteria	X	X					X									
Medical History	X															
Review of Interim Medical History		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
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 Physical Examination, if Indicated		X			X		X			X	X	X	X	X	X	X
ECG[8]		X[9]			X		X[9]			X	X	X	X	X		
Cardiac Biomarkers (Troponin T, CRP, ESR)[10]		X[11]			X		X[11]			X	X	X	X	X		
Nasal Swab Collection for SARS-CoV-2 PCR	X														X[7]	
Blood Collection for Safety Labs	X[1]				X[2]		X			X[2]		X[2]	X[2]		X[2]	X[2]
Blood Collection for HBsAg, Anti-HCV, SARS-CoV-2 Serology[3], HIV	X											X[3]				
Blood Collection for Cellular Immune Assays		X			X		X				X		X	X	X	
Blood Collection for Antibody Assays		X				X	X				X	X	X	X	X	X
Pregnancy Test (Women of Childbearing Potential)	X[12]	X[12]					X[12]									

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V12**	**V13**	**Unsch Visit**	**Early Term Visit**
Study Day(s)	**SCR -30 to -1**	**Day 1**	**Day 2 +1d**	**Day 4 +2d**	**Day 8 +2d**	**Day 15 ±2d**	**Day 29 ±3d**	**Day 30 +1d**	**Day 32 +2d**	**Day 37 +2d**	**Day 58 ±3d**	**Day 86 ±3d**	**Day 209 ±3d**	**Day 394[16] ±7d**		
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[4]	X[4]
Adverse Events		X	X	X	X	X	X	X	X	X	X				X[5]	X[5]
SAEs/AESIs Including PIMMCs/MAAEs/NOCMCs[13]	X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Visit[6]			X	X				X	X							
Saliva Collection for Antibodies		X			X	X	X			X			X			

Abbreviations: AESI, adverse event of special interest; BP, blood pressure; ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MAAE, Medically Attended Adverse Event; NOCMC, New Onset Chronic Medical Condition; SAE, serious adverse event; PCR, polymerase chain reaction; PIMMC, Potentially Immune-Mediated Medical Condition; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, screening; Unsch, unscheduled

1 Includes white blood cells (WBCs), hemoglobin (Hb), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatine kinase (CK), serum creatinine, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
2 Includes WBC, Hb, PLT, ALT, AST, ALP, total bilirubin, CK, and creatinine
3 Includes SARS-CoV-2 serology (N-specific) only
4 If within 7 days after each vaccination (prime or boost dose)
5 If prior to Visit 10
6 Can be phone, text, or e-mail contact
7 A nasal swab for SARS-CoV-2 should be performed within 3 days of COVID-19 symptoms and repeated after 7 days.
8 ECG data will include heart rate and RR, PR, QT, and QRS durations.
9 ECG will be performed up to 72 hours before the 1st and up to 72 hours before the 2nd study vaccinations.
10 Cardiac biomarker assessments will include troponin T, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).
11 Cardiac biomarker assessment will be performed before 1st and 2nd doses of vaccination.
12 Cohort 6 only: women of childbearing potential must have a negative urine or serum pregnancy test at screening for eligibility purposes and within 24 hours prior to each study vaccination.

13 AESIs, including serologically or virologically confirmed SARS-CoV-2 infection and severity of COVID-19, PIMMCs, MAAEs, and NOCMCs will be collected from the time of first vaccination throughout the entire study.
14 SAEs occurring after signing of the informed consent form (ICF) will be recorded and reported to the sponsor or designee by the investigator within 24 hours of becoming aware of the SAE.
15 In case of second dose delay (±3), all safety visits (Visit 07 to Visit 12) will be scheduled based on the day of the second dose (e.g., Visit 07 will occur 1 day after delayed second dose and not on Day 30). All visits will shift based on the second dose without changing the time interval between 2 consecutive visits.
16 Cohorts 3 and 4 will complete Visit 13 (Day 394) if the visit window occurs prior to the last study participant completing Visit 12 (Day 209). Cohort 6 will not complete Visit 13 (Day 394).

4 INTRODUCTION

4.1 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 2 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]

4.1.1 Coronaviruses

Coronaviruses are enveloped positive-stranded ribonucleic acid (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 kb. 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 to produce a nested set of messenger RNA (mRNA) molecules with common 3′ ends. There are 4 main sub-groups known as alpha, beta, gamma, and delta coronaviruses. SARS-CoV-2 is a novel *betacoronavirus* like 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.[7,8,9,10,11]

The genomes of SARS-CoV and SARS-CoV-2 possess 4 genes that encode the Spike (S), Membrane (M), Nucleocapsid (N), and Envelope (E) proteins. The 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-2 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 (ACE-2) 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 ACE-2 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 M protein has a short N-terminal domain that projects on the external surface of the envelope and spans the envelope 3 times, leaving a long C terminus inside the

envelope. The M protein plays an important role in viral assembly. The N protein 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 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.

4.1.2 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 >60 years old.[15,16] The current outbreak due to SARS-CoV-2 (i.e., COVID-19) has a high age-related mortality rate and has rapidly spread worldwide with over 151 million cases of infection and over 3 million deaths reported as of April 2021. Development of an effective and safe COVID-19 vaccine is under way to limit the occurrence of debilitating or lethal COVID-19 and to control the spread in the general population. 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. In August 2021, the United States (US) Food and Drug Administration (FDA) announced full approval of the Pfizer/BioNTech vaccine in the US only. Other available vaccines are still under emergency use authorization (EUA) in the US or United Kingdom (UK) to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV.

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 2 decades, the scientific community and the biopharmaceutical industry have been asked to respond urgently to several 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 1 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] The current pandemic saw the availability of experimental vaccines to initiate Phase 1 clinical trials in approximately 3 months, the first Emergency Use Approval was issued 9 months later by the Food and Drug Administration in the US. One year after the onset of

the pandemic, only 262 million people (3.4% of the world population) have been vaccinated worldwide.

4.1.3 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 to address the needs of populations worldwide.[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.[6] 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 12-15 months remains unclear. Neutralizing antibody titers and the associated memory B-cell response are short lived in SARS-recovered patients:[20] in previous SARS epidemics, the SARS-CoV-specific immunoglobulin M (IgM) and immunoglobulin A (IgA) response lasted less than 6 months, while virus-specific immunoglobulin G (IgG) titer peaked 4 months post infection and markedly declined after 1 year.[21,22,23,24,25,26,27] Similarly, neutralizing antibodies to SARS-CoV-2 have been shown to rapidly decrease following infection.[28,29,30] The duration of protection against SARS-CoV-2 following vaccination is currently unknown. Neutralizing antibodies against the S glycoprotein have been detected up to 6 months after the second boost of mRNA-1273 but appear to wane faster in elderly subjects.[31] Furthermore, the correlation of neutralizing antibody titers with vaccine efficacy is yet uncharacterized, pending ongoing studies.

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 FcγR recognition of antibody Fc domains.[32] This phenomenon has constrained development of a vaccine against dengue,[33] and similar biology has been observed in some pre-clinical models with coronavirus vaccines that elicit humoral responses.[34,35] This effect has not been observed so far with currently available vaccines against SARS-CoV-2.

Unbalanced immune responses to coronavirus vaccines may also cause iatrogenic pulmonary toxicity through other mechanisms, perhaps related to excessive innate immune activation.[36,37] This has been observed in several animal models examining vaccine candidates for SARS and MERS,[38,39] including in non-human primates (NHPs).[40] One type of unbalanced response associated with significant increased pathology is vaccine-associated enhanced respiratory disease (VAERD). VAERD is a distinct clinical syndrome that may occur 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.[41,42] In addition, accentuated T helper cell type 2 (Th2) responses can lead to eosinophilic inflammatory recruitment and airway

hyperresponsiveness.[43] Such an adverse effect appears associated with a Th2 response, strongly suggesting that a more T helper cell type 1 (Th1)-biased response is critical for optimal vaccine responses.[14,44,45,46]

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.[47] T-cell epitopes (TCE) 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.[48,49,50,51,52,53,54,55,56,57,58,59] 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.[18,48,59,60,61,62] Similarly, $CD4^+$ and $CD8^+$ TCE have been identified in convalescent patients after SARS-CoV-2 infection.[63,64,65] The $CD4^+$ and $CD8^+$ T-cells targeted M, S and N proteins as well as nsp3, nsp4, ORF3a and ORF8, among others. Importantly, SARS-CoV-2-reactive CD4+ T-cells were also identified in unexposed subjects, suggesting cross-reactive T-cell recognition between different strains of coronaviruses.[65]

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.[14,66] However, none of the vaccine candidates currently in clinical development against SARS-CoV-2 comprehensively target $CD8^+$ TCE outside of Spike.

4.2 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 to kill virally infected cells. SARS-CoV-2 convalescent patients exhibit both elements of this adaptive immune response[67] even though neutralizing antibody titers may be low.[68]

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, Gritstone has been delivering neoantigens (mutated "non-self" epitopes) via 2 vaccine platforms: a replication deficient chimpanzee adenovirus (ChAd) 68 vector for the prime vaccination, and for boost vaccinations, a self-amplifying mRNA (SAM) vector 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, so far, has been well tolerated without any dose-limiting toxicities (DLTs) observed, 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- and B-cell immunity to protect healthy individuals.

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, Gritstone has 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 with ChAd followed with SAM boosts. 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 vaccines.

Despite the differences in age-related health issues, young adults are usually grouped with older adults in most COVID clinical trials for purposes of data collection.[79] In March 2020, the Centers for Disease Control reported the young adults from 20 to 44 years of age comprised 20% of hospitalizations and 12% were admitted to the intensive care unit.[80] Immunogenicity in 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 older adults.[1,69]

A strong immune response in older adult subjects, as has been shown with the Gritstone vaccine 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,[70] which in turn may explain the higher mortality rate observed in older patients infected with SARS-CoV-2.

A key question is whether the induction of a B-cell response with neutralizing antibody to SARS-CoV-2 by currently available first-generation COVID-19 vaccines (or by natural infection) will adequately protect subjects and if so, for how long. While the delivery of additional doses of authorized vaccines may prolong this initial B-cell response, particularly in older adult subjects, boosting with GRT-R910 may provide more durable and broader protection against SARS-CoV-2 infection, similar to the enhanced immunity seen with SARS-CoV-2 convalescent patients who have been subsequently vaccinated.[78] Another key question is whether neutralizing antibodies solely targeting the S glycoprotein will protect against emerging variants of SARS-CoV-2. Early data point to a decrease in neutralizing antibody activity in sera from vaccinated subjects against variants of concern following immunization with some of the available first-generation COVID-19 vaccines. Retrospective analysis of SARS-CoV-2 infections in participants in the Kaiser Southern California (US) health system suggests that waning immunity in subjects vaccinated with the Pfizer vaccine is more likely to account for reduced effectiveness than the impact of the increased prevalence of the delta variant of SARS-CoV-2. A retrospective cohort study recently published in the Lancet explains the decrease in vaccine effectiveness, claiming that our own immune systems are to blame rather than the resistance of the delta variant. In the current situation, SARS-CoV-2 variants with mutations in the S protein not only make people more susceptible to getting an infection with underlying disease but have also raised the concern that recovered individuals can be reinfected, and the current vaccine will become less effective.[71]

4.2.1 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.[73,74,75,76,77] 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 (vp), or as synthetic SAM produced after in vitro transcription. SAM cannot form infectious vp as only the RNA is capable of further amplification and lacks the viral sequences necessary to generate new vp.

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 subgenomic promoter (SGP) of the parent VEEV, but the structural proteins in the subgenomic region are replaced by the antigens of therapeutic interest. This structural engineering results in high levels of antigen expression without formation of the infectious vp 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. To date, Gritstone's SAM has been administered as vaccine boosts to 50 patients with advanced cancers in combination with nivolumab, and in some patients, with ipilimumab. Patients have received and tolerated well up to 8 monthly SAM boosts (dose ranging from 30 to 300 mcg) 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.

4.2.2 Purpose of Study

This Phase 1 clinical trial will explore the ability of a novel vector SAM (GRT-R910) vaccine and novel SARS-CoV-2 epitope cassettes (extending COVID antigenic vaccine content beyond Spike) to safely broaden and expand B-cell and T-cell immune responses to SARS-CoV-2 in subjects ≥60 years of age for Cohorts 1, 2, 3, and 4 and ≥18 to ≤59 years of age for Cohort 6.

The dose of GRT-R910 that generates the strongest immunogenicity while maintaining tolerability and safety will be identified during this Phase 1 clinical trial for subsequent trials and will also provide proof-of-concept that genetic and viral vector platforms can be mixed and matched, which will provide much needed information in light of the risk over time that immune

responses induced by first-generation mRNA and adenoviral vectored vaccines, especially in elderly subjects, will wane.

4.3 Benefit/Risk Assessment

The benefit/risk assessment for a SAM-directed vaccine (including GRT-R910) to target SARS-CoV-2 is currently being evaluated in a first-in-human Phase 1 study assessing heterologous prime-boost (ChAd prime followed by SAM boost) and homologous prime-boost (SAM prime followed by SAM boost) in naïve subjects above the age of 18 years (NCT04776317). Based on additional prior clinical experience with SAM vectors used as boosts (up to 8 boosts per patient) currently in Phase 2 in patients with advanced cancers (NCT03953235, NCT03639714), the vaccinations are expected to result in mild to moderate local 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 SAM-based vectors in general, and GRT-R910, is expected to be lower in older adult subjects compared to younger ones. 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.

4.3.1 Dose Justification

Two different doses (10 or 30 mcg) of GRT-R910 will be administered to healthy adults who were previously vaccinated with a first-generation COVID-19 vaccine (Cohorts 1 and 2; AstraZeneca), an adenoviral COVID-19 vaccine (Cohort 3; AstraZeneca, Janssen), or an mRNA-based COVID-19 vaccine (Cohorts 4 and 6; Pfizer/BioNTech, Moderna). The 10 mcg dose of GRT-R910 was selected for use in Cohorts 3, 4, and 6 by evaluating the balance of immunogenicity and reactogenicity of a single dose of GRT-R910 in Cohorts 1 and 2.

The choice of 10 or 30 mcg for the starting dose of GRT-R910 is supported by the following observations (see the Investigator's Brochure for more details) and hypotheses:

- In non-human primates, human-equivalent doses of SAM-LNP:MAG of up to 300 mcg are safe and generate T-cell immunity to the vaccine's epitopes.
- Preliminary data in NHP using a SAM-Spike vaccine suggest a trend towards improved T-cell responses when administered at 30 mcg compared to 300 mcg.
- In cancer patients (including elderly subjects with advanced cancers) treated in Phase 1-2 studies (NCT03953235, NCT03639714), doses of SAM-based neoantigen vaccines up to 300 mcg are safe and induce T-cell responses against the vaccine's epitopes. Doses as low as 30 mcg administered as boosts post an adenoviral prime produce equally robust immune responses with lower reactogenicity than 100 mcg and 300 mcg.
- In otherwise healthy subjects (i.e., not at risk of immunodeficiency due to cancer or its treatment), the hypothesis is that lower doses of SAM-based vaccines compared to cancer patients should be effective at inducing an immune response while lowering the risk of reactogenicity.

- A 4-month interval after the second administration of AstraZeneca's first-generation COVID-19 vaccine should optimally allow for understanding the immune response specific to GRT-R910's epitopes.
- From an immunogenicity standpoint, 2-dose administration of GRT-R910 is expected to provide an optimal boost against SARS-CoV-2 Spike antigen and TCE in the form of a B-cell response (neutralizing antibodies in particular) as well as de novo T-cell responses against the TCE encoded by GRT-R910.
- From a patient compliance standpoint in Cohorts 1 and 2, a single dose of GRT-R910 following the initial 2 injections of AstraZeneca's first-generation COVID-19 vaccine is deemed an acceptable option for subjects ≥60 years of age if they are not willing to receive a second dose of GRT-R910.

4.3.2 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, having nasal swabs collected, intramuscular (IM) injection, possible reactions to the study product (GRT-R910), and breach of confidentiality.

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.

4.3.3 Risks of GRT-R910

GRT-R910 has been administered to human participants prior to the initiation of this study. As of 04 October 2021, 13 subjects have received GRT-R910 in the Phase 1 clinical trial (NCT04776317). At the time of initiation of this protocol, safety and immunogenicity are consistent with prior vaccines using the gritstone SAM platform.

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 06 May 2021, 141 doses of SAM encoding for cancer-associated neoantigens have been administered to 48 cancer patients in ongoing Phase 1-2 clinical trials.

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.[73,74,75,76,77] In August 2021, the US FDA announced full approval of the Pfizer/BioNTech vaccine in the US only. In addition, more than 150 million doses of these mRNA vaccines have now been given to persons in the US alone. In clinical trials of mRNA vaccines, adverse events (AEs) have been quite similar to those observed with adenovirus-based vectors, except for the absence of cases of

vaccine-induced thrombotic thrombocytopenia. 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 (PEG) in the LNP component of these vaccines, which is different in Gritstone's GRT-R910.

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 6 May 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 mcg with 10 patients to date receiving the 300 mcg dose as bilateral intramuscular injections. All patients received concomitant doses of intravenous (IV) nivolumab at 480 mg flat dose. Most patients also received concomitant doses of ipilimumab subcutaneously at a 30 mg flat dose. No DLTs 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 2 patients developing transient signs and symptoms of myositis and rhabdomyolysis. While auto-immune myositis is a known toxicity of nivolumab and/or ipilimumab, the role of the vaccine vectors and/or their antigenic cassettes cannot be formally excluded.

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 SAM-based vaccine, GRT-R910, encoding antigens of SARS-CoV-2 in healthy subjects at a dose of up to 100 mcg. In the current proposed study, where subjects will have received a first-generation vaccine (prime-boost), lower doses of GRT-R910 are anticipated to be sufficient to boost and expand the initial immune response. Hence, low doses of GRT-R910 will be assessed, specifically 10 mcg and 30 mcg.

Risks to subjects receiving the study products are expected to primarily involve mild to moderate local 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, myalgia, and arthralgia. 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 Gritstone's SAM, 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.

4.3.4 Risks to Privacy

Subjects will be asked to provide data concerning health. This information will be kept confidential within the limits of the local law and consistent with the guidelines of the General Data Protection Regulation (EU) 2016/279 of the European Parliament ("GDPR") and the Health Insurance Portability and Accountability Act for US sites. All study records in physical form will be kept in a locked file cabinet or maintained in a locked room at the participating site, with controlled entry to prevent unauthorized access. Electronic files will be password protected and encrypted at rest and in transit. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the health data that is collected. Any publications from this trial will not use information that will identify subjects by name, and such information may be anonymized, pseudonymized, or de-identified as applicable. 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 Gritstone's and its affiliates, the Ethics Committee (EC), and the Medicines and Healthcare Products Regulatory Agency (MHRA) and will be subject to strict confidentiality provisions regarding any patient data.

4.3.5 Risks of Genetic Testing

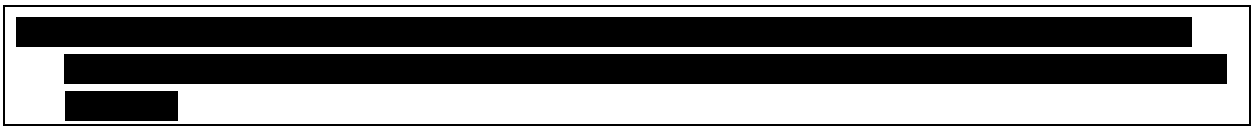
Any genetic data generated will be kept private. There may be a risk that information resulting from research genetic testing could be misused for discriminatory purposes. However, national laws provide protections against genetic discrimination. Researchers will need to maintain confidentiality in order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

4.3.6 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.

5 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints (Outcome Measures)
Primary	
• To assess the safety and tolerability of 2 different doses (10 or 30 mcg) of GRT-R910 when administered to healthy adults ≥60 years of age who were previously vaccinated with a first-generation COVID-19 vaccine (Cohorts 1 and 2; AstraZeneca) • To assess the safety and tolerability of a 10 mcg dose of GRT-R910 when administered to healthy adults (≥18 years of age) who were previously vaccinated with an mRNA-based COVID-19 vaccine (Pfizer/BioNTech, Moderna)	• Occurrence of solicited local reactogenicity signs and symptoms for 7 days after GRT-R910 vaccination • Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days after GRT-R910 vaccination • Occurrence of unsolicited AEs for 28 days after last study-administered GRT-R910 vaccination • Change from baseline for clinical safety laboratory parameters 7 days after last study-administered GRT-R910 vaccination • Occurrence of SAEs and adverse events of special interest (AESIs), including potentially immune-mediated medical conditions (PIMMCs), medically attended adverse events (MAAEs), and new onset chronic medical conditions (NOCMCs), throughout the entire study after GRT-R910 vaccination
Secondary	
• To assess the cellular and humoral immunogenicity of GRT-R910 when administered to volunteers (≥60 years of age for Cohorts 1, 2, 3, and 4 and ≥18 to ≤59 years of age for Cohort 6) who were previously vaccinated with an mRNA-based COVID-19 vaccine (Pfizer/BioNTech, Moderna)	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization in serum samples • Response rate, magnitude, and breadth of SARS-CoV-2 specific T-cells as assessed by interferon (IFN)-γ enzyme-linked immunospot (ELISpot) for 10 subjects per cohort
[redacted]	
[redacted]	



6 STUDY DESIGN

6.1 Overall Design

This is a multi-center, open-label, dose-escalation design study to examine dose, safety, tolerability, and immunogenicity of GRT-R910, an investigational SAM SARS-CoV-2 vaccine when administered to healthy adults 18 years and older who were previously vaccinated with a first-generation COVID-19 vaccine (Cohorts 1 and 2; AstraZeneca), an adenoviral COVID-19 vaccine (Cohort 3; AstraZeneca, Janssen), or an mRNA-based COVID-19 vaccine (Cohorts 4 and 6; Pfizer/BioNTech, Moderna) (Figure 1).

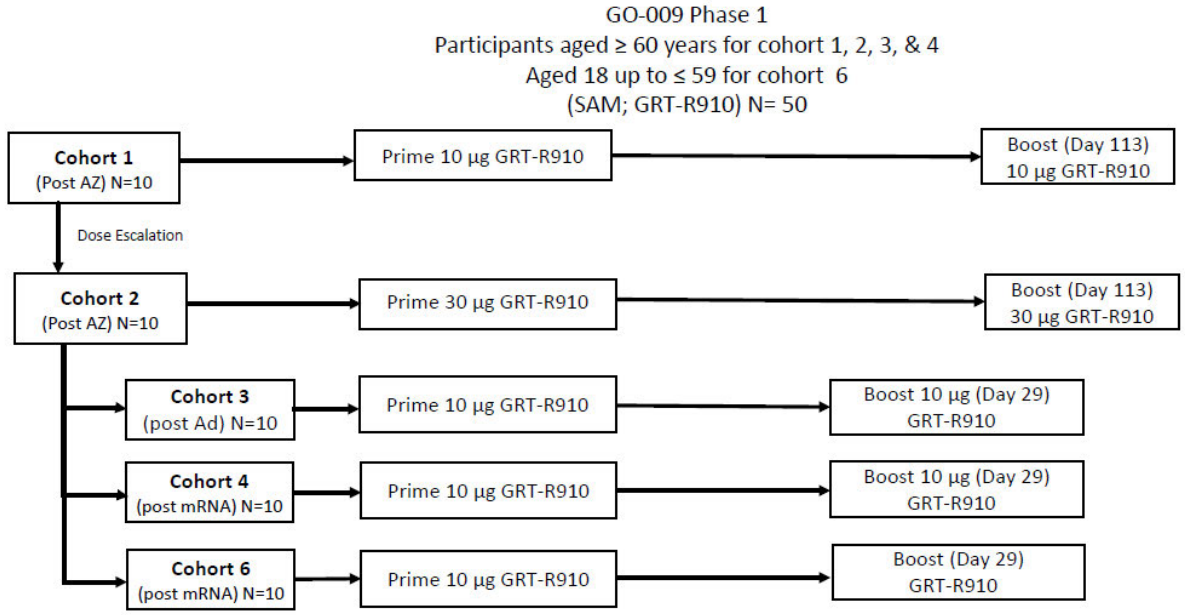
In Cohorts 1 and 2, healthy adults ≥60 years of age (N=10, including 2 sentinels per cohort) will receive 2 doses of GRT-R910 (homologous prime-boost) at 1 of 2 dose levels (10 mcg or 30 mcg) at least 2 months after receiving AstraZeneca's COVID-19 prime and boost vaccine. The GRT-R910 booster dose will be administered 113 days (16 weeks) after the prime. In Cohorts 3 and 4, healthy adults ≥60 years of age (N=10) will receive 2 doses of GRT-R910 (homologous prime-boost) 10 mcg (dose selected from Cohorts 1 and 2) at least 2 months after receiving an adenoviral COVID-19 vaccine (Cohort 3; AstraZeneca, Janssen), or an mRNA-based COVID-19 vaccine (Cohort 4; Pfizer/BioNTech, Moderna). In Cohort 6, healthy adults ≥18 to ≤59 years of age (N=10) will receive 2 doses of GRT-R910 (homologous prime-boost) 10 mcg (dose selected from Cohorts 1 and 2) at least 2 months after receiving an adenoviral COVID-19 vaccine or an mRNA-based COVID-19 vaccine (Cohort 6; Pfizer/BioNTech, Moderna). The GRT-R910 booster dose will be administered 28 days after the prime.

Sentinel dosing in Cohorts 1 and 2 will consist of 2 volunteers in each cohort dosed 72 hours ahead of the remainder of each cohort, with the remainder of the volunteers dosed at the same dose level only if no halting rules are met. Enrollment in Cohort 2 will only proceed if safety data from all volunteers in Cohort 1 meet the dose-escalation rules. There will be no sentinel dosing in Cohorts 3, 4, and 6. The dose for Cohorts 3, 4, and 6 was selected from Cohorts 1 and 2 after evaluation of reactogenicity, safety, and initial immunogenicity. Dose selection will be determined by the Gritstone clinical team in consultation with the PI(s).

The reactogenicity and immunogenicity data assessed after the first dose of GRT-R910 will inform selection of the GRT-R910 dose to be tested in future studies. The 10 mcg dose of GRT-R910 was selected for use in Cohorts 3, 4, and 6 by evaluating the balance of immunogenicity and reactogenicity of a single dose of GRT-R910 in Cohorts 1 and 2.

Injection will be given intramuscularly as a prime-boost at least 2 months after the last administration of a SARS-CoV-2 vaccine either approved for emergency supply or approved for use by the MHRA for prevention of SARS-CoV-2. Subjects should refrain from a subsequent boost with an emergency supply or approved SARS-CoV-2 vaccine for a minimum of 4 months after the second dose of study vaccine.

Figure 1 Study Flow Chart



6.2 Dose Justification

GRT-R910 will be assessed at doses of 10 mcg and 30 mcg. Dose justification is discussed in Section 4.3.1.

6.3 End of Study Definition

Subjects from Cohorts 1 and 2 (NOT receiving booster dose) will be followed for 12 months, subjects from Cohorts 1 and 2 (receiving booster dose) will be followed for 16 months, subjects from Cohorts 3 and 4 will be followed for up to 13 months, and subjects from Cohort 6 will be followed for 7 months. Vaccinated subjects will be carefully monitored for exposure and infection to SARS-CoV-2 throughout the study.

7 STUDY POPULATION

The study population will include healthy adults 18 years and older, as determined by medical history, physical examination, 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 to the participant.

Eligible participants will consist of individuals ≥60 years of age for Cohorts 1, 2, 3, and 4, and ≥18 to ≤59 years of age for Cohort 6 who have received AstraZeneca's COVID-19 vaccine (Cohorts 1 and 2), an adenoviral COVID-19 vaccine (Cohort 3), or an mRNA-based COVID-19 vaccine (Cohorts 4 and 6) as part of a clinical trial or under the national deployed vaccine program. All participants should have completed their 2-dose regimen of the first-generation vaccine at least 2 months prior to study entry.

The following eligibility criteria will be used:

7.1 Inclusion Criteria

Subjects eligible to participate in this trial must meet all 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 males or post-menopausal females ≥60 years of age at enrollment for Cohorts 1, 2, 3, and 4.
4. Are males or females ≥18 to ≤59 years of age at enrollment for Cohort 6.
5. For Cohorts 1 and 2, have received AstraZeneca's AZD1222 COVID-19 prime and boost vaccine (Covishield®, Vaxzevria®), with the last dose received at least 2 months or more prior to Day 1.
6. For Cohort 3, have received a primary series of an adenoviral (AstraZeneca AZD1222 [Covishield®, Vaxzevria®] or Janssen [Janssen COVID-19 Vaccine]) COVID-19 vaccine (under emergency supply procedures or upon full approval and may have received booster doses of an authorized vaccine), with the last dose received at least 2 months or more prior to Day 1.
7. For Cohorts 4 and 6, have received a primary series of an mRNA (Pfizer/BioNTech [Comirnaty®] or Moderna [Spikevax®]) COVID-19 vaccine (under emergency supply procedures or upon full approval and may have received booster doses of an authorized vaccine), with the last dose received at least 2 months or more prior to Day 1.
8. Agree to refrain from blood donation during the course of the study.
9. Women of childbearing potential (WOCBP)* must agree to avoid pregnancy and be willing to use a highly effective method of contraception** consistently for 30 days prior to the first study vaccine and for at least 60 days after the last study vaccine.

   *A subject is considered a WOCBP if she is 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.
   **Highly effective methods of birth control include the following: oral contraceptives, injection hormonal contraceptive, implant hormonal contraceptive, hormonal patch,

intrauterine device, abstinence, monogamous with a vasectomized partner, non-male sexual relationship.
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicidal products, barrier methods (such as cervical sponge, diaphragm, or condom with spermicide), and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
Note: Vasectomized male partner is considered a highly effective birth control method, provided that partner is the sole sexual partner of the female trial participant who is of childbearing potential and that the vasectomized male has received medical assessment of the surgical success.

10. WOCBP must have a negative urine or serum pregnancy test within 24 hours prior to each study vaccination.
11. Male subjects of childbearing potential must agree to the use of condoms to ensure effective contraception with a female partner from the time of study vaccination until 3 months after vaccination. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after the last vaccination. Male subjects of childbearing potential are biological males who are post-pubertal and considered fertile until permanently sterile by bilateral orchiectomy or vasectomy.
12. Plan to remain living in the area for the duration of the study.
13. Clinical screening laboratory evaluations: white blood cells (WBCs), hemoglobin (Hb), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatine kinase (CK), serum creatinine, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are within normal reference ranges at the clinical laboratory 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 laboratory value outside the reference range that is thought to be clinically insignificant by a site investigator must be discussed with Gritstone's Medical Officer prior to enrollment.

7.2 Exclusion Criteria

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

1. History of prior confirmed COVID-19 (Cohorts 1 and 2).
2. History of prior confirmed (polymerase chain reaction [PCR] or antigen test positive) COVID-19 infection as confirmed by a diagnostic laboratory less than 16 weeks (112 days) prior to enrollment (Cohorts 3, 4, and 6).
3. Positive for SARS-CoV-2 (N-specific) antibody testing and had a history of upper respiratory illness consistent with COVID-19 within the 112 days prior to enrollment (Cohorts 3, 4, and 6).

4. Prior receipt of a SARS-CoV-2 vaccine other than one of the following:
   a. AstraZeneca's AZD1222 (Covishield®, Vaxzevria®)
   b. JNJ-78436735
   c. Pfizer/BioNTech (Comirnaty®)
   d. Moderna (Spikevax®)

   Other approved or investigational vaccines with an LNP component, or any other approved or investigational vaccine likely to impact the interpretation of the trial data are excluded.
5. On current treatment or prevention agents with activity against SARS-CoV-2.
6. Participation in another research study involving receipt of an investigational product in the 60 days preceding enrollment or planned use during the study period.
7. Receipt or planned receipt of any live, attenuated vaccine within 28 days before or after study vaccination.
8. Receipt or planned receipt of any subunit or killed vaccine within 14 days before or after vaccination.
9. Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of first study vaccination or at any time during the study.
10. Breastfeeding, pregnant, or planning to become pregnant during the course of the study.
11. Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection with CD4+ T-cells < 400/mm^3, 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).

    *Seropositivity for HIV, hepatitis B surface antigen (HBsAg) or hepatitis C virus (antibodies to HCV) does not constitute an exclusion criterion if infection is not active (negative PCR, organ function tests within normal limits).
12. 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 PEG component of the vaccine).
13. Any history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
14. Any history of anaphylaxis, including but not limited to reaction to vaccination.
15. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
16. History of serious ongoing, unstable psychiatric condition that in the opinion of the investigator would interfere with study participation.
17. Bleeding disorder (e.g., Factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.
18. Suspected or known current alcohol abuse that in the opinion of the investigator would impede compliance with the protocol and schedules of assessments. Suspected or known drug abuse in the 5 years preceding enrollment.
19. 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.

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

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

7.2.2 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 schedules of assessments (Table 1, Table 2, Table 3), or withdrawn from dosing at the discretion of the investigator.

- Acute illness at the time of vaccination. Acute illness 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. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the site's PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol. In particular, subjects should be afebrile for 72 hours without antipyretics prior to receiving study vaccination. Fever is defined as oral temperature of >38.0°C (100.4°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 and be given at least 15 days after the inactivated vaccine or 29 days after the live vaccine.

7.2.3 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's 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 Gritstone.

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

- Study non-compliance to protocol requirements that in the opinion of the participating site's 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.
- Request of primary care provider, the EC, MHRA, or Gritstone.
- Medical disease or condition, or new clinical finding(s) for which, in the opinion of the participating site's 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.

7.2.4 Follow-up for Subjects That Discontinued Study Intervention

If a clinically significant finding is identified, including, but not limited to, changes from baseline, after enrollment, the participating site's 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 or approved 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 any time.

An unscheduled visit will occur, if possible, prior to the receipt of EUA or approved vaccine. The remaining study procedures should be completed as indicated by the schedules of assessments 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.
- Vital signs (blood pressure [BP], heart rate, oral temperature).
- Immunogenicity evaluations.

7.2.5 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.
- Decision by 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 EC, as applicable. Study subjects will be contacted, and appropriate follow-up will be conducted, as necessary.

Gritstone will notify regulatory authorities as applicable.

7.2.6 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 3 documented contact attempts via telephone calls, e-mail, 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.

8 STUDY TREATMENT

8.1 Description of Study Treatment

This Phase 1 study will assess the safety, immunogenicity, and reactogenicity of GRT-R910, an investigational product being developed as a SARS-CoV-2 vaccine. GRT-R910 is a vaccine vector containing an expression cassette encoding for SARS-CoV-2 spike protein and TCE.

8.1.1 GRT-R910

GRT-R910 (SAM-LNP) is a SAM vector based on VEEV. [redacted]

[redacted]

8.2 Study Treatment Administration and Dose

8.2.1 Formulation, Packaging, and Labeling

8.2.1.1 GRT-R910

[redacted]

8.3 Acquisition/Distribution

[redacted]

All study products will be inspected visually 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's PI or responsible person should immediately contact the site's assigned contract research organization (CRO) Clinical Research Associate or Gritstone's Global Clinical Study Manager for further instructions before any additional vaccinations are administered. Based on the information collected, Gritstone will determine whether the affected study product(s) can be used. If the affected study product(s) cannot be used, the participating sites will receive specific instructions on how to return the affected study product(s) to Gritstone 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 Gritstone. Additional instructions for quarantine and Gritstone contact information are provided in the protocol-specific manual of procedures (MOP).

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

Table 4 Dosing and Administration

	N	**GRT-R910 Prime Day 1**	**GRT-R910 Boost 113 days (16 weeks [-3d/+21d]) after prime**
Cohort 1[a]	10[b]	10 mcg	10 mcg
Cohort 2[a]	10[b]	30 mcg	30 mcg
	N	**GRT-R910 Prime Day 1**	**GRT-R910 Boost 28 days after prime**
Cohort 3[c]	10	10 mcg[d]	10 mcg
Cohort 4[c]	10	10 mcg[d]	10 mcg
Cohort 6[e]	10[e]	10 mcg[d]	10 mcg
TOTAL	**50**		

a Healthy adults ≥60 years of age at least 2 months after receiving AstraZeneca's COVID-19 prime and boost vaccine.
b Cohort will include 2 sentinel subjects.
c Healthy adults ≥60 years of age at least 2 months after receiving an adenoviral COVID-19 vaccine (Cohort 3) or an mRNA-based COVID-19 vaccine (Cohort 4).
d Dose selected from Cohorts 1 and 2.
e Healthy adults ≥18 to ≤59 years of age at least 2 months after receiving an mRNA-based COVID-19 vaccine (Cohort 6).

8.5 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.

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

All study products will be stored and shipped from Gritstone 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's PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site's 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: Gritstone 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 Gritstone); 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 [redacted], whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. Gritstone's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the Gritstone-approved clinical monitoring plan (CMP).

Vials may be destroyed in accordance with site-specific standard operating procedures (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-R910 should be retained by the clinical research sites until the end of the study. If for any reason unused vials of GRT-R910 must be disposed of at the clinical sites, written authorization must be obtained from the Gritstone 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 Gritstone's Clinical Project Manager should be retained with the investigational product accountability records.

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

8.6.1 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's 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's PI or responsible person should immediately contact the site's assigned CRO Clinical Research Associate or Gritstone's Global Clinical Study Manager for further instructions before any additional vaccinations are administered. Based on the information collected, Gritstone will determine whether the affected study product(s) can be used. If it cannot be used, the participating sites will receive specific instructions on how to return the affected study product(s) to Gritstone Clinical Material Services or destroy it on-site. Additional instructions for quarantine and Gritstone 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 sites are 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.

9 STUDY ASSESSMENTS AND PROCEDURES

All study assessments and procedures will be performed at the time points presented in the schedules of assessments (Table 1, Table 2, Table 3). Descriptions of all clinical and laboratory evaluations are presented in Section 10.

9.1 Screening

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 eligibility criteria 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 enrollment to this trial.

Abnormal clinical findings from the medical history, physical examination, or blood tests at screening will be assessed. 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.

9.2 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 Good Clinical Practice (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's PI, or the study staff. Following a deviation(s), corrective actions should be developed by the participating sites and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of each site's PI and study staff to use continuous vigilance to identify and report protocol deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to Gritstone per the protocol deviation reporting procedures. Protocol deviations must be sent to the EC per their guidelines. The participating site's PI and study staff are responsible for knowing and adhering to the EC requirements.

10 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

10.1 Clinical Evaluations

Complete medical history will be obtained by interviewing the subjects at the screening 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 screening 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 10.1.1.

At the screening visit (Visit 00), a physical examination will be performed by a study clinician licensed to make medical diagnoses. On Day 1 (Visit 01) prior to GRT-R910 vaccination and at follow-up visits after the initial GRT-R910 vaccination, a targeted physical examination may be performed by a study clinician licensed to make medical diagnoses, if indicated based on subject's interim medical history.

Vital signs (oral temperature, pulse, and blood pressure) 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.

WOCBP must have a negative urine or serum pregnancy test at screening for eligibility purposes for Cohort 6.

Height and weight will be collected on the screening visit to determine body mass index (BMI).

Electrocardiograms (ECGs) will be performed at the time points presented in the Schedule of Assessments (Table 2 and Table 3). The ECG data will include heart rate and RR, PR, QT, and QRS durations. The investigator will be responsible for providing the interpretation of clinical significance for all ECG results.

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 GRT-R910 vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic. AESIs, including serologically or virologically confirmed SARS-CoV-2 infection and severity of COVID-19, PIMMCs, MAAEs, and NOCMCs will be collected from the time of first vaccination throughout the entire study. Any SAE occurring after signing of the ICF will be recorded and reported to the sponsor or designee by the investigator

within 24 hours of becoming aware of the SAE. If the SAE occurs after signing of the ICF and before the first (prime) dose, it will be reported on the medical history electronic case report form (eCRF). If the SAE occurs after the first (prime) dose, it will be reported on the AE eCRF.

All subjects will complete a subject memory aid through 7 days after each GRT-R910 vaccination. Subject memory aids will be reviewed with the subjects for AEs (solicited local and systemic reactions and unsolicited AEs) during telephone, e-mail, or text contacts or at a clinic visit, as appropriate.

Reactogenicity assessments will include an assessment of solicited AEs occurring from the time of GRT-R910 vaccination on Day 1 through Day 8 after GRT-R910 vaccination, which includes an assessment of local 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, and nausea.

10.1.1 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 eCRF are limited to those taken within 30 days prior to the first study vaccination and for 12 months after GRT-R910 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 GRT-R910 should not be used during the trial reporting period (until approximately 12 months after GRT-R910 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 7.2). In addition, the site's 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.

10.1.2 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.

10.2 Laboratory Evaluations

10.2.1 Clinical Laboratory Evaluations

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 GRT-R910, the subject's clinical screening laboratory evaluations prior to each vaccination must be confirmed to meet the eligibility criteria as outlined in the Subject Inclusion Criteria (see Section 7.1).

The following tests will be performed by the local laboratory: WBC, Hb, PLT, ALT, AST, ALP, total bilirubin, CK, creatinine, PT/INR, aPTT, HIV serology, hepatitis B surface antigen, and hepatitis C antibody. 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 GRT-R910 will include WBC, Hb, PLT, ALT, AST, ALP, total bilirubin, CK, and creatinine.

Cardiac biomarker assessments will be performed for Cohorts 1 and 2 (subjects receiving booster dose) and Cohorts 3 and 4, and 6 to assess the potential risk of myocarditis with GRT-R910. Cardiac biomarker assessments include troponin T, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

10.2.2 Research Assays

Serum samples collected for Immunogenicity assays prior to and post administration of GRT-R910 vaccine per the schedules of assessments (Table 1, Table 2, Table 3) will be assessed for SARS-CoV-2 antibody binding. Neutralizing antibody titers will be assessed against SARS-CoV-2 pseudoviruses. Peripheral blood mononuclear cells (PBMCs) will be extracted utilizing sodium heparin tubes, which are provided by Gritstone as noted in the laboratory manual and the corresponding requisition sheets. Multiple time points will be assessed via ex vivo IFN-γ ELISpot using overlapping 15mer peptide pools covering Spike and TCE regions to assess magnitude, breadth, and kinetics of T-cell responses. [redacted]

10.2.3 Samples for Genetic/Genomic Analysis

10.2.3.1 Genetic/Genomic Analysis

Remaining PBMC samples will be stored and 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 polymorphism (SNP) arrays, transcriptomic analysis, evaluation of the immune response to the vaccine, and/or evaluation of any AE from the vaccine.

10.2.3.2 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.

10.2.3.3 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.

10.2.3.4 Laboratory Specimen Preparation, Handling, and Storage

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

10.2.3.5 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.

11 ASSESSMENT OF SAFETY

11.1 Assessing and Recording Safety Parameters

Safety will be assessed by the frequency and severity of:

- SAEs occurring from the time of study consent throughout the entire study (reported to the sponsor or designee by the investigator within 24 hours of becoming aware of the SAE);
  - If the SAE occurs after signing of the ICF and before the first (prime) dose, it will be reported on the medical history eCRF. If the SAE occurs after the first (prime) dose, it will be reported on the AE eCRF.
- Solicited AEs (reactogenicity events occurring from the time GRT-R910 vaccination through 7 days after GRT-R910 vaccination);
- Reactogenicity local reactions (including erythema, induration/edema, pain, and tenderness);
- Reactogenicity systemic reactions (including fever, chills, fatigue, malaise, myalgia, arthralgia, headache, and nausea);
- Clinical safety laboratory AEs occurring from the time of GRT-R910 vaccination through approximately 7 days after GRT-R910 vaccination (parameters to be evaluated include WBC, Hb, PLT, ALT, AST, ALP, total bilirubin, CK, and creatinine);
- Unsolicited AEs (non-serious AEs occurring from the time of GRT-R910 vaccination through approximately 28 days after GRT-R910 vaccination);
- AESIs (including serologically or virologically confirmed SARS-CoV-2 infection and severity of COVID-19, PIMMCs, MAAEs, and NOCMCs occurring from the time of the first study vaccination throughout the entire study).

11.1.1 Adverse Events (AEs)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment.

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 local 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 electronic case report form (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 GRT-R910 or alternate etiology (if not related to study product) (assessed only by those with the training and authority to make a diagnosis), date of resolution, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship to GRT-R910. 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 adverse event, the event will be reported either as a study endpoint or as an AE (not both).

11.1.1.1 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 GRT-R910 vaccination.

Solicited AEs (i.e., reactogenicity) will be collected using a memory aid and recorded on the appropriate DCF from the time of GRT-R910 vaccination through 7 days after each GRT-R910 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

11.1.1.2 Unsolicited Adverse Events

Unsolicited non-serious AEs will be captured for 28 days following each GRT-R910 vaccination. In addition, AESIs, including PIMMCs, MAAEs, and NOCMCs, will be captured throughout the entire study following GRT-R910 vaccination.

11.1.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as follows: “An AE or suspected adverse reaction is considered serious if, in the view of either the participating site’s 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

- 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

All SAEs will be reviewed and evaluated by Gritstone or designee by the investigator within 24 hours of becoming aware of the SAE and will be sent to the EC, if required. If the SAE occurs after signing of the ICF and before the first (prime) dose, it will be reported on the medical history eCRF. If the SAE occurs after the first (prime) dose, it will be reported on the AE eCRF.

11.1.3 Suspected Unexpected Serious Adverse Reaction (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 Investigator's Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

11.1.4 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.

11.1.4.1 Severity of Adverse Events

All AEs or SAEs will be assessed for severity, according to the toxicity grading scales in the US Food and Drug Administration 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 the protocol study team and Gritstone, and will be sent to the EC, if required.

11.1.4.2 Relationship to Study Product

For each reported adverse reaction, the participating site's PI or qualified designee must assess the relationship of the event to GRT-R910 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.

11.1.5 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 or severe COVID-19. AESIs also include 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, Guillain-Barre syndrome, acute disseminated encephalomyelitis, vasculitis, anaphylaxis, vaccine-associated enhanced respiratory disease, thrombocytopenia, and thrombotic events.

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

11.2 Reporting Procedures

Solicited local and systemic reactogenicity events will be documented and reported from the time of GRT-R910 vaccination through 7 days after GRT-R910 vaccination.

Clinical safety laboratory AEs will be documented and reported before GRT-R910 vaccination and 7 days after each GRT-R910 vaccination.

Unsolicited non-serious AEs will be documented and reported from the time of the GRT-R910 vaccination through 28 days after each GRT-R910 vaccination.

AESIs including PIMMCs/MAAEs/NOCMCs will be documented and reported from the time of the initial GRT-R910 vaccination throughout the entire study.

SAEs occurring after signing of the ICF will be recorded and reported to the sponsor or designee by the investigator within 24 hours of becoming aware of the SAE. If the SAE occurs after signing of the ICF and before the first (prime) dose, it will be reported on the medical history eCRF. If the SAE occurs after the first (prime) dose, it will be reported on the AE eCRF.

11.2.1 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.

SAEs will be submitted immediately (within 24 hours of the site's awareness) to the sponsor via a CRO in paper form via facsimile or e-mail. Contacts for SAE reporting can be found in the Study Manual.

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 Gritstone/PPD Pharmacovigilance Group and should be provided as soon as possible.

Gritstone's Medical Monitor and Clinical Project Manager will be notified of the SAE by Gritstone/PPD Pharmacovigilance Group. Gritstone's 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's PI or appropriate sub-investigator licensed to make medical diagnoses becomes aware of an SAE that is suspected to be related to study product, the site's PI or appropriate sub-investigator licensed to make medical diagnoses will report the event to the Gritstone/PPD Pharmacovigilance Group.

AESIs that meet SAE criteria will be reported on an SAE form within 24 hours of the site's awareness to the Gritstone/PPD Pharmacovigilance Group. In addition, for documentation and medical assessment purposes, AESIs that do not meet SAE criteria will also be reported on an SAE form within the period for AE reporting to the Gritstone/PPD Pharmacovigilance Group; however, the narrative will indicate that the AESI did not meet SAE criteria.

11.2.2 Regulatory Reporting for Studies Conducted Under Gritstone-Sponsored CTA

Following notification from the participating site's PI or appropriate sub-investigator, Gritstone, as the CTA sponsor, will report any SUSAR in a safety report and will notify all participating PIs (i.e., all PIs to whom the sponsor is providing study product under its Investigational New Drug Application [IND]) of potential serious risks from clinical studies or any other source, as soon as possible. Gritstone will report to the MHRA 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 safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in International Council for Harmonisation (ICH)/GCP guidelines. Relevant follow up information to a safety report will be submitted as soon as the information is available. Upon request from MHRA, Gritstone will submit to MHRA 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 MHRA at least annually in a summary format.

11.3 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 each GRT-R910 vaccination.

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

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

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

The site's 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 Sections 7.1 and 7.2 and the protocol-specific MOP.

11.4 Sentinel Dosing

Sentinel dosing in Cohorts 1 and 2 will consist of 2 volunteers in each cohort dosed 72 hours ahead of the remainder of each cohort, with the remainder of the volunteers dosed at the same dose level only if no halting rules are met. Enrollment in Cohort 2 will only proceed if safety data from all volunteers in Cohort 1 meet the dose-escalation rules. There will be no sentinel dosing in Cohorts 3, 4, and 6.

11.5 Dose Escalation

After the planned 10 volunteers enrolled in Cohort 1 have completed their 7-day reactogenicity assessments, Day 8 safety laboratory assessments after vaccination, and no study halting rules have been met, GRT-R910 will be escalated to 30 mcg in Cohort 2.

Determinations of when to move from sentinels to the rest of the cohort, and for dose escalation in Cohort 2, are made by the protocol team consisting of all investigators and selected Gritstone team members (sub-investigators may be included).

11.6 Halting Rules

In the event a halting rule is met, all dosing will immediately stop, and a substantial amendment must be submitted and approved by the competent authority where required prior to allowing restart of any dosing:

- An unscheduled safety analysis will be required for approval of further enrollment, and
- Further administration of the vaccines is suspended for ALL subjects until an assessment by the study team takes place.
- All dosing will immediately stop.

11.6.1 Study Halting Criteria

- Any subject experiences an SAE within 28 days after administration of GRT-R910, considered related to GRT-R910.
- Any subject experiences laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of GRT-R910 that is considered related to GRT-R910.
- Any subject experiences ulceration, abscess, or necrosis at the injection site related to GRT-R910 administration.
- Four (4) or more subjects experience an allergic reaction such as generalized urticaria (defined as occurring at 3 or more body parts) within 72 hours (3 days) after administration of GRT-R910 that is considered related to GRT-R910.
- Five (5) or more subjects after <u>prime</u> dosing experience:
  - A Grade 3 unsolicited AE in the same preferred terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding that lasts at least 48 hours after administration of GRT-R910 and is considered related to GRT-R910.
  - A clinical laboratory abnormality within 28 days after administration of GRT-R910 that is classified as a Grade 3 AE and is considered related to GRT-R910.

- Five (5) or more subjects after booster dosing experience:
  - A Grade 3 unsolicited AE in the same preferred terms based on the MedDRA coding that lasts at least 48 hours after administration of GRT-R910 and is considered related to GRT-R910.
  - A clinical laboratory abnormality within 28 days after administration of GRT-R910 that is classified as a Grade 3 AE and is considered related to GRT-R910.

GRT-R910 administration and enrollment may resume only after review of the AEs that caused the halt in dosing results in recommendation to permit further study GRT-R910 administration and enrollments, and a substantial amendment has been submitted and approved prior to allowing restart of any dosing.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

This is a Phase 1, multi-center, open-label study of GRT-R910 used as a boost vaccine following prior vaccination with a first-generation vaccine, 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 the GRT-R910 vaccine in healthy adults 18 years and older. No hypothesis testing comparing the different vaccine schedule and cohorts will be performed.

12.2 Sample Size Considerations

The targeted sample size for each of the study cohorts was determined based on previous Phase 1 studies. Recruitment for GRT-R910 boost vaccination schedules will target enrolling 50 volunteers as follows:

- Cohort 1 (N=10, including 2 sentinels): 10 mcg GRT-R910 (after AstraZeneca) 2 doses, homologous prime-boost, booster dose will be 113 days (16 weeks) after the prime for adults ≥60 years of age.
- Cohort 2 (N=10, including 2 sentinels): 30 mcg GRT-R910 (after AstraZeneca) 2 doses, homologous prime-boost, booster dose will be 113 days (16 weeks) after the prime for adults ≥60 years of age.
- Cohort 3 (N=10): 10 mcg GRT-R910 (dose selected from Cohorts 1 and 2) after adenovirus-based vector vaccine, homologous prime-boost, booster dose will be 28 days after the prime for adults ≥60 years of age.
- Cohort 4 (N=10): 10 mcg GRT-R910 (dose selected from Cohorts 1 and 2) after mRNA vaccine, homologous prime-boost, booster dose will be 28 days after the prime for adults ≥60 years of age.
- Cohort 6 (N=10): 10 mcg GRT-R910 (dose selected from Cohorts 1 and 2) after mRNA vaccine, homologous prime-boost, booster dose will be 28 days after the prime for adults ≥18 to ≤59 years of age.

Sample size and power analysis 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 SAEs (see Section 11.1.2) can be expressed by the true event rate above which at least 1 SAE would likely be observed.

For each group of 10 subjects, there is an 89% chance of observing at least 1 event if the true rate is 20% or higher.

Binomial probabilities of observing at least 1 event among groups of size 10, 20, or 30 overall are presented in Table 5 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 5 Probability (%) of Detecting at Least 1 Adverse Event Under Different Incidence Rates

Incidence Rate (%)	Sample Size = 10	Sample Size = 20	Sample Size = 30
0.01	0.10	0.20	0.30
0.1	1.00	1.98	2.96
1.0	9.56	18.21	26.03
2.0	18.29	33.24	45.45
5.0	40.13	64.15	78.54
10.0	65.13	87.84	95.76
20.0	89.26	98.85	99.88

12.3 Treatment Assignment Procedures

12.3.1 Assignment Procedures

Cohorts 1 and 2 will be enrolled sequentially following dose-escalation rules. Two sentinels in each cohort will be observed for 72 hours for safety in each dose cohort. If no halting rules are met after the 2 sentinels in each cohort have been observed for 72 hours after study vaccination, the remaining 8 volunteers will be enrolled in each cohort.

The dose for Cohorts 3, 4, and 6 was selected from Cohorts 1 and 2 after evaluation of reactogenicity, safety, and initial immunogenicity. Dose selection will be determined by the Gritstone clinical team in consultation with the PI(s). Cohorts 3, 4, and 6 will be enrolled in parallel. There will be no sentinel dosing in Cohorts 3, 4, and 6.

12.3.2 Masking Procedures

Subjects and site staff will be unblinded as to subjects' cohort assignments.

12.4 Final Analysis Plan

This section describes the final study analyses. All safety data from enrolled subjects will be analyzed according to dose cohort and overall. 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 any dose of GRT-R910.

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 immunogenicity analysis population, defined as individuals who receive GRT-R910 at the expect dose level within the expected visit window and with at least some post-dose immunogenicity data.

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.

12.4.1 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.

12.4.2 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 GRT-R910 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 GRT-R910 vaccination through 28 days after GRT-R910 vaccination. Unsolicited AEs will be coded by MedDRA for preferred term and system organ class (SOC). All SAEs will be collected from the time of GRT-R910 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 1 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-vaccination visits.

12.4.3 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. Response will be defined as a 4-fold increase in antibody titer over baseline. Definitions of response as a 2-fold or 8-fold rise may also be explored. The number and percent of subjects achieving seroconversion by group and timepoint will be summarized,

including 95% exact confidence intervals. 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 time point. ELISpot results will be summarized by cytokine, group, peptide pool/stimulant, and time point using summary statistics and 95% confidence intervals.

12.4.4 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.

12.4.5 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.

13 ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol, and according to the Declaration of Helsinki, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), the ICH E6 Guideline for GCP, ICH-GCP, and applicable laws. This protocol, protocol amendments, IB (if applicable), and any accompanying material will be submitted by the investigator to an EC for review and approval, as required by institution policies and applicable law. Documentation of EC approval of the protocol and ICF will be forwarded to the sponsor prior to patient recruitment.

The investigator will be responsible for the following:

- Ensuring a signed ICF exists for each patient enrolled in this study
- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with applicable national law and/or local regulations and in agreement with the requirements, policies, and procedures established by the EC
- Providing oversight of the conduct of the study at the sites and adherence to requirements of 21 CFR, ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.2 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patients or his/her legally authorized representative and answer all questions regarding the study. Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign an ICF that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the EC or study center. The medical record must include a statement that written ICF was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the ICF must also sign the ICF. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study before undergoing any study-related procedures. A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative and the original signed and dated ICF must be maintained with the patient's study records.

13.2.1 Other Informed Consent Procedures

Subject willingness to receive the GRT-R910 vaccine will be assessed and documented on the ICF.

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.

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 GRT-R910 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.

The stored samples will be labeled with anonymized identifiers 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 EC 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. 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 coronavirus vaccines, diagnostics, or therapeutics.

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 the 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 sites 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.

13.2.2 Secondary Use of Stored Specimens and Data

The research staff will seek the subjects' consent for extra and residual specimens to be stored and used for secondary research, including but not limited to immunological assays. The rights

and privacy of human subjects who participate in secondary 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 Gritstone's 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 technology and analytical methods raises the risk of re-identification, even when specimens are de-identified.

13.2.2.1 Consent for Secondary Research 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. Any use of the sample or data, however, will be presented in a separate protocol and require separate EC approval.

13.2.2.2 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 anonymized identifiers 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 EC review of the secondary research using coded specimens is required.

Residual/Repository Research Samples, upon written request and approval from Gritstone and any approvals required by the clinical research sites, may be shared for secondary research with investigators at the participating sites, with researchers at other sites or other institutions, or company-designated research laboratories. The samples will not be sold or used directly for production of any commercial product. Gritstone will authorize shipment from the Gritstone 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.

13.2.2.3 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All the individual subject data collected during this study will be made available after de-identification. The 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 Gritstone and any approvals required by the clinical research sites, data may be shared for secondary research with investigators/researchers. The data will be available for only the purpose outlined in the approved proposal.

13.3 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 Gritstone 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, with subject information appropriately anonymized, pseudonymized, or de-identified before any discussion of individual subject information. The study monitors 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 sites will permit access to such records to third parties only upon written request, and subject to any applicable privacy laws.

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 sites will be identified only by a coded number. Records will be coded and transported using secure transport containers. Study staff will ensure the subject is interviewed in a private location.

13.4 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 expenses related to their participation in this trial. Compensation will be in accordance with the local EC policies and procedures, and subject to EC approval.

If it is determined by the site's PI 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 sites. No financial compensation will be provided to the subject by Gritstone to the subject, or by the participating sites for any injury suffered due to participation in this trial.

14 SUPPORTING DOCUMENTATION

14.1 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. The clinical research sites will permit authorized representatives of Gritstone, 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, subjects' memory aid 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.

15 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written Gritstone-accepted site quality management plan, each participating site and its subcontractors are responsible for conducting routine QA and quality control (QC) activities to internally monitor study progress and protocol compliance. The site's PI 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's PI will ensure all study personnel are appropriately trained and current documentations are maintained on-site.

The DCC will implement QC procedures beginning with the data entry system and generate data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating sites for clarification and resolution.

16 DATA HANDLING AND RECORD KEEPING

16.1 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's PI and other study personnel on making corrections to the data collection forms and eCRF.

16.2 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's PI or appropriate sub-investigator.

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

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

16.3 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 Annex 11compliant internet data entry system provided by the study DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

16.4 Types of Data

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

16.5 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. 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's PI when these documents no longer need to be retained. The participating clinical research sites must contact Gritstone for authorization prior to the destruction of any study records.

17 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 PPD. Details of clinical site monitoring are documented in a 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 the participating clinical research sites, study staff and all study documentation according to the Gritstone/PPD-approved site monitoring plan. Study monitors will meet with all participating site's PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

18 PUBLICATION POLICY

18.1 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.

18.2 Human Data Sharing Plan

This study will be conducted in accordance with Gritstone publication and data sharing policies and regulations, which ensures that the public has access to the published results of Gritstone-funded research via the digital archive PubMed Central upon acceptance for publication.

18.3 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 peer-reviewed scientific journal.

19 REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. Feb 15 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

2. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. Apr 2020;5(4):536-544. doi:10.1038/s41564-020-0695-z

3. Peiris JS, Yuen KY, Osterhaus AD, Stohr K. The severe acute respiratory syndrome. *N Engl J Med*. Dec 18 2003;349(25):2431-41. doi:10.1056/NEJMra032498

4. Arabi YM, Balkhy HH, Hayden FG, et al. Middle East Respiratory Syndrome. *N Engl J Med*. Feb 9 2017;376(6):584-594. doi:10.1056/NEJMsr1408795

5. World Health Organization (WHO). *Coronavirus disease 2019 (COVID-19) Situation Report –51. Data as reported by national authorities by 10 AM CET 11 March 2020.* . 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10

6. Masters P, Perlman S. *Coronaviridae*. 6th ed. vol 2. Fields Virology. Lippincott Williams & Wilkins, a Wolters Kluwer business; 2013:2456.

7. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. *Proc Natl Acad Sci U S A*. Apr 28 2020;117(17):9241-9243. doi:10.1073/pnas.2004999117

8. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020;6:14. doi:10.1038/s41421-020-0153-3

9. Eden JS, Rockett R, Carter I, et al. An emergent clade of SARS-CoV-2 linked to returned travellers from Iran. *Virus Evol*. Jan 2020;6(1):veaa027. doi:10.1093/ve/veaa027

10. Stefanelli P, Faggioni G, Lo Presti A, et al. Whole genome and phylogenetic analysis of two SARS-CoV-2 strains isolated in Italy in January and February 2020: additional clues on multiple introductions and further circulation in Europe. *Euro Surveill*. Apr 2020;25(13)doi:10.2807/1560-7917.ES.2020.25.13.2000305

11. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. *Gene Rep*. Jun 2020;19:100682. doi:10.1016/j.genrep.2020.100682

12. Yuan M, Wu NC, Zhu X, et al. A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. *Science*. 2020:eabb7269. doi:10.1126/science.abb7269

13. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. Mar 30 2020;doi:10.1038/s41586-020-2180-5

14. Channappanavar R, Zhao J, Perlman S. T-cell-mediated immune response to respiratory coronaviruses. *Immunol Res*. Aug 2014;59(1-3):118-28. doi:10.1007/s12026-014-8534-z

15. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med*. Mar 18 2014;160(6):389-97. doi:10.7326/M13-2486

16. Mizumoto K, Saitoh M, Chowell G, Miyamatsu Y, Nishiura H. Estimating the risk of Middle East respiratory syndrome (MERS) death during the course of the outbreak in the Republic of Korea, 2015. *Int J Infect Dis*. Oct 2015;39:7-9. doi:10.1016/j.ijid.2015.08.005

17. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. *New England Journal of Medicine*. 2020;doi:10.1056/NEJMp2005630

18. Martin JE, Louder MK, Holman LA, et al. A SARS DNA vaccine induces neutralizing antibody and cellular immune responses in healthy adults in a Phase I clinical trial. *Vaccine*. Nov 2008;26(50):6338-43. doi:10.1016/j.vaccine.2008.09.026

19. Enjuanes L, Dediego ML, Alvarez E, Deming D, Sheahan T, Baric R. Vaccines to prevent severe acute respiratory syndrome coronavirus-induced disease. *Virus Res*. Apr 2008;133(1):45-62. doi:10.1016/j.virusres.2007.01.021

20. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. Jan 6 2021;doi:10.1126/science.abf4063

21. Chen W, Xu Z, Mu J, et al. Antibody response and viraemia during the course of severe acute respiratory syndrome (SARS)-associated coronavirus infection. *J Med Microbiol*. May 2004;53(Pt 5):435-438. doi:10.1099/jmm.0.45561-0

22. Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH. Disappearance of antibodies to SARS-associated coronavirus after recovery. *N Engl J Med*. Sep 13 2007;357(11):1162-3. doi:10.1056/NEJMc070348

23. Lee N, Chan PK, Ip M, et al. Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome. *J Clin Virol*. Feb 2006;35(2):179-84. doi:10.1016/j.jcv.2005.07.005

24. Liu W, Fontanet A, Zhang PH, et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *J Infect Dis*. Mar 15 2006;193(6):792-5. doi:10.1086/500469

25. Temperton NJ, Chan PK, Simmons G, et al. Longitudinally profiling neutralizing antibody response to SARS coronavirus with pseudotypes. *Emerg Infect Dis*. Mar 2005;11(3):411-6. doi:10.3201/eid1103.040906

26. Wu LP, Wang NC, Chang YH, et al. Duration of antibody responses after severe acute respiratory syndrome. *Emerg Infect Dis*. Oct 2007;13(10):1562-4. doi:10.3201/eid1310.070576

27. Zhang L, Zhang F, Yu W, et al. Antibody responses against SARS coronavirus are correlated with disease outcome of infected individuals. *J Med Virol*. Jan 2006;78(1):1-8. doi:10.1002/jmv.20499

28. Robbiani DF, Gaebler C, Muecksch F, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature*. Aug 2020;584(7821):437-442. doi:10.1038/s41586-020-2456-9

29. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med*. Aug 2020;26(8):1200-1204. doi:10.1038/s41591-020-0965-6

30. Marot S, Malet I, Leducq V, et al. Rapid decline of neutralizing antibodies against SARS-CoV-2 among infected healthcare workers. *Nat Commun*. Feb 8 2021;12(1):844. doi:10.1038/s41467-021-21111-9

31. Doria-Rose N, Suthar MS, Makowski M, et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *New England Journal of Medicine*. 2021;doi:10.1056/NEJMc2103916

32. Wan Y, Shang J, Sun S, et al. Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. *J Virol*. Feb 14 2020;94(5)doi:10.1128/JVI.02015-19

33. Waggoner JJ, Katzelnick LC, Burger-Calderon R, et al. Antibody-Dependent Enhancement of Severe Disease Is Mediated by Serum Viral Load in Pediatric Dengue Virus Infections. *J Infect Dis*. Apr 1 2020;doi:10.1093/infdis/jiz618

34. Roberts A, Deming D, Paddock CD, et al. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. *PLoS Pathog*. Jan 2007;3(1):e5. doi:10.1371/journal.ppat.0030005

35. Chen J, Lau YF, Lamirande EW, et al. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T-cells are important in control of SARS-CoV infection. *J Virol*. Feb 2010;84(3):1289-301. doi:10.1128/JVI.01281-09

36. Zhao J, Van Rooijen N, Perlman S. Evasion by stealth: inefficient immune activation underlies poor T-cell response and severe disease in SARS-CoV-infected mice. *PLoS Pathog*. Oct 2009;5(10):e1000636. doi:10.1371/journal.ppat.1000636

37. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. *J Pathol*. Jan 2015;235(2):185-95. doi:10.1002/path.4454

38. Zhao J, Perlman S. T-cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. *J Virol*. Sep 2010;84(18):9318-25. doi:10.1128/JVI.01049-10

39. Bolles M, Deming D, Long K, et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. *J Virol*. Dec 2011;85(23):12201-15. doi:10.1128/JVI.06048-11

40. van den Brand JM, Haagmans BL, van Riel D, Osterhaus AD, Kuiken T. The pathology and pathogenesis of experimental severe acute respiratory syndrome and influenza in animal models. *J Comp Pathol*. Jul 2014;151(1):83-112. doi:10.1016/j.jcpa.2014.01.004

41. Polack FP, Teng MN, Collins PL, et al. A role for immune complexes in enhanced respiratory syncytial virus disease. *J Exp Med*. Sep 16 2002;196(6):859-65. doi:10.1084/jem.20020781

42. Polack FP, Hoffman SJ, Crujeiras G, Griffin DE. A role for nonprotective complement-fixing antibodies with low avidity for measles virus in atypical measles. *Nat Med*. Sep 2003;9(9):1209-13. doi:10.1038/nm918

43. Graham BS, Henderson GS, Tang YW, Lu X, Neuzil KM, Colley DG. Priming immunization determines T helper cytokine mRNA expression patterns in lungs of mice challenged with respiratory syncytial virus. *J Immunol*. Aug 15 1993;151(4):2032-40.

44. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol*. Oct 2020;20(10):615-632. doi:10.1038/s41577-020-00434-6

45. Graham BS. Rapid COVID-19 vaccine development. *Science*. May 29 2020;368(6494):945-946. doi:10.1126/science.abb8923

46. Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to Phase 3 vaccine candidates. *Lancet*. Nov 14 2020;396(10262):1595-1606. doi:10.1016/S0140-6736(20)32137-1

47. Phan T. Genetic diversity and evolution of SARS-CoV-2. *Infect Genet Evol*. Feb 21 2020;81:104260. doi:10.1016/j.meegid.2020.104260

48. Chen H, Hou J, Jiang X, et al. Response of memory CD8+ T-cells to severe acute respiratory syndrome (SARS) coronavirus in recovered SARS patients and healthy individuals. *J Immunol*. Jul 1 2005;175(1):591-8. doi:10.4049/jimmunol.175.1.591

49. Zhou M, Xu D, Li X, et al. Screening and identification of severe acute respiratory syndrome-associated coronavirus-specific CTL epitopes. *J Immunol*. Aug 15 2006;177(4):2138-45. doi:10.4049/jimmunol.177.4.2138

50. Xu X, Gao X. Immunological responses against SARS-coronavirus infection in humans. *Cell Mol Immunol*. Apr 2004;1(2):119-22.

51. Wang YD, Sin WY, Xu GB, et al. T-cell epitopes in severe acute respiratory syndrome (SARS) coronavirus spike protein elicit a specific T-cell immune response in patients who recover from SARS. *J Virol*. Jun 2004;78(11):5612-8. doi:10.1128/JVI.78.11.5612-5618.2004

52. Wang B, Chen H, Jiang X, et al. Identification of an HLA-A*0201-restricted CD8+ T-cell epitope SSp-1 of SARS-CoV spike protein. *Blood*. Jul 1 2004;104(1):200-6. doi:10.1182/blood-2003-11-4072

53. Tsao YP, Lin JY, Jan JT, et al. HLA-A*0201 T-cell epitopes in severe acute respiratory syndrome (SARS) coronavirus nucleocapsid and spike proteins. *Biochem Biophys Res Commun*. May 26 2006;344(1):63-71. doi:10.1016/j.bbrc.2006.03.152

54. Lv Y, Ruan Z, Wang L, Ni B, Wu Y. Identification of a novel conserved HLA-A*0201-restricted epitope from the spike protein of SARS-CoV. *BMC Immunol*. Dec 3 2009;10:61. doi:10.1186/1471-2172-10-61

55. Peng H, Yang LT, Wang LY, et al. Long-lived memory T lymphocyte responses against SARS coronavirus nucleocapsid protein in SARS-recovered patients. *Virology*. Aug 1 2006;351(2):466-75. doi:10.1016/j.virol.2006.03.036

56. Li T, Xie J, He Y, et al. Long-term persistence of robust antibody and cytotoxic T-cell responses in recovered patients infected with SARS coronavirus. *PLoS One*. Dec 20 2006;1:e24. doi:10.1371/journal.pone.0000024

57. Oh HL, Chia A, Chang CX, et al. Engineering T-cells specific for a dominant severe acute respiratory syndrome coronavirus CD8 T-cell epitope. *J Virol*. Oct 2011;85(20):10464-71. doi:10.1128/JVI.05039-11

58. Li CK, Wu H, Yan H, et al. T-cell responses to whole SARS coronavirus in humans. *J Immunol*. Oct 15 2008;181(8):5490-500. doi:10.4049/jimmunol.181.8.5490

59. Yang L, Peng H, Zhu Z, et al. Persistent memory CD4+ and CD8+ T-cell responses in recovered severe acute respiratory syndrome (SARS) patients to SARS coronavirus M antigen. *J Gen Virol*. Oct 2007;88(Pt 10):2740-8. doi:10.1099/vir.0.82839-0

60. Peng H, Yang LT, Li J, et al. Human memory T-cell responses to SARS-CoV E protein. *Microbes Infect*. Aug 2006;8(9-10):2424-31. doi:10.1016/j.micinf.2006.05.008

61. Libraty DH, O'Neil KM, Baker LM, Acosta LP, Olveda RM. Human CD4(+) memory T-lymphocyte responses to SARS coronavirus infection. *Virology*. Nov 25 2007;368(2):317-21. doi:10.1016/j.virol.2007.07.015

62. Tang F, Quan Y, Xin ZT, et al. Lack of peripheral memory B-cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J Immunol*. Jun 15 2011;186(12):7264-8. doi:10.4049/jimmunol.0903490

63. Tarke A, Sidney J, Kidd CK, et al. Comprehensive analysis of T-cell immunodominance and immunoprevalence of SARS-CoV-2 epitopes in COVID-19 cases. *bioRxiv*. Dec 9 2020;doi:10.1101/2020.12.08.416750

64. Mateus J, Grifoni A, Tarke A, et al. Selective and cross-reactive SARS-CoV-2 T-cell epitopes in unexposed humans. *Science*. Oct 2 2020;370(6512):89-94. doi:10.1126/science.abd3871

65. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T-cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell*. Jun 25 2020;181(7):1489-1501 e15. doi:10.1016/j.cell.2020.05.015

66. Janice Oh HL, Ken-En Gan S, Bertoletti A, Tan YJ. Understanding the T-cell immune response in SARS coronavirus infection. *Emerg Microbes Infect*. Sep 2012;1(9):e23. doi:10.1038/emi.2012.26

67. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nature Medicine*. 2020/03/16 2020;doi:10.1038/s41591-020-0819-2

68. Wu F, Wang A, Liu M, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *medRxiv*. 2020:2020.03.30.20047365. doi:10.1101/2020.03.30.20047365

69. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020:S2213-2600(20)30079-5. doi:10.1016/S2213-2600(20)30079-5

70. Salam N, Rane S, Das R, et al. T-cell ageing: effects of age on development, survival & function. *Indian J Med Res*. 2013;138(5):595-608.

71. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet*. 2021;398(10309):1407-1416. doi:10.1016/S0140-6736(21)02183-8.

72. Bloom K, van den Berg F, Arbuthnot P. Self-amplifying RNA vaccines for infectious diseases. *Gene Ther*. Oct 22 2020;doi:10.1038/s41434-020-00204-y

73. Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature*. Oct 2020;586(7830):567-571. doi:10.1038/s41586-020-2622-0

74. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N Engl J Med*. Dec 17 2020;383(25):2427-2438. doi:10.1056/NEJMoa2028436

75. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. Dec 30 2020;doi:10.1056/NEJMoa2035389

76. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. Dec 31 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

77. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med*. Dec 17 2020;383(25):2439-2450. doi:10.1056/NEJMoa2027906

78. Gazit S, Shlezinger R, Perez G, et al. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. *medRxiv*. 2021.08.24.21262415. doi:10.1101/2021.08.24.21262415

79. Stroud C, Walker LR, Davis M, et al. Investing in the health and well-being of young adults. *Journal of Adolescent Health*. 2015;56(2):127-9.

80. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020 website. *MMWR Morb Mortal Wkly Rep.* 2020;69:343–346.