Protocol

Protocol for: Atmar RL, Lyke KE, Deming ME, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med. DOI: 10.1056/NEJMoa2116414

This trial protocol has been provided by the authors to give readers additional information about the work.

Supplement Describing Protocol DMID #21-0012 versions and Statistical Analysis Plan

This supplement contains the following items:

A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines

DMID Protocol Number: 21-0012

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

Version Number: 1.0

14 April 2021

STATEMENT OF COMPLIANCE

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

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

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

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

Site Investigator Signature:

Signed: _____ Date: _____

Name, Credentials

Title

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1. PROTOCOL SUMMARY

1.1 Synopsis

Title: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines.

Phase: Phase 1/2

Population: Approximately 400 healthy individuals aged ≥ 18 years

Sites: Approximately 12 clinical research sites.

Rationale:

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causative agent of the coronavirus disease of 2019 (COVID-19) pandemic, has infected over 126 million people worldwide and resulted in over 2.7 million deaths, including > 548,000 in the United States (March 27, 2021, WHO; www.who.int). Multiple Phase 3 efficacy trials of SARS-CoV-2 vaccine constructs are underway or in long-term follow-up in the U.S, and these studies have supported 3 Emergency Use Authorizations (EUAs) for COVID vaccines. The emergence of variant strains has raised concerns about the breadth of immunity and protection achieved by the current vaccines. WHO SAGE and CDC ACIP have identified the safety and immunogenicity of mixed schedules as a critical and immediate research priority to inform policy on the use of mixed schedules.

Knowledge of the safety, tolerability, and immunogenicity of a boost vaccine using a heterologous platform with the homologous or variant spike lineage administered after an EUA primary dosing is a critical piece of information needed to inform public health decisions. The heterologous boost strategy will also provide an opportunity to thoroughly evaluate innate, cellular, and humoral immune responses elicited from the multiple prime boost combinations using very similar immunogens, utilizing mRNA, adenovirus- vectored, and protein-based platforms. As new vaccines are manufactured to emerging variants, these foundational data will be key to the evaluation of future variant and heterologous prime-boost strategies. This phase 1/2 clinical trial will evaluate the safety and immunogenicity of different heterologous delayed doses (boosts) in those who received an EUA vaccine (either prior to participation in this trial, or as part of this trial).

Objectives:

Primary:

1. To evaluate the safety and reactogenicity of delayed heterologous or homologous vaccine doses after EUA dosed vaccines:

    - Local and systemic solicited adverse events for 7 days following the delayed boost dose.
    - Adverse Events from Dose 1 to 28 days following delayed boost dose.

- Related MAAEs, SAEs, and AESI from Dose 1 on study to month 12 months after last dose on study.

2. To evaluate humoral immunogenicity of heterologous booster vaccines following EUA dosing.

Exploratory:

1. To assess, in at least a subset of samples, the B cell immune response following EUA vaccination and delayed boost;
2. To assess, in at least a subset of samples, the SARS-CoV-2 protein-specific T cell responses following EUA vaccination and delayed boost

Study Design:

This Phase 1/2 study will evaluate the safety, tolerability, immunogenicity of different SARS-CoV-2 vaccine delayed boost at >12 weeks. This study will be composed of two different cohorts:

1. A cohort of persons previously vaccinated with an EUA vaccine who will be boosted with a homologous or heterologous vaccine strain on a homologous or a heterologous platform (Table 1); and
2. A cohort of persons who are prospectively vaccinated with EUA standard dosing and who will be available for rapid assessment of a heterologous boost at some point in the future (Table 2).

EUA-dosed Cohort: Cohort 1 will recruit persons who have previously received COVID-19 vaccine under EUA dosing guidelines, in the prior 12-20 weeks. Eligible individuals will be stratified by age (18-55 years or > 56 years) in a 1:1 ratio (N = 25/group). Subjects will be sequentially enrolled to receive one of the available delayed boost options (Table 1). A total of 50 per group will be recruited for the EUA-dosed Cohort 1. This study is designed to be adaptive, and as more vaccines become available under EUA or new variants of available EUA vaccine become available, the number of groups may be expanded. Participants will be assessed for safety and tolerability endpoints following administration of a delayed boost.

Table 1: EUA-dosed Cohort 1

Group	Sample Size*	EUA Dosing Scheme	Interval (weeks)	Delayed Booster Vaccination	Strategy Tested
1E	**50**	Previously dosed Janssen – Ad26.COV2-S	12-20	Moderna- mRNA-1273	 Same Strain Heterologous platform
2E	**50**	Previously dosed Moderna – mRNA-1273	12-20	Moderna- mRNA-1273	 Control - Same Strain & platform
3E	**50**	Previously dosed Pfizer/BioNTech – mRNA- BNT162b2	12-20	Moderna- mRNA-1273	 Same Strain Similar platform

*Sample cohort size, N = 50, two age strata: 18-55 years (n = 25), 56+ years (n = 25)

Prospective Cohort: Cohort 2 will recruit persons who are naïve to COVID-19 vaccine and infection (by history). These individuals will be given a vaccine as part of the study that matches the vaccine/dose available under an EUA. Currently, this includes the Moderna mRNA-1273 vaccine only, but it could include other vaccines in the future. Cohorts from this pool will then be available to be boosted with a novel homologous or heterologous variant lineage spike proteins or heterologous platform delayed boost as part of an adaptive design meant to respond quickly to circulating SARS-CoV-2 variants. As new vaccines are manufactured to emerging variant lineages, these dosed "pools" of study participants will enable rapid deployment of delayed booster constructs.

Prioritization of Cohort 1 versus Cohort 2 enrollment will be determined by availability of EUA-dosed vaccines, status of distribution, and current epidemiology. Cohort 1 and 2 may enroll simultaneously.

Table 2: Prospective Cohort 2

Group	Sample Size*	First Vaccination**	Interval	Second Vaccination88	Interval (Weeks)	Delayed Booster Vaccination
1	**250**	Moderna-mRNA-1273	28d	Modern- mRNA-1273	>12	Novel homologous or heterologous variant or heterologous platform boost

*Aged ≥ 18 years

** As part of an adaptive design, products newly awarded EUA can be added (e.g., Janssen Ad26.COV2.S and Novavax NVX-CoV2373)

Duration of Study: Approximately 4 years

Duration of participation per subject: Up to 2 years (approximately 12 months after delay boost inoculation)

Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Participants must meet all of the following criteria to be eligible to participate in this study:

1. Individuals ≥ 18 years of age at the time of consent.
2. Received and completed COVID-19 vaccine under EUA dosing guidelines at least 12 weeks and no more than 20 weeks prior to enrollment (Cohort 1 only).
3. Willing and able to comply with all scheduled visits, vaccination plan, laboratory tests and other study procedures.
4. Determined by medical history, targeted physician examination and clinical judgeme
5.
6. nt of the investigator to be in good health.

   Note: Heathy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.
7. Female participants of childbearing potential may be enrolled in the study, if all of the following apply:

   - Practiced adequate contraception for 28 days prior to the first dose of vaccine (Day 1),
   - Has agreed to continue adequate contraception through 3 months following the booster dose,
   - Has a negative pregnancy test at screening and on the day of the first vaccine dose (Day 1),
   - Is not currently breastfeeding.

Exclusion Criteria:

Participants meeting any of the following criteria will be excluded from the study:

1. Known history of SARS-CoV-2 infection.
2. Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or SARS-CoV-2 monoclonal antibody in the preceding 90 days or current/planned simultaneous participation in another interventional study.
3. Receipt of SARS CoV-2 vaccine prior to study entry (Cohort 2 only).

4. A history of anaphylaxis, urticaria, or other significant adverse reaction requiring medical intervention after receipt of a vaccine or nanolipid particles.
5. Receipt of any investigational study product within 28 days prior to enrollment.
6. Received or plans to receive a vaccine within 28 days prior to the first dose (Day 1) or plans to receive a non-study vaccine within 28 days prior to or after any dose of study vaccine (with exception for seasonal influenza vaccine within 14 days of study vaccine).
7. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with intramuscular injections or blood draws.
8. Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.
9. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to Day 1.
10. Received immunoglobulin, blood-derived products, within 90 days prior to first study vaccination.
11. An immediate family member or household member of this study's personnel.
12. Is acutely ill or febrile 72 hours prior to or at vaccine dosing (fever defined as ≥ 38.0°C/100.4°F). Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

Safety

- The study will use halting rules for booster vaccination in the study overall and not EUA dosed vaccinations to individual subjects. See Section 7.1 for details.
- This study will use a Safety Monitoring Committee (SMC) for objective oversight of the study. SMC reviews are required for study halting.

1.2 Schedule of Activities (SOA)

Table 3: SOA for EUA-dosed Cohort 1

Study Day	D-28 to D-1	1	8[b]	15	29	91	169	366	Illness/ Unscheduled Visit	Early Termination Visit
Visit Number	00[a]	1	2	3	4	5	6	7		
Window (+/-)		0	1	2	2	7	7	14		
Informed Consent[a]	X									
Eligibility Criteria	X	X								
Medical History	X	X								
Vaccination[c]		X								
Concomitant Meds		X	X	X	X					
Interim History		X	X	X	X	X	X	X	X	X
Physician Exam - Targeted	X	X		X	X	X	X	X	X	X
Vital Signs[d]	X	X		X	X				X	X
Height/Weight (BMI)[a]	X									
Urine β-HCG[e]		X								
Memory Aid, Solicited AEs		X	X	X[f]						
Unsolicited AEs		X	X	X	X					
SAEs, Protocol specified AESIs, MAAEs, and NOCMCs			X	X	X	X	X	X	X	X
Nasal swab for PCR & Sequencing									X[g]	
Immunoassays										
Serum- Humoral Assays		32		32	32	32	32	32		32
PBMC Cellular Assays & plasma		64		64			64	64		64
Daily Volume (mL)		96		96	32	32	96	96		96
Cumulative Volume (mL)		96		192	224	256	352	448		

[a] Optional screening visit – informed consent and height/weight only performed at screening or Day 1

[b] Telephone visit

[c] Delayed booster dose based upon assignment to Groups 1E-3E (and/or future groups added as adaptive design)

[d] Vital signs before and after booster vaccination. Otherwise, only as clinically indicated

[e] For women of childbearing potential, a negative urine pregnancy on Day 1 will be performed with negative results confirmed before dosing

[f] Collect 7-day Memory Aid and assess for delayed onset local reactions

[g] Collect nasal swab for PCR. Sequencing will be performed on all Illness visit-confirmed SARS-CoV-2 specimens.

Table 4: SOA for Prospective Cohort 2:

Study Day	D-28 to D-1	1	8[b]	29	36[b]	43	Delayed Boost to occur > 12 weeks from completion of EUA dosing.	1B	15B	29B	91B	169B	366B	Illness/ Unsch Visit	Early Term Visit
Visit Number	00[a]	1	2	4	5	6		7	8	9	10	11	12		
Window (+/-)		0	1	2	7	7			2	2	7	7	28		
Informed Consent[a]	X														
Eligibility Criteria	X	X		X				X							
Medical History	X														
Vaccination		X[c]		X[c]				X[d]							
Concomitant Meds	X	X	X	X	X	X		X	X	X					
Interim History		X	X	X	X	X		X	X	X	X	X	X	X	X
Physician Exam - Targeted	X	X		X		X		X	X	X	X	X	X	X	X
Vital Signs[e]	X	X		X				X	X	X				X	
Height/Weight (BMI)[a]	X														
Urine β-HCG[f]		X		X				X							
Memory Aid, Solicited AEs		X	X	X	X			X	X[g]						
Unsolicited AEs		X	X	X	X	X		X	X	X					
SAEs, Protocol specified AESIs, MAAEs, and NOCMCs			X	X	X	X		X	X	X	X	X	X	X	X
Nasal swab for PCR & Sequencing														X[h]	
Immunoassays															
Serum- Humoral Assays		32		32		32		32	32	32	32	32	32		32
PBMC Cellular Assays & plasma		64*		64*		64*		64	64		64	64	64		64
Daily Volume (mL)		96		32		32		96	96	32	96	96	96		96
Cumulative Volume (mL)		96		128		160		256	352	384	480	576	672		

[a] Optional screening visit – informed consent and height/weight only performed at screening or Day 1

[b] Telephone visit

[c] EUA-dosing with 28-day interval – new constructs may be added as EUA is awarded and vaccine available

[d] Delayed booster dose based upon assignment of variant and/or heterologous vaccine constructs added as adaptive design. If no booster administered; volunteer will not proceed to additional visits except for unscheduled illness visits

[e] Vital signs before and after vaccination. Otherwise, only as clinically indicated.

[f] For women of childbearing potential, a negative urine pregnancy test on Days 1 and 1B (delayed boost) will be performed with negative results confirmed prior to each dosing

[g] Collect 7-day Memory Aid for delayed booster dose and assess for delayed onset local reactions

[h] Collect nasal swab for PCR. Sequencing will be performed on all Illness visit-confirmed SARS-CoV-2 specimens.

*Collection of PBMC for cellular assays is performed at the discretion of the site, based on the capacity for PBMC processing

2. INTRODUCTION

2.1 Background and Study Rationale

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first detected in Wuhan, Hubei Province, China in December 2019. The corresponding illness designation, coronavirus disease 2019 (COVID-19), was declared as a pandemic respiratory illness on 11 May 2020.[1] As of 3 April 2021, it has infected over 130 million people worldwide and resulted in over 2.8 million deaths, including > 554,000 in the United States.[1,2]

Five Phase 3 efficacy trials of SARS-CoV-2 vaccine constructs are underway or in long-term follow-up in the U.S., through U.S. government efforts funded by the Biomedical Advanced Research and Development Authority (BARDA) and National Institutes of Health (NIH). Vaccine testing centers have prioritized research studies as part of three Phase 3, 2-dose trials in various stages of conduct (Moderna, AstraZeneca/Oxford, Novavax), one Phase 3 single-dose trial (Janssen – 2-dose testing underway internationally) and one privately funded, 2-dose trial (Pfizer/BioNTech). The ModernaTX, Inc mRNA-1273 and Pfizer/BioNTech BNT162b2 mRNA platforms encode for the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S-2P) in a prefusion conformation, derived from the Wuhan-Hu-1 strain.[3] The Janssen Pharmaceutical/Johnson & Johnson COVID-19 Vaccine (Ad26.COV.2) is composed of recombinant, replication-incompetent human adenovirus type 26, encoding a prefusion-stabilized SARS-CoV-2 spike antigen.[4] Studies of the Pfizer and Moderna mRNA vaccines demonstrated high efficacy against all symptomatic and severe disease and received Emergency Use Authorization (EUA) on December 12 and 18, 2020, respectively. Similarly, Janssen Pharmaceuticals reported 66% vaccine efficacy with a single dose and high-level protection against severe disease and death. FDA EUA was issued on February 26, 2021. AstraZeneca/Oxford's (ChAdOx-2) is expected to undergo FDA review for EUA shortly and Novavax is rapidly approaching its Phase 3 endpoint for interim analysis of vaccine efficacy. It is anticipated that the U.S. could have up to 5 different COVID-19 products under EUA by the end of second quarter 2021.

The optimization and distribution of SARS-CoV-2 vaccines is of critical public health priority. The inability to mass-vaccinate the world's population in a timely fashion is resulting in ongoing high-level transmission and accelerated emergence of variants with mutations in the S protein. Moreover, the evolution of variant strains may favor immune escape or reinfection among previously infected or vaccinated individuals. A variant first identified in South Africa (B.1.351) is associated with increased transmission, higher viral burden, and possibly increased mortality in infected persons.[5] The emergence of variant strains has raised concerns about the breadth of immunity and protection achieved by the current vaccines. Pivotal studies testing both viral vector and adjuvanted protein technologies had lower efficacy in regions where B.1.351 was known to be circulating.[6,7] Sera from individuals vaccinated with mRNA-based vaccines had a 6-to-9-fold reduction in neutralizing activity against a B.1.351-matched pseudovirion relative to a Wuhan-matched pseudovirion.[8,9] WHO SAGE and CDC ACIP have identified the safety and immunogenicity of mixed schedules as a critical and immediate research priority to inform policy on the use of mixed schedules. Vaccine manufacturers are working on variant booster candidates

to optimize efficacy against the B.1.1.7, B.1.351 and Brazilian P1 and P2 rapidly emerging variants with receptor binding domain mutations. For example, mRNA-1273.211, like mRNA-1273, encodes the prefusion stabilized S protein of SARS-CoV-2, but incorporates the key mutations present in the B.1.351 viral strain. A phase 1 clinical trial to examine the immunological benefit of boosting subjects previously vaccinated with mRNA-1273 (DMID 20-0003) with the B.1.351 strain-specific S protein is underway.

Prime-boost strategies may enhance immunogenicity through complementary stimulation of humoral and T cell immune pathways. In contrast, the immune response to booster doses of certain vaccines, such as the adenovirus vector vaccines, may be limited by pre-existing antibody and/or enhanced by longer dosing intervals. Thus, the order of delivery of heterologous SARS-CoV-2 vaccine platforms may result in immune responses that are greater or less than homologous regimens of the same vaccine. In a murine model, a self-amplifying RNA vaccine followed by the adenovirus vectored vaccine (ChAdOx1-nCoV-19/AZD1222) was shown to induce high titers of neutralizing antibodies (although was not tested against a two-dose homologous regimen).[10] In humans, the Gam-COVID-Vac combined vector vaccine consisting of rAD26 carrying the full-length glycoprotein S (rAD26-S) (prime) and rAd5-S administered after 21 days as a boost, demonstrated 91.6% efficacy in adults < 60 years of age and illustrates the potential vaccine efficacy with a heterologous prime/boost strategy.[11] The United Kingdom (UK) announced plans (4 Feb 2021) to test a mix-and-match approach (at 4- and 12-week intervals) with currently UK-approved vaccines. Testing of the Pfizer/BioNTech's (BNT162b2) followed by AstraZeneca/Oxford's (ChAdOx-2) and vice versa is underway in the UK.

Knowledge of the safety, tolerability, and immunogenicity of a delayed heterologous boost vaccine incorporating a similar or variant spike administered following EUA dosing regimens might induce immunity to variant circulating strains and improve upon breadth and durability of protection. Utilizing the EUA-dosed COVID-19 vaccines available (currently mRNA-1273, mRNA-BNT162b2, and AD26.COV2.S), we propose to evaluate innate, cellular, and humoral immune responses elicited from multiple prime boost combinations, utilizing the mRNA with homologous spike protein as a boost while seeking to avoid duplicating trial designs currently in planning stages or in process. As part of an adaptive design, we anticipate adding groups with variant-lineage spike proteins and other vaccine platforms such as the adenovirus vectored platforms as booster doses, subject to availability.

2.1.1 Public Readiness and Emergency Preparedness Act

The study vaccines, mRNA-1273, mRNA-BNT162b2, and Ad26.COV.2, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273. The PREP Act provides immunity for covered persons from liability unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 10, 2020 and is retroactively effective from February 4, 2020.

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

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

If the Secretary of DHHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the initial immunization with mRNA-1273 vaccine and delayed booster inoculation of mRNA-1273, 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.

Risks of mRNA-1273

Immediate systemic allergic reactions (e.g., anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein.[12]

Anaphylactic reactions have occurred after administration of the Moderna and the Pfizer mRNA COVID-19 vaccines in vaccination campaigns under Emergency Use Authorization (EUA) in the United States. Most of these reactions had onset within 30 minutes of vaccination, most of these events occurred in persons with a prior history of allergy, and nearly all were women. The currently estimated risk of an anaphylactic reaction to the Moderna EUA COVID-19 vaccine is about 3 events per million vaccinations.

As a precaution, all subjects will remain under observation at the study site for at least 30 minutes after injection.

Infrequently, people who have received dermal fillers might experience swelling at or near the site of filler injection (usually face or lips) following administration of a dose of an mRNA COVID-19 vaccine. The swelling appears to be temporary and resolves with medical treatment, including corticosteroid therapy. COVID-19 vaccines can be administered to people who have received injectable dermal fillers who have no contraindications or precautions for vaccination.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by ModernaTX, Inc containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection. A small percentage of participants may experience late local inflammatory reactions, with onset seven or more days after, usually the first, vaccination, and characterized by redness in the deltoid area of the upper arm and/or pain or itching.[13] These reactions are self-limited and are not a contraindication to subsequent vaccinations in the vaccination series.

The majority of local and systemic solicited adverse events (AEs) observed after injection with mRNA-1273 at the 100-mcg dose level have been mild to moderate in severity. The most commonly reported systemic AEs were headache, myalgia, fatigue, chills, and fever.[13] In the majority of cases, the reactions resolved spontaneously within several days. Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline, pre-vaccination (Day 1) values over time. The clinical significance of these observations is unknown.

There is limited experience with administration of a third dose of the mRNA COVID-19 vaccines, and it is possible that the third dose may be associated with more frequent or more severe adverse events.

Further details are provided in the current IB for mRNA-1273.

Risks to Privacy

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

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

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

Risks of Genetic Testing

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

2.2.2 Known Potential Benefits

In cohort 2, there is the potential for protection against symptomatic SARS-CoV-2 infection following receipt of an EUA vaccine. There is no direct benefit to the subjects in Cohort 1 or from the booster vaccination in Cohort 2. There is potential benefit to society resulting from insights gained from participation in this study due to the emerging threat of the SARS-CoV-2 outbreak. Data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 demonstrated 94.1% efficacy of the vaccine as a two-vaccination series versus placebo against SARS-CoV-2 infection. The doses and vaccination strategies used in this trial may or may not alter this protection.

3. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of delayed heterologous or homologous vaccine doses after EUA dosed vaccines.	• Local and systemic solicited adverse events for 7 days following the delayed boost dose. • Adverse Events from Dose 1 to 28 days following delayed boost dose Related MAAEs, SAEs, and AESI from Dose 1 on study to month 12 months after last dose on study.
• To evaluate the breadth of the humoral immune responses of heterologous and homologous delayed boost regimens following EUA dosing	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization titers in serum samples as assessed via a range of assays at all timepoints.
Secondary	
• None	• None
Exploratory	
• To assess, in at least a subset of samples, the B cell immune response following EUA vaccination and delayed boost	• Magnitude, phenotype and percentage of SARS-CoV-2 specific B cells, as measured by flow cytometry and targeted B cell subset analysis at time points post-vaccination and/or delayed boost.
• To assess, in at least a subset of samples, the SARS-CoV-2 protein-specific T cell responses following EUA vaccination and delayed boost	• Magnitude, phenotype, and percentage of cytokine producing S protein T cells as measured by flow cytometry at time points post-vaccination and/or delayed boost.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• To evaluate breakthrough symptomatic SARS-CoV-2 infection and sequence strains to assess for variant spike lineage	• To perform sequence analysis on breakthrough NAAT-confirmed COVID-19 strains to assess for variant spike lineage

4. STUDY DESIGN

4.1 Overall Design

This is a phase 1/2, open-label clinical trial in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed (>12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; mRNA-BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson) This is an adaptive design and may add arms (and increase sample size) as vaccines are awarded EUA and/or variant lineage spike vaccines are manufactured or become available. Enrollment will occur at approximately twelve domestic clinical research sites.

This study includes two cohorts. Cohort 1 will provide rapid information about the safety, reactogenicity, and immunogenicity of delayed boost in a previously EUA-dosed group. This cohort can inform near term public health decisions if the variant virus becomes more widespread. Cohort 2 is an adaptive cohort that will evaluate, in a prospective fashion, the safety, reactogenicity and immunogenicity of EUA-dosed vaccine followed by delayed boost. Pools of subjects will be recruited to receive EUA-dosed vaccine and will be assigned, at a later date, to a delayed booster vaccine based on availability of vaccine product, to enable rapid implementation based on situational assessment of need. This cohort will take longer to provide information on the immunogenicity of delayed boost, but it may assume priority in enrollment as it is important to inform future public health strategies and as access to COVID-19 vaccine becomes more widespread. As Cohorts 1 and 2 are in different populations, they can be enrolled in parallel or prioritized as determined by DMID/IDCRC needs.

Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and > 56 years) who received previously COVID-19 vaccine at EUA dosing (two vaccinations of mRNA-1273 at the 100 mcg dose, two vaccinations of mRNA-BNT162b2 at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the $5x10^{10}$ vp dose). Those subjects will be offered enrollment into this study 12-20 weeks after they received the last dose of their EUA vaccine. Subjects will receive an open-label delayed boost that is assigned to each of the approximately twelve domestic trial sites.

1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by:
    - Group 1E – A 100-mcg dose of mRNA-1273
2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by:
    - Group 2E – A 100-mcg dose of mRNA-1273
3. Previously EUA-dosed vaccination with Pfizer/BioNTech - mRNA-BNT162b2 at 30 mcg for two doses followed by:
    - Group 3E – A 100-mcg dose of mRNA-1273

The anticipated sample size of each group is approximately 25 subjects 18 through 55 years of age and approximately 25 subjects 56 years of age and older for a total of 50 subjects per group.

Subjects in Cohort 1 will receive a single intramuscular (IM) injection of the designated delayed booster vaccine and will be followed through 12 months after vaccination. A telephone visit will occur at Day 8 and in-person follow-up visits will occur on Days 15 and 29, as well as 3, 6, and 12 months after the vaccination.

Table 6. Cohort 1 Treatment Arms

Arm	Sample Size	Booster Vaccination Product and Dose
1E	~50	100 mcg mRNA-1273
2E	~50	100 mcg mRNA-1273
3E	~50	100 mcg mRNA-1273

Summary of Treatment Arms:

- 1E – Evaluates a heterologous platform booster dose of mRNA-1273 among persons who previously received an Ad26.COV2.S EUA vaccination series
- 2E- As a bridging arm evaluates a homologous platform third boosting dose of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series
- 3E – Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received a mRNA-BNT162b2 EUA vaccination series

Cohort 2 will include approximately 250 participants per group aged $\geq$ 18 years of age who have not received a COVID-19 vaccine and have no known history of COVID-19 or SARS-CoV-2 infection. They will be assigned to receive COVID-19 vaccine under EUA dosing (as outlined in Table 7). Additional pools of subjects can be included as additional COVID-19 vaccines are awarded EUA (e.g., Janssen – Ad26.COV2.S or Novavax- NVX-CoV2373). These pools of participants will be assigned a novel homologous or heterologous variant boost or heterologous platform boost at a minimum of 12 weeks following receipt of EUA dosing and followed through 12 months after the last vaccination. A telephone visit will occur one week after each primary EUA

vaccination. In person follow-up visits will occur on 14 days following completion of EUA vaccinations and on days 14, and 28 days after the booster dose, as well as 3, 6, and 12 months post the booster vaccination.

Table 7: Cohort 2 Treatment Arms

Group	Sample Size	First Vaccination	Second Vaccination		Booster Vaccination	
		Product and Dose	Interval	Product and Dose	Interval	Product and Dose
1	250	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273	> 12 weeks	Novel homologous/ heterologous variant or heterologous platform boost

For both Cohorts 1 and 2, reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays.

After the IND is in effect, IRB review and approval, and site activation, the participating sites will begin recruitment outreach efforts, which can include fliers, letters, telephone calls, etc. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the participating site. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use. Screening can occur up to 28 days prior to the first dose and is optional prior to Dose 1.

Schedule of assessments are found in **Section 1.2, Schedule of Activities.**

4.2 Scientific Rationale for Study Design

This phase 1/2 clinical trial is designed as an open-label study, without administration of a placebo formulation. An open-label study will facilitate the need for rapid review and dissemination of study data for public health reasons.

4.3 Justification for Doses

The dosages selected are those authorized under EUA.

In the Phase 1 clinical trial, DMID 20-0003, mRNA-1273, administered as two injections 28 days apart, was investigated at dosages of 25, 50, 100 and 250 mcg in subjects 18 through 55 years of age, and at dosages of 25, 50, and 100 mcg in older cohorts (56-70 years of age and >71 years of age).[14,15] The 100-mcg dose induced higher antibody titers than the 25-mcg dose, whereas the 250-mcg dose did not lead to significant increases. The Phase 2 trial of mRNA-1273 evaluated doses

of 50 mcg and 100 mcg, administered as a two-vaccination series, in 600 adults ≥18 years of age. The safety profile of both formulations was acceptable.[16] Anti-SARS-CoV-2 S binding and neutralizing antibodies were induced by both dose levels of mRNA-1273 within 28 days after the first vaccination and rose substantially to peak titers by 14 days after the second vaccination, exceeding levels of convalescent sera from COVID-19 patients. The antibodies remained elevated through the last timepoint assessed at 57 days. Binding and neutralizing antibody responses were generally comparable in participants who received the 100 mcg mRNA-1273 and the 50 mcg dose at all time points and across the age groups of ≥18 to <55 years and ≥55 years. These findings support the evaluation of mRNA-1273 and mRNA-1273.351 at total dosages of 50 or 100 mcg per vaccination. The primary efficacy analysis from the Phase 3 trial evaluating a two-dose schedule of a 100-mcg mRNA-1273 vaccine led to the issuance of the EUA and initiation of a vaccination campaign in the United States.

The Phase 1 study of BNT162b1 (which encodes the RBD) vs. BNT162b2 (which encodes the full-length spike protein) produced by Pfizer/BioNTech administered at two injections 21 days apart, was investigated at dosages of 10, 20, 30 and 100 mcg in subjects 18 through 55 years of age and 65 through 85 years of age.[17] BNT162b2 was associated with lower incidence and severity of systemic reactions compared to BNT162b1, and both produced similar levels of neutralizing antibody which superseded convalescent serum results. The lower incidence of systemic reactions was particularly apparent in older subjects. The 50% and 90% neutralizing antibody titers exceeded convalescent serum at 7 and 14 d after the second dose. Based upon these data, the 30-mcg dose was taken into Phase 2a/3 trials. The results of the Phase 2a/3 trial demonstrated that BNT162b2 administered as two injections, 21 days apart, at a 30-mcg dose, conferred 95% protection against COVID-19 in persons ≥16 years of age.[18] The primary efficacy analysis from the Phase 3 trial led to the issuance of the EUA and initiation of a vaccination campaign in the United States.

The Phase 1/2a study of the AD26.COV2.S vaccine evaluated two dosage levels ($5x10^{10}$ vp and $1x10^{11}$ vp) based upon prior vaccine studies with the Ad26 platform.[19] Both formulations administered as a single dose had favorable safety and immunogenicity profiles,[20] yielding high and comparable humoral and cellular immune response rates. The lower dose had a more favorable reactogenicity profile and was selected for Phase 3 trial evaluation that demonstrated its protective efficacy.[19]

5. STUDY POPULATION

Two cohorts will be enrolled. For Cohort 1, approximately 150 individuals (50 subjects/group; Groups 1E-3E) 18 years of age and older, stratified into two age groups (18-55 years and >56 years at 1:1 ratio), who are in good health and received EUA dosed vaccinations of mRNA-1273, BNT162b2 or Ad26.COV2.S will be invited to participate in this study.

For Cohort 2, approximately 250 individuals (250 subjects/group), ≥18 years of age, who have never been vaccinated against SARS-CoV-2 or are not known to have been infected with SARS-CoV-2 and meet all eligibility criteria will be enrolled. The target population should reflect the community at large. Future groups may be added as additional EUA vaccines become available.

The estimated time from initiation of enrollment to complete enrollment in this clinical trial is approximately 4 weeks (though could take longer). However, owing to the adaptive nature of the design, new groups may be added to Cohort 1 or 2 dependent upon manufacture of variant lineage spike protein-based vaccine constructs or vaccines newly awarded EUA. An optional screening period can occur up to 28 days prior to the first vaccination.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572. No exemptions are granted on Subject Inclusion or Exclusion Criteria in DMID-sponsored studies.

5.1 Inclusion Criteria

See Inclusion Criteria in Synopsis

5.2 Exclusion Criteria

See Exclusion Criteria in Synopsis.

5.2.1 Exclusion of specific populations

The effects on the fetus are not known; therefore, pregnant women will not be eligible for the trial. Children will not be included in this trial as presently there are no safety or efficacy data in adults for the variant strain. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including these populations.

5.3 Inclusion of Vulnerable Subjects

Not Applicable

5.4 Lifestyle Considerations

During this study subjects are asked to:

- Follow public health guidance on preventing SARS-CoV-2 infection.
- Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.

5.5 Screen Failures

A screening visit is optional. However, if screening assessments are performed, the participating site PI or qualified designee is to review the inclusion and exclusion criteria and determine the subject's eligibility for the study.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason for ineligibility. Subjects who are found to be ineligible will be told the reason for ineligibility.

5.6 Strategies for Recruitment and Retention

5.6.1 Recruitment

Potential subjects will learn about the study via IRB-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry and local advertisements/flyers. Screening will begin with a brief IRB-approved telephone call from study staff. Information about the study will be presented to potential subjects and questions about their health and ability to comply with the study visit schedule will be asked of potential subjects to presumptively determine eligibility. Appointments will be made at the research clinic for potential subjects who are interested in the study for further screening procedures and additional protocol-specific information.

5.6.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment/baseline visits and restriction of enrollment to persons who can attend all study visits. Participating subjects will be reminded of subsequent visits during each visit, and study staff will contact subjects prior to appointments. Study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

5.6.3 Compensation Plan for Subjects

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the amount contingent on completing study procedures.

5.6.4 Costs

There is no cost to subjects for the research tests, procedures/evaluations or 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.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Study Product Description

Product 1: mRNA-1273

mRNA-1273 (0.2 mg/mL) is an LNP dispersion containing an mRNA that encodes for the pre fusion stabilized S protein of the Wuhan-Hu-1 strain of SARS-CoV-2. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and PEG2000 DMG.

6.1.2 Dosing and Administration

mRNA-1273 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL).

For Cohort 2, the second dose of mRNA vaccine will be administered preferably in the same arm used for the first dose. For Cohort 2, the booster dose of vaccine will also be administered preferably in the same arm used for the first dose.

The pharmacist will prepare a single dose for each subject based on cohort assignment.

See the protocol-specific Manual of Procedures (MOP) for detailed information on the preparation, labeling, storage, and administration of vaccine for each cohort. Vaccine preparation will be performed by the participating site's research pharmacist on the same day of vaccine administration to the subject.

The expiration time of the dosing syringe containing the prepared mRNA study vaccines is 8 hours at room temperature after the solution is drawn into the dosing syringe.

6.1.3 4.1Dose Modifications

No dose modifications.

6.2 Accountability/Handling/Storage/Preparation

6.2.1 Acquisition and Accountability

Product: mRNA-1273

Will be provided by HHS-OWS Research Allocation via the DMID repository:

DMID Clinical Materials Services Contract
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Phone: 240-477-1350
Fax: 240-477-1360
Email: DMID.CMS@thermofisher.com

All study products will be shipped to the clinical research site upon request and approval from DMID.

Accountability

The participating site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Study product accountability records and dispensing logs should include, but are not limited to the following: DMID protocol number; name, dosage form, strength of the study product; capture vial numbers assigned sequentially by the pharmacists as vials/syringes are used (number uniquely, do not start over at 1 or repeat numbers), manufacturer or other source; control, lot number or other identification number; expiration or retest date; date of receipt of the study product; quantity received from supplier; subject identification number; quantity dispensed as amount or dose per subject; balance of study product currently available;

disposition of study product if not dispensed to a study subject (e.g., disposed/destroyed or retuned to supplier as per protocol or protocol-specific MOP or as directed by DMID); date of vaccine preparation/administration, time of vaccine preparation, expiration of vaccine preparation; and amount of vaccine withdrawn for administration. Time of vaccine administration to the subject will be recorded on the appropriate data collection form (DCF). All study product(s), including the amount of study product, diluent (0.9% NaCl for injection, USP), and vial admixtures, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the DMID-approved clinical monitoring plan (CMP).

Once all subject dosing is complete, the pharmacy staff should retain or dispose of used study products and complete study product accountability procedures in accordance with site-specific standard operating procedures (SOPs). This applies to:

- used and unused mRNA-1273 vials
- mRNA-1273 cartons

All used supplies noted above may either be sequestered from the unused supplies and retained until study conclusion or until study product accountability has occurred by the monitor and written notification stating retention is no longer required is received or may be destroyed in accordance with site-specific SOPs with a second pharmacy staff member's observation and verification as documented in the pharmacy log. Refer to the protocol-specific MOP for details on storing used study product vials.

Destruction

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, disposition of unused and used study product vials should occur as noted:

- Unused and used study product vials:
    - Should be destroyed on-site following applicable site procedures or by the site's selected destruction vendor. Following the site's procedure for the destruction of hazardous material or study product destruction policy/SOP when destroying used and unused items.
    - A certificate of destruction or documentation of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.
- Used syringes may be destroyed in accordance with site-specific SOPs.

6.2.2 Formulation and Appearance

Product: mRNA-1273

mRNA-1273 is provided as a sterile liquid for injection, white to off-white dispersion in appearance.

Each of the study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal Law to Investigational Use."

6.2.3 Product Storage and Stability

Product: mRNA-1273

mRNA-1273 vials are stored frozen between -25º to -15ºC. Vials can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use. Unpunctured vials may be stored between 8° to 25°C for up to 12 hours. Do not refreeze. Store in the original carton to protect from light.

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

mRNA-1273 must be stored in a secure area with limited access (pharmacy staff only) and must be stored frozen. The freezer should have an automated temperature recording and alert system. There must be an available back-up freezer. The freezers must be connected to a back-up generator, or alternate plan in the event of a power failure. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any mRNA-1273 that was not temperature controlled during shipment or during storage to the pharmacy staff. Such mRNA-1273 will be retained for inspection by the pharmacy staff and disposed of according to approved methods.

6.2.4 Preparation

Refer to the protocol-specific MOP for details about preparation.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Treatment Assignment Procedures

Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6: GCP, screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the electronic data capture (EDC) system that the IDCRC Statistical and Data Science Unit (SDSU) develops and manages through the Statistical Center for HIV/AIDS Research (SCHARP) at the Fred Hutchinson Cancer Research Center.

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subjects will be enrolled.

6.3.2 Randomization and Blinding

Subjects in Cohorts 1 and 2 will not be randomized to study intervention. The study will be open label and study sites will administer product to which they have been assigned.

6.3.3 Blinding and Masking Procedures

This study is unblinded.

6.4 Study Intervention Compliance

Each dose of study product will be administered by a member of the clinical research team that is qualified and licensed to administer the study product. Administration and date, time, and location of injection will be recorded on the appropriate DCF.

6.5 Concomitant Therapy

Concomitant medications include only prescription medications and vaccines received outside of the study taken by the subject at the time of enrollment through 28 days after the last vaccination. At each study visit, if there are new SAEs, Protocol Specified AESIs, MAAEs, or NOCMCs, concomitant medications should be recorded on the appropriate DCF.

6.5.1 Rescue Medicine

Not Applicable

6.5.2 Non-Research Standard of Care

Not Applicable

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Halting Criteria

The study will be halted in a given group if any of the following events occur following booster dose only:

1- Any subject experiences an SAE after administration of the vaccine that is considered related to vaccine.

2- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of vaccine that is considered related to vaccine.

3- Any subject experiences ulceration, abscess or necrosis at the injection site that is considered related to vaccine administration.

4- Two (2) or more subjects experience an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of vaccine that is considered related to vaccine.

5- Three (3) or more subjects experience a Grade 3 AE (unsolicited) related to vaccine administration, in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding.

7.1.2 Criteria for Continuation of Dosing and Redosing

In the event a halting rule is met:

- an unscheduled safety analysis by the SMC will be required for approval of further enrollment
- further administration of any study vaccine boost within the specific group, is suspended for ALL subjects within that group until an assessment by the SMC takes place.

7.1.3 Discontinuation of Study Intervention

For Cohort 2, prior to receiving the second and third vaccination, subjects will be reassessed. The following events constitute contraindications to any further administration of study vaccines. If any of these events occur during the study prior to the second vaccination, the subject must not receive the second vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination. For Cohort 2, Group 1, if any of these events occur after the second vaccination and before the third vaccination the subject must not receive the third vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination.

- Any clinically significant medical condition that, in the opinion of the participating site PI or appropriate sub-investigator, poses an additional risk to the subject if he/she continues to participate in the study.
- Confirmed SARS-CoV-2 infection.
- Anaphylaxis or unexpected systemic hypersensitivity reaction following the administration of a prior study vaccination.
- Any SAE judged to be related to vaccine.
- Pregnancy.

- New information becomes available that makes further participation unsafe or interferes with the evaluation of responses.
- Termination of this trial.

7.1.3.1 Delay of Study Vaccination

If any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date.

- Acute moderate or severe infection with or without fever at the time of vaccination.
- Fever, defined as oral temperature ≥38.0°C (100.4°F) at the time of vaccination.

Subjects with a minor illness without fever, as assessed by the participating site PI or appropriate sub-investigator, can be administered vaccines. Subjects with an oral temperature of 38.0°C (100.4°F) or higher will be re-contacted within the window specified in the SOA and re-evaluated for eligibility.

It is preferred that the vaccination still occur within the window specified in the SOA if possible but delays outside the windows are permitted (would still be a protocol deviation).

7.1.4 Follow-up for Subjects that Discontinued Study Intervention

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

7.2 Subject Withdrawal from the Study 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.
- Initial vaccine is not administered.

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

- Subject becomes pregnant before receiving the second or third dose of vaccine.
- Study non-compliance to protocol requirements that in the opinion of the participating site PI or appropriate sub-investigator poses an increased risk or compromises the validity of the data.
- Lost to follow-up.

- If the subject met an exclusion criterion for participation in the study (either newly developed or not previously recognized) that precludes further study participation.
- Request of primary care provider, the IRB, FDA, or NIAID.
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the participating site PI or appropriate sub-investigator might compromise the safety of the subject, interferes with the subject's successful completion of this study, or interferes with the evaluation of responses.
- If any AE or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- Any SAE judged to be related to vaccine.

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

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.

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.

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

7.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-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 ASSESSMENTS AND PROCEDURES

8.1 Screening and Immunogenicity Assessments

8.1.1 Screening or Enrollment/Baseline Procedures

There is a small amount of risk to subjects who report that they are in good health but have an unknown health problem at the time of the enrollment/baseline visit. Screening assessments can occur up to 28 days before or at the subject's first vaccination visit (Day 1). At the screening (optional) or enrollment/baseline visit, and prior to any other study-related activities, the participating site PI or appropriate sub-investigator will provide the subject with detailed study information and will obtain written informed consent.

Some or all of the following assessments are performed during the screening (optional) or enrollment/baseline visit to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain medical history.
- Review pre-study medications and therapies at screening and record on the appropriate DCF. Review of adult vaccinations, including any other SARS-CoV-2 or other experimental coronavirus vaccines.
- Review any participation in investigational trials in the last 6 months.
- Measure vital signs (HR, BP, and oral temperature), and height and weight for determination of BMI.
- Targeted physical examination based upon symptoms elicited in the medical history
- Review of birth control history with female subjects of childbearing potential.
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
- Urine pregnancy test (in women of childbearing potential).
- Review inclusion and exclusion criteria.

The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

Study subjects who qualify for inclusion will be contacted and scheduled for enrollment and first vaccination within the window for enrollment unless the screening and vaccination are scheduled on the same day.

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

A subject may be re-screened if there is a transient disease status (e.g., subject complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening at a later date (e.g., a medication taken within exclusionary window at the time of first screening that would not be within exclusionary window at a later rescreen).

No subjects may be screened more than twice due to a screening failure result as defined above.

Subjects will be provided the results of abnormal clinical findings necessitating follow-up at the discretion of the participating site PI or appropriate sub-investigator. Research laboratory results will not be provided to the subject.

The screening and first vaccination procedures both can be conducted at the enrollment/baseline visit.

8.1.2 Immunogenicity Evaluations

Serological Immunogenicity Assays:

The following serological immunogenicity assays may be performed:

- IgG ELISA to SARS-CoV-2 proteins.
- Neutralization assays using different strains of SARS-CoV-2 pseudovirus.
- Neutralization assay using different strains of live SARS-CoV-2.
- Quadriplex MSD assay (Nucleocapsid protein, Receptor binding domain, spike protein and variant spike protein)

Preparation of blood samples and shipping instructions for serological immunogenicity assays are outlined in the protocol-specific MOP. Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline serum for serological immunogenicity assays is collected.

Cellular Immunology Assays:

This trial may also investigate B and T cell immune responses using multiparametric flow cytometry.

Refer to the protocol-specific immune monitoring plan for details.

Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the protocol-specific MOP.

The volume of venous blood to be collected for immunogenicity evaluations is presented in Table 8 and Table 9.

8.1.3 Samples for Genetic/Genomic Analysis

8.1.3.1 Genetic/Genomic Analysis

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

8.1.3.2 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.

8.1.3.3 Management of Results

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

8.2 Safety and Other Assessments

Study procedures are specified in the SOA. A study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator, will be responsible for all study-related medical decisions.

- Medical history:
    - A complete medical history will be obtained by interview of subjects at the screening (optional) or enrollment/baseline visit. Subjects will be queried regarding a history of significant medical disorders.
    - At all subsequent visits an interim medical history will be obtained by interview of subjects and any changes since the previous clinic visit or telephone call will be noted. The interim medical history should include an assessment to identify intercurrent Protocol Specified AESIs, MAAEs, and NOCMCs.
- Physical examination:
    - A symptom-directed (targeted) physical examination will be performed if indicated at any timepoint at the discretion of the participating site PI or appropriate sub-investigator, if necessary, to evaluate AEs.
    - Reactogenicity assessments of solicited AEs, occurring from the time of each vaccination through 7 days post vaccination, will include an assessment of injection site reactions–erythema, edema/induration and pain, as well as systemic reactions–fever, fatigue, chills, myalgia (exclusive of the injection site), arthralgia, headache, and nausea. Pre-administration reactogenicity assessments will be performed immediately prior to each vaccination to establish baseline, then the vaccination will be given.
    - Subjects will be observed in the clinic for at least 30 minutes post each vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AEs/SAEs will be recorded on the appropriate DCF prior to discharge from the clinic. The vaccination site will also be examined 7 days after vaccination.
- Vital signs: Vital sign measurements will include systolic and diastolic BP, HR, and oral temperature. Vital signs will be measured at timepoints specified in the SOA. On vaccination days, vital sign measurements will be collected prior to vaccine administration. Vital signs assessed on Day 1 prior to the first vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.

- Urine pregnancy test: Urine pregnancy test will be performed locally by the site laboratory within 24 hours prior to each vaccination, and as needed at interim or unscheduled visits for all women of childbearing potential. Results must be confirmed as negative prior to enrollment on Day 1 and administration of each vaccination as applicable.

- Memory aid:
  - All subjects will complete a Memory Aid from the time of each vaccination through 7 days post each vaccination. Memory Aids will be reviewed with the subjects for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs and concomitant medications during telephone calls 7 days after each vaccination. Based on the information collected, subjects may be asked to return to the clinic for evaluation. Memory Aids will be collected, and subjects will be assessed for delayed onset local reactions 14 days after booster vaccination (initial vaccination in Cohort 1, delayed vaccination in Cohort 2). Memory aids will be collected 7 days after each vaccination in the initial part of Cohort 2.

Table 8: Venipuncture Volumes for Cohort 1 (One Vaccination – EUA Dosed Cohort)

Study Day	-28 to -1	1	8	15	29	91	169	366	Early Termination Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05	06	07		
Vaccination		X								
Serum for Serological Immunogenicity Assays[1]		16		16	16	16	16	16	16[2]	96
PBMCs (and Plasma) for Cellular Immunology Assays		64		64			64	64	64[2]	256
Serum for Secondary Research		16		16	16	16	16	16	16[2]	96
Per Visit Blood Volume Total (mL)		96		96	32	32	96	96	96[2]	352
Cumulative Blood Volume (mL) (prior 56 days)		96	96	192	224	32	96	96		
Running Blood Volume Total (mL)		96	96	192	224	256	352	448		

[1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected.

[2] These blood volumes are not included in the blood volume totals.

Table 9: Venipuncture Volumes for Cohort 2: (Up to Three Vaccinations)

Study Day	-28 to -1	1	8	29	36	43		1B	15B	29B	91B	169B	366B	Early Termination Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	7	7	Delayed Boost to occur > 12 weeks from completion of EUA dosing.	0	2	2	7	7	28		
Study Visit	Screening (optional) 00	01	02	04	05[3]	06[3]		07[3]	08[4]	09[4]	10[4]	11[4]	12[4]		
Vaccination		X		X											
Serum for Serological Immunogenicity Assays[1]		16		16		16		16	16	16	16	16	16	16[2]	165
PBMCs (and Plasma) for Cellular Immunology Assays		96						64	64		64	64	64	64[2]	340
Serum for Secondary Research		16		16		16		16	16	16	16	16	16	16[2]	
Per Visit Blood Volume Total (mL)		96		32		32		96	96	32	96	96	96	96[2]	505
Cumulative Blood Volume (mL) (prior 56 days)		96	96	128	128	160		96	192	224	96	96	96		
Running Blood Volume Total (mL)		96	96	128	128	160		256	352	384	480	576	672		

[1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected.
[2] These blood volumes are not included in the blood volume totals.
[3] Visits 05-07 windows should be based off the actual Visit 04 date.

[4] Visits 08-12 windows should be based off the actual Visit 07 date.

8.2.1 Procedures to be Followed in the Event of Abnormal Clinical Findings

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

All abnormal clinical findings that occur post vaccination will be considered AEs.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related [21 CFR 312.32 (a)]. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

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

All AEs will be assessed for severity and relationship to study intervention (Section 8.3.3). Reporting of all AEs, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after the last vaccination. After 28 days post last vaccination through the end of study, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be reported as AEs.

All AEs, solicited and unsolicited, will be captured on the appropriate DCF. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator), date of resolution, seriousness, and outcome. AEs occurring during the study-collection and reporting period will be documented appropriately regardless of relationship.

AEs will be followed to resolution or stabilization.

8.8.1.1 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.

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

For this study, solicited AEs will be:

- Injection site Pain
- Injection site Erythema
- Injection site Edema/Induration
- Headache
- Fatigue
- Myalgia
- Arthralgia
- Nausea
- Fever
- Chills

Subjects will also be assessed for delayed onset local reactions through 14 days post each vaccination.

8.3.1.2 Unsolicited Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from study staff or revealed by observation, physical examination or other diagnostic procedures must be recorded on the appropriate DCF.

Unsolicited AEs of all severities will be reported from the time of study product administration through 28 days post last vaccination.

After 28 days post last vaccination through the end of study, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs (as detailed in Section 8.3.2) will be reported as AEs.

8.3.1.3 Special Reporting of Adverse Events

Not Applicable

8.3.2 Definition of Serious Adverse Event (SAE)

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

- Death,
- a life-threatening AE,
- inpatient hospitalization or prolongation of existing hospitalization,

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

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

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

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

All SAEs will be recorded on the appropriate SAE DCF.

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

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

8.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

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

8.3.4 Classification of an Adverse Event

The determination of seriousness, severity and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs and classify AEs based upon medical judgment. This includes, but is not limited to, physicians, physician assistants and nurse practitioners.

8.3.4.1 Severity of Adverse Events

All AEs and SAEs will be assessed for severity, according to the toxicity grading scales in the FDA "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 specific 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.

8.3.4.2 Relationship to Study Intervention

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

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

For this study:

- solicited AEs will be collected for 7 days post each vaccination.
- unsolicited AEs will be collected until 28 days post last vaccination.
- SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from Day 1 through the end of the study.

8.3.6 Adverse Event Reporting

8.3.6.1 Investigators Reporting of AEs

Information on all AEs should be recorded on the appropriate DCF. All clearly related signs, symptoms and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a clinical laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual clinical laboratory abnormality. Each AE will also be described in terms of

duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.3.7 Serious Adverse Event Reporting

8.3.7.1 Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as an SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

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

SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the SCHARP's EDC system. Refer to the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID Medical Monitor 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 participating site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the participating site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

8.3.7.2 Regulatory Reporting of SAEs

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

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

8.3.8 Reporting Events to Subjects

Subjects will be informed of any AEs or SAEs that occur as part of their participation in this trial.

8.3.9 Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest (AESIs) represent any events for which additional data (besides the standard AE data) are desired. 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 is required. Such an event may require 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) may also be required. These may be at the request of the regulatory agency, industry partner or DMID, and driven by a regulatory requirement, or known or potential risk from the product or class. Non-structured data similar to SAEs will be collected for AESIs. AESIs encompass the following terms:

- Protocol Specified AESIs: See Section 12, Appendix A.
    - All suspected cases of anaphylaxis should be recorded. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis should be reported as a potential case of anaphylaxis.
- 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 a hospitalization, emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason; and considered related to study product.

All AESIs are assessed, recorded, and followed as described above under AEs. AESIs that meet SAE criteria will be reported on an SAE form within 24 hours to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

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

SAE Email Address: PVG@dmidcroms.com

In addition, 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 DMID Pharmacovigilance Group; however, the narrative will indicate that the AESI did not meet SAE criteria.

8.3.10 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs following the booster dose (through three months after boost) should be reported to the sponsor on the appropriate DCF. Pregnancy should be followed to outcome.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UPs)

The Department of Health and Human Services (DHHS) OHRP considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the SDSU/study sponsor within 24 hours of the participating site PI or appropriate sub-investigator becoming aware of the event per the above-described SAE reporting process.
- UPs that are SAEs will be collected from Day 1 through the end of the study.
- Any other UP will be reported to the IRB and to the SDSU/study sponsor within 3 days of the participating site PI or appropriate sub-investigator becoming aware of the problem.
- UPs that are not SAEs will be collected from Day 1 through 28 days after last vaccination.

8.4.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this trial.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

This is a phase 1/2, open-label, multi-site clinical trial that is not designed to test a specific hypothesis. Rather, it is intended to obtain preliminary estimates in healthy adults of the safety, reactogenicity, and immunogenicity of delayed heterologous SARS-CoV-2 vaccine dosing (boost) after receipt of EUA vaccines.

9.2 Sample Size Determination

9.2.1 Sample Size Calculation for the Safety Endpoint

Rare AEs are not demonstrable in a clinical study of this size; however, the probabilities of observing one or more AEs given various true event rates are presented in Table 10. With the assumption that all enrolled subjects will likely complete immunizations and safety visits in this relatively short duration study, the following statistical considerations apply. With approximately 50 subjects in each group there is a 99.5% chance of observing at least one AE of probability 10%. Similarly, with approximately 25 subjects in each of the age subgroups, there is a 92.8% chance of observing at least one AE of probability 10%. Therefore, if no AEs of a given type occur in a Cohort 1group, we can be relatively confident that they will occur in fewer than 10% of people once the vaccine is implemented.

Probabilities of observing one or more AEs, assuming an attrition rate of approximately 10% (N = 45, N = 22), are also shown in Table 10.

9.2.2 Sample Size Calculation for the Immunogenicity Endpoints

A co-primary objective of this study is to evaluate the magnitude of SARS-CoV-2 specific antibody titers in serum samples. This objective is descriptive in nature and will be accomplished by estimating 95% confidence intervals (CI) for the geometric mean titer (GMT) at each timepoint when samples are collected.

Table 10: Probability of Observing an Adverse Event for Various Event Rates in one vaccine schedule group (or age subgroup), assuming no attrition (N = 50 or N = 25) or approximately 10% attrition (N = 45 or N = 22).

N	"True" Event Rate	Probability of Observing ≥ 1 events (%)	N	"True" Event Rate	Probability of Observing ≥ 1 events (%)
50	0.1%	4.9	45	0.1%	4.4
	0.5%	22.2		0.5%	20.2
	1.0%	39.5		1.0%	36.4
	2.0%	63.6		2.0%	59.7
	3.0%	78.2		3.0%	74.6
	4.0%	87.0		4.0%	84.1
	5.0%	92.3		5.0%	90.1
	10.0%	99.5		10.0%	99.1
	15.0%	>99.9		15.0%	99.9
	20.0%	>99.9		20.0%	>99.9
	30.0%	>99.9		30.0%	>99.9
N	**"True" Event Rate**	**Probability of Observing ≥ 1 events (%)**	**N**	**"True" Event Rate**	**Probability of Observing ≥ 1 events (%)**
25	0.1%	2.5	22	0.1%	2.2
	0.5%	11.8		0.5%	10.4
	1.0%	22.2		1.0%	19.8
	2.0%	39.7		2.0%	35.9
	3.0%	53.3		3.0%	48.8
	4.0%	64.0		4.0%	59.3
	5.0%	72.3		5.0%	67.6
	10.0%	92.8		10.0%	90.2
	15.0%	98.3		15.0%	97.2
	20.0%	99.6		20.0%	99.3
	30.0%	>99.9		30.0%	>99.9

The precision with which the GMT can be estimated from observed data depends on the standard deviation (SD) of the measurements, on the logarithmic scale, and the sample size. Table 11 displays two-sided 95% confidence intervals for the GMT for several values of the observed antibody titer. Table 11 also shows results assuming up to 10% attrition.

Table 11: Two-sided 95% confidence intervals based on observing a particular average loge-antibody titer in subjects' vaccine groups and age subgroups.

Observed average $\log_e$ antibody titer	SD of $\log_e$ antibody titer	95% confidence interval of GMT in vaccine group		95% confidence interval of GMT in age subgroup	
		N = 50	N = 45*	N = 25	N = 22*
$\log_e$ (5)	0.5	(4.3, 5.8)	(4.3, 5.8)	(4.1, 6.1)	(4, 6.2)
$\log_e$ (20)		(17.4, 23.1)	(17.2, 23.2)	(16.3, 24.6)	(16, 25)
$\log_e$ (50)		(43.4, 57.6)	(43, 58.1)	(40.7, 61.5)	(40.1, 62.4)
$\log_e$ (100)		(86.8, 115.3)	(86.1, 116.2)	(81.4, 122.9)	(80.1, 124.8)
$\log_e$ (250)		(216.9, 288.2)	(215.1, 290.5)	(203.4, 307.3)	(200.3, 312)
$\log_e$ (500)		(433.8, 576.3)	(430.3, 581)	(406.8, 614.6)	(400.6, 624.1)
$\log_e$ (1000)		(867.5, 1152.7)	(860.5, 1162.1)	(813.5, 1229.2)	(801.2, 1248.2)
$\log_e$ (5)	1.0	(3.8, 6.6)	(3.7, 6.8)	(3.3, 7.6)	(3.2, 7.8)
$\log_e$ (20)		(15.1, 26.6)	(14.8, 27)	(13.2, 30.2)	(12.8, 31.2)
$\log_e$ (50)		(37.6, 66.4)	(37, 67.5)	(33.1, 75.6)	(32.1, 77.9)
$\log_e$ (100)		(75.3, 132.9)	(74, 135)	(66.2, 151.1)	(64.2, 155.8)
$\log_e$ (250)		(188.2, 332.2)	(185.1, 337.6)	(165.5, 377.8)	(160.5, 389.5)
$\log_e$ (500)		(376.3, 664.3)	(370.2, 675.2)	(330.9, 755.5)	(320.9, 779)
$\log_e$ (1000)		(752.6, 1328.7)	(740.5, 1350.4)	(661.8, 1511)	(641.9, 1558)

* Assumes approximately 10% attrition.

9.3 Populations for Analyses

The safety analysis population includes all enrolled subjects who received one dose of study vaccine. Analyses for the safety population will include safety reported through the end of the study. The modified intent-to-treat (mITT) population includes all subjects who received at least one dose of vaccine and contributed both pre- and at least one post-vaccination venous blood sample for immunogenicity testing for which valid results were reported.

In the final analysis, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis. The per protocol (PP) population will then be defined – and this includes all subjects in the mITT subset with the following exclusions:

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

9.4 Statistical Analyses

Interim analyses of safety, reactogenicity, and immunologic response data will be done, as needed.

The final analysis will be performed after the final data lock and clinical study report (CSR) completed when all primary safety endpoint data and all secondary immunogenicity endpoint data are available and received by the SDSU. Any available data from the exploratory immunogenicity endpoints may also be included in the CSR. Remaining exploratory immunogenicity endpoint data may be included in an addendum to the CSR, publication of manuscript(s), or other report(s). Abbreviated analysis plans that describe planned analyses to facilitate dissemination of study data for public health reasons, including manuscript publication(s), will be developed by the SDSU. A full statistical analysis plan (SAP) will be developed by the SDSU and finalized prior to the primary data lock.

9.4.1 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.

9.4.2 Analysis of the Primary Endpoint(s)

Section 9.4.4 describes the analyses of Safety Endpoints, which is one of the co-primary endpoints of this protocol.

9.4.3 Analysis of the Secondary Endpoint(s)

Descriptive summaries of immunogenicity data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a per-protocol (PP) analysis may also be performed.

Geometric Mean Titers (GMT) and Geometric Mean Fold Rise (GMFR) from baseline of SARS-CoV-2 specific antibody binding and neutralization titers will be calculated, along with 95% CIs, for all groups, at each timepoint. Summaries will also be displayed graphically. Rates of seroconversion, defined as a 4-fold increase in antibody titer over baseline, will also be reported for all groups, at each timepoint, along with 95% CIs.

9.4.4 Safety Analyses

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

Solicited AEs will be summarized by severity for each day post vaccination (Days 1-8) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed using standard techniques, such as exact confidence intervals (CI), to summarize the proportion of subjects reporting each symptom, any application site symptom, and any systemic symptom.

Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after the last vaccination. Unsolicited AEs will be coded by MedDRA for preferred term and system organ class (SOC). SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first vaccination through the end of the study. The numbers of SAEs, Protocol Specified AESIs and MAAEs will be reported by detailed listings showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA categories will be computed.

9.4.5 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 arm and cohort.

9.4.6 Planned Interim and Early Analyses

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community. Early analyses will include safety and immunogenicity as described in Sections 0, 0 and 0. Further, the protocol team will review data periodically to confirm no halting criteria have been met as described in Section 0.

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

9.4.6.1 Interim Safety Analyses

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

The SMC will review cumulative AE data after all subjects for each group in Cohort 1 have been dosed and completed Day 8. The SMC will also review cumulative AE data after all subjects in a given booster group have been dosed and completed Day 8. Given the safety database known for EUA vaccines, there is no routine mandatory review by the SMC during the EUA dosing in cohort 2 unless halting rules are triggered.

9.4.6.2 Interim Immunogenicity Review

Interim data review of immunogenicity will be performed as often as needed to inform public health decisions.

Statistical analyses of secondary immunogenicity endpoints, by vaccine schedule group, may be performed when subjects have completed key immunogenicity visits. Immunogenicity reviews may be shared with the SMC, as determined by DMID.

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

9.4.6.3 Interim Immunogenicity and Safety Review

Interim analyses of safety, reactogenicity, and immunologic response data may be done, as needed.

9.4.7 Sub-Group Analyses

Subgroup analyses, by age group, may be performed. Detailed information will be provided in the Statistical Analysis Plan.

9.4.8 Tabulation of Individual Subject Data

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

9.4.9 Exploratory Analyses

Summaries and analysis of cellular assay data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a PP analysis may also be performed.

The magnitude, phenotype and percentage of innate immune cells and SARS-CoV-2 specific B cells will be summarized at each timepoint by arm.

The magnitude, phenotype and percentage of cytokine producing S protein-specific T cells will be summarized at each timepoint by arm.

Breakthrough NAAT-confirmed, SARS-CoV-2 infections will be sequenced to assess for the presence of variant spike lineage proteins.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

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

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

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

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

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

10.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a subject's informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed. The participating site PI or other study staff may obtain oral or written information for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject if the process is approved by the IRB.

At the first study visit, informed consent will be obtained and documented before any study procedures are performed. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study

interventions/products, risks and discomforts, the expected duration of the subject's participation in the trial, any expected benefits to the subject, and alternative treatments and procedures that may be available to the subject. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

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

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

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

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

New information will be communicated by the participating site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

10.1.1.1 Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

Not Applicable

10.1.1.2 Other Informed Consent Procedures

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

Subjects will be asked to consent specifically to genetic testing on primary and secondary research samples, including but not limited to transcriptomics and DNA sequencing. DNA sequencing data will be kept private. DNA data may be used to produce commercial antibody-based therapeutics. Subjects will not share in profits or commercial rights to those products.

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

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

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

Samples designated for secondary research use may be used for additional immunological assessments that may include but are not limited to antibody epitope mapping, B and T cell repertoire determination, non-traditional immune assay development, determination of innate immune factors and the ability of vaccine-induced antibodies to cross-react to different proteins and virus strains. These blood samples might be used in new or different immunological laboratory tests, to provide information for the development of new vaccines or therapeutics, or for the studies of SARS-CoV-2 or other infections. Secondary research using DNA may also be warranted to understand genetic factors involved in vaccination failures.

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

There are no direct benefits to the subject for extra specimens collected or from 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 additional volume of blood collected, such as anemia. Risks for loss of privacy and confidentiality are described below.

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

Human Genetic Testing

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

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

10.1.2 Study Termination and Closure

In Section 7, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

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

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

If the study is prematurely terminated, the PI will promptly inform study subjects and the IRB as applicable. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule. The PI will assure appropriate follow-up for the subjects, as necessary.

The sponsor will notify regulatory authorities as applicable.

10.1.3 Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples and genetic tests, and all other information generated

during participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the participating site PI, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The participating site will permit access to such records.

All source records, including electronic data, will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the participating site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the participating site. Names or readily identifying information will not be released unless DMID approves and it aligns with the consent form, or according to laws for required reporting.

Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and re-identified data could potentially be used to discriminate against or stigmatize subjects, their families, or groups. In addition, there may be unknown risks.

As this research is funded by the NIH, it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality (COC). By this policy, researchers cannot be forced to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

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

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

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

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

10.1.4 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ‘‘primary’’ or ‘‘initial’’ activity, such as the data and samples collected in this protocol. This section will detail the samples and data available for secondary research. Any use of the sample or data, however, will be presented in a separate protocol and require separate IRB approval.

10.1.4.1 Samples for Secondary Research

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

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

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

Residual/Repository Research Samples, upon written request and approval from DMID and any approvals required by the site or network, may be shared for secondary research with investigators at the participating site, with researchers at other Infectious Disease Clinical Research Consortium (IDCRC) sites or other institutions, or company-designated research laboratories. The samples will not be sold or used directly for production of any commercial product. DMID will authorize shipment from the DMID CMS.

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

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

10.1.4.2 Data Sharing for Secondary Research

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

secondary research with investigators/researchers. The data will be available for only the purpose outlined in the approved proposal.

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

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

10.1.5 Key Roles and Study Governance

This study is sponsored by DMID. Decisions related to this study will be made by the protocol team, which includes representatives from the participating site (PI), DMID (sponsor), VRC, and ModernaTX, Inc. Key Roles are noted in the protocol-specific MOP.

10.1.6 Safety Oversight

10.1.6.1 Safety Monitoring Committee (SMC)

The SMC is an independent group of at least 2-3 experts that monitors subject safety and advises DMID. SMC members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The SMC will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

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

Given the frequency and urgency to review data, the SMC will not need to meet (unless halting rules are met), and materials will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

The SMC will review cumulative AE data after all subjects in Cohort 1 have been dosed and completed Day 8. The SMC will also review cumulative AE data after all subjects in Cohort 2 have been dosed and prior to the second vaccination (preferably after all subjects have completed Day 8).

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

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

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

10.1.7 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 is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are documented in a 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, electronic case report forms (eCRFs), ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study staff and all study documentation according to the DMID-approved CMP. Study monitors will meet with all participating site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

10.1.8 Quality Control (QC) and Quality Assurance (QA)

To ensure the reliability of study data, the participating site will develop a Clinical Quality Management Plan (CQMP). The CQMP will describe:

- routine internal quality control (QC) and QA activities
    - for the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
    - independent of sponsor site monitoring.
- a process for addressing data quality issues (i.e., collecting, recording), and reporting findings in a timely manner); systemic issues (i.e., protocol conduct, non-compliance, human subject protections), and implementation and evaluation of Corrective and Preventative Action Plan (CAPA) procedures.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the participating site under the supervision of the participating site PI. The participating site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation, including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory data, will be entered by the participating site into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by SCHARP. The data system includes password protection and internal quality

checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The IDCRC SDSU and SCHARP will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to DMID.

10.1.9.2 Study Record Retention

Study-related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records, should be maintained for a period of 2 years following the date a marketing application is approved for the investigational 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 such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research.

10.1.9.3 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. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. 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.

10.1.10 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific MOP or GCP requirements, or

any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

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

It is the responsibility of the participating site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The participating site PI and study staff are responsible for knowing and adhering to their IRB requirements. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

10.1.11 Publication and Data Sharing Policy

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

10.1.12 Human Data Sharing Plan

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

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

10.1.13 Genomic Data Sharing (GDS) Plan

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

10.1.14 Publication

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

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

10.1.15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

10.2.1 Research Related Injuries

For any potential research related injury, the participating site PI or designee will assess the subject. Study staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the vaccine. As needed, referrals to appropriate health care facilities will be provided to the subject. The participating site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial.

If it is determined by the participating site 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 staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the vaccine. No financial compensation will be provided to the subject by NIAID, NIH, the vaccine manufacturer, or the participating site for any injury suffered due to participation in this trial.

For this protocol, the study vaccines, mRNA-1273, manufactured by ModernaTX, Inc. are covered under the PREP Act, as described in Section 2.1.1.

10.3 Abbreviations

Table 12: Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
PBMC	Peripheral Blood Mononuclear Cell

BMI	Body Mass Index
BP	Blood Pressure
°C	Degrees Celsius
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
COC	Certificate of Confidentiality
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
CQMP	Clinical Quality Management Plan
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EUA	Emergency Use Authorization
°F	Degrees Fahrenheit

FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GWAS	Genome-Wide Association Studies
HEENT	Head, Ears, Eyes, Nose, and Throat
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HR	Heart Rate
HRSA	Health Resources and Services Administration
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDCRC	Infectious Disease Clinical Research Consortium
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LNP	Lipid Nanoparticle
m	Meter
MAAE	Medically Attended Adverse Event
mcg	Microgram

MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mg	Milligrams
MI	Myocardial Infarction
min	Minute
mITT	Modified Intent-To-Treat
mL	Milliliter
mm Hg	Millimeter of Mercury
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
N	Number (typically refers to subjects)
NAAT	Nucleic Acid Amplification Test
NaCl	Sodium Chloride
NDA	New Drug Application
NEUT	Neutralizing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Condition
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
OWS	Operation Warp Speed
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PREP Act	Public Readiness and Emergency Preparedness Act
QA	Quality Assurance
QC	Quality Control
RBD	Receptor Binding Domain

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	SARS Coronavirus
SARS-CoV-2	SARS Coronavirus 2
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SD	Standard Deviation
SDSP	Study Data Standardization Plan
SDSU	Statistical and Data Science Unit
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th	T helper
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
vp	Viral Particles
VRC	Vaccine Research Center
WBC	White Blood Cell
WHO	World Health Organization
WIV1	Chinese Horseshoe Bat Coronavirus WIV1

10.4 Protocol Amendment History

Table 13: Protocol Amendment History

This is the initial protocol with no amendment history at this time.

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12. APPENDIX A: Adverse Events of Special Interest (AESIs) Terms

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in the protocol. The following AESIs are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of a COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction

Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc.) • Include all cases that meet the following criteria: o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; o OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days o OR Urine volume ≤0.5 ml/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc.) • Include all cases that meet the following criteria o > 3-fold elevation above the upper normal limit for ALT or AST o OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 x10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome

Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (e.g., gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: o Guillain-Barre Syndrome o Acute disseminated encephalomyelitis (ADEM) o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by: o sudden onset AND o rapid progression of signs and symptoms AND o involving two or more organ systems, as follows: o Skin/ mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes o Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation o Respiratory: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea o Gastrointestinal: diarrhea, abdominal pain, nausea, vomiting • Follow reporting procedures in protocol.
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome

	• Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome)

A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines

DMID Protocol Number: 21-0012

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

Version Number: 4.0

20 August 2021

STATEMENT OF COMPLIANCE

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

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

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

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

Site Investigator Signature:

Signed: _____ Date: _____

Name, Credentials

Title

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1. PROTOCOL SUMMARY

1.1 Synopsis

Title: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines.

Phase: Phase 1/2

Population: Approximately 950 healthy individuals aged ≥ 18 years

Sites: Approximately 12 clinical research sites.

Rationale:

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causative agent of the coronavirus disease of 2019 (COVID-19) pandemic, has infected over 182 million people worldwide and resulted in over 3.9 million deaths, including > 605,000 in the United States (July 02, 2021, WHO; www.who.int). Multiple Phase 3 efficacy trials of SARS-CoV-2 vaccine constructs are underway or in long-term follow-up in the U.S, and these studies have supported 3 Emergency Use Authorizations (EUAs) for COVID vaccines. The emergence of variant strains has raised concerns about the breadth of immunity and protection achieved by the current vaccines. WHO SAGE and CDC ACIP have identified the safety and immunogenicity of mixed schedules as a critical and immediate research priority to inform policy on the use of mixed schedules.

Knowledge of the safety, tolerability, and immunogenicity of a boost vaccine using a heterologous platform with the homologous or variant spike lineage administered after an EUA primary dosing is a critical piece of information needed to inform public health decisions. The heterologous boost strategy will also provide an opportunity to thoroughly evaluate innate, cellular, and humoral immune responses elicited from the multiple prime boost combinations using very similar immunogens, utilizing mRNA, adenovirus- vectored, and protein-based platforms. As new vaccines are manufactured to emerging variants, these foundational data will be key to the evaluation of future variant and heterologous prime-boost strategies. This phase 1/2 clinical trial will evaluate the safety and immunogenicity of different heterologous delayed doses (boosts) in those who received an EUA vaccine (either prior to participation in this trial, or as part of this trial).

Objectives:

Primary:

1. To evaluate the safety and reactogenicity of delayed heterologous or homologous vaccine doses after EUA dosed vaccines:

- Local and systemic solicited adverse events for 7 days following the delayed boost dose.
- Adverse Events from Dose 1 to 28 days following each vaccination and delayed boost dose.
- MAAEs, SAEs, NOCMCs, and AESIs from Dose 1 on study to month 12 months after last dose on study.

2. To evaluate humoral immunogenicity of heterologous booster vaccines following EUA dosing.

Exploratory:

1. To assess, in at least a subset of samples, the B cell immune response following EUA vaccination and delayed boost;
2. To assess, in at least a subset of samples, the SARS-CoV-2 protein-specific T cell responses following EUA vaccination and delayed boost;
3. To evaluate breakthrough symptomatic SARS-CoV-2 infection and sequence strains to assess for variant spike lineage.

Study Design:

This Phase 1/2 study will evaluate the safety, tolerability, immunogenicity of different SARS-CoV-2 vaccine delayed boost at ≥12 weeks. This study will be composed of two different cohorts:

1. A cohort of persons previously vaccinated with an EUA vaccine who will be boosted with a homologous or heterologous vaccine strain on a homologous or a heterologous platform (Table 1); and
2. A cohort of persons who are prospectively vaccinated with EUA standard dosing and who will be available for rapid assessment of a heterologous boost at some point in the future (Table 2).

EUA-dosed Cohort: Cohort 1 will recruit persons who have previously received COVID-19 vaccine under EUA dosing guidelines, completing their regimen at least 12 weeks prior to enrollment. Eligible individuals will be stratified by age group (18-55 years or ≥ 56 years) in a 1:1 ratio (N = 25/group). Subjects will be sequentially enrolled to receive one of the available delayed boost options (Table 1). A total of approximately 50 per group will be recruited for each group (combination of EUA primary vaccination plus booster) in Cohort 1. This study is designed to be adaptive, and as more vaccines become available under EUA or new variants of available EUA vaccine become available, the number of groups may be expanded. Participants will be assessed for safety and tolerability endpoints following administration of a delayed boost.

Table 1: EUA-dosed Cohort 1

Group	Sample Size*	EUA Dosing Scheme	Interval (weeks)	Delayed Booster Vaccination	Strategy Tested
1E	**50**	Previously dosed Janssen – Ad26.COV2-S	≥12	Moderna- mRNA-1273	Same Strain Heterologous platform
2E	**50**	Previously dosed Moderna – mRNA-1273	≥12	Moderna- mRNA-1273	Control - Same Strain & platform
3E	**50**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Moderna- mRNA-1273	Same Strain Similar platform
4E	**50**	Previously dosed Janssen – Ad26.COV2-S	≥12	Janssen – Ad26.COV2.S	Control - Same Strain & platform
5E	**50**	Previously dosed Moderna – mRNA-1273	≥12	Janssen – Ad26.COV2.S	Same Strain Heterologous platform
6E	**50**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Janssen – Ad26.COV2.S	Same Strain Heterologous platform
7E	**50**	Previously dosed Janssen – Ad26.COV2-S	≥12	Pfizer/BioNTech – BNT162b2	Same Strain Heterologous platform
8E	**50**	Previously dosed Moderna – mRNA-1273	≥12	Pfizer/BioNTech-BNT162b2	Same Strain Similar platform
9E	**50**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Pfizer/BioNTech – BNT162b2	Control - Same Strain & platform
10E	**50**	Previously dosed Janssen – Ad26.COV2-S	≥12	Moderna- mRNA-1273.211	Variant Strain Heterologous platform
11E	**50**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Moderna- mRNA-1273.211	Variant Strain Similar platform
12E	**50**	Previously dosed Janssen – Ad26.COV2-S	≥12	Moderna- mRNA-1273 50 mcg	Same Strain Heterologous platform
13E	**50**	Previously dosed Moderna – mRNA-1273	≥12	Moderna- mRNA-1273 50 mcg	Control - Same Strain & platform
14E	**50**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Moderna- mRNA-1273 50 mcg	Same Strain Similar platform

*Sample cohort size, N = approximately 50, two age strata: 18-55 years (n ≈ 25), ≥ 56 years (n ≈ 25)

Prospective Cohort: Cohort 2 will recruit persons who are naïve to COVID-19 vaccine and infection (by history). These individuals will be given a vaccine as part of the study that matches the vaccine/dose available under an EUA. Cohorts from this pool will then be available to be boosted with a novel homologous or heterologous variant lineage spike proteins or heterologous platform delayed boost as part of an adaptive design meant to respond quickly to circulating SARS-CoV-2 variants. As new vaccines are manufactured to emerging variant lineages, these dosed "pools" of study participants will enable rapid deployment of delayed booster constructs.

Prioritization of Cohort 1 versus Cohort 2 enrollment will be determined by availability of EUA-dosed vaccines, status of distribution, and current epidemiology. Cohorts 1 and 2 may enroll simultaneously.

Table 2: Prospective Cohort 2

Group	Sample Size*	First Vaccination**	Interval	Second Vaccination**	Interval (Weeks)	Delayed Booster Vaccination
1	**250**	Moderna-mRNA-1273	28d	Moderna-mRNA-1273	≥12	Novel homologous or heterologous variant or heterologous platform boost

*Aged ≥ 18 years
** As part of an adaptive design, products newly awarded EUA can be added as programmatically needed.

Duration of Study: Approximately 4 years

Duration of participation per subject: Up to 2 years (approximately 12 months after delay boost inoculation)

Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Participants must meet all of the following criteria to be eligible to participate in this study:

1. Individuals ≥ 18 years of age at the time of consent.
2. Received and completed COVID-19 vaccine under EUA dosing guidelines at least 12 weeks prior to enrollment (Cohort 1 only).
3. Willing and able to comply with all scheduled visits, vaccination plan, laboratory tests and other study procedures.
4. Determined by medical history, targeted physical examination and clinical judgement of the investigator to be in good health.

Note: Heathy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

5. Female participants of childbearing potential may be enrolled in the study, if all of the following apply:

   - Practiced adequate contraception for 28 days prior to the first dose of vaccine (Day 1),
   - Has agreed to continue adequate contraception through 3 months following the booster dose,
   - Has a negative pregnancy test at screening and on the day of the first study vaccine dose (Day 1),
   - Is not currently breastfeeding.

Exclusion Criteria:

Participants meeting any of the following criteria will be excluded from the study:

1. Known history of SARS-CoV-2 infection.
2. Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or SARS-CoV-2 monoclonal antibody in the preceding 90 days or current/planned simultaneous participation in another interventional study.
3. Receipt of SARS CoV-2 vaccine prior to study entry (Cohort 2 only).
4. A history of anaphylaxis, urticaria, or other significant adverse reaction requiring medical intervention after receipt of a vaccine or nanolipid particles.
5. Receipt of any investigational study product within 28 days prior to enrollment.
6. Received or plans to receive a vaccine within 28 days prior to the first dose (Day 1) or plans to receive a non-study vaccine within 28 days prior to or after any dose of study vaccine (with exception for seasonal influenza vaccine within 14 days of study vaccine).
7. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with intramuscular injections or blood draws, or previously experienced thrombosis with thrombocytopenia (TTS) or heparin-induced thrombocytopenia.
8. Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.
9. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to Day 1.

10. Received immunoglobulin, blood-derived products, within 90 days prior to first study vaccination.
11. An immediate family member or household member of this study's personnel.
12. Is acutely ill or febrile 72 hours prior to or at vaccine dosing (fever defined as ≥ 38.0°C/100.4°F). Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

Safety

- The study will use halting rules for booster vaccination in the study overall and not EUA dosed vaccinations to individual subjects. See Section 7.1 for details.
- This study will use a Safety Monitoring Committee (SMC) for objective oversight of the study. SMC reviews are required for study halting.

1.2 Schedule of Activities (SOA)

Table 3: SOA for EUA-dosed Cohort 1

Study Day	D-28 to D-1	1	8[b]	15	29	91	169	366	Illness/ Unscheduled Visit	Early Termination Visit
Visit Number	00[a]	1	2	3	4	5	6	7		
Window (+/-)		0	1	2	2	7	7	14		
Informed Consent[a]	X									
Eligibility Criteria	X	X								
Medical History	X	X								
Vaccination[c]		X								
Concomitant Meds		X	X	X	X					
Interim History		X	X	X	X	X	X	X	X	X
Physical Exam - Targeted	X	X		X	X	X	X	X	X	X
Vital Signs[d]	X	X		X	X				X	X
Height/Weight (BMI)[a]	X									
Urine β-HCG[e]		X								
Memory Aid, Solicited AEs		X	X	X[f]						
Unsolicited AEs		X	X	X	X					
SAEs, Protocol specified AESIs, MAAEs, and NOCMCs			X	X	X	X	X	X	X	X
Nasal or NP swab for PCR & Sequencing									X[g]	
Immunoassays										
Serum- Humoral Assays		32		32	32	32	32	32		32
PBMC Cellular Assays & plasma		64		64			64	64		64
Daily Volume (mL)		96		96	32	32	96	96		96
Cumulative Volume (mL)		96		192	224	256	352	448		

[a] Optional screening visit – informed consent and height/weight only performed at screening or Day 1

[b] Telephone visit

[c] Delayed booster dose based upon assignment to Groups 1E-3E (and/or future groups added as adaptive design)

[d] Vital signs before and after booster vaccination. Otherwise, only as clinically indicated

[e] For women of childbearing potential, a negative urine pregnancy on Day 1 will be performed with negative results confirmed before dosing

[f] Review 7-day Memory Aid data.

[g] Collect nasal or NP swab for PCR (x2). Sequencing will be performed on all Illness visit-confirmed SARS-CoV-2 specimens.

Table 4: SOA for Prospective Cohort 2:

Study Day	D-28 to D-1	1	8[b]	29	36[b]	43	Delayed Boost to occur ≥12 weeks from completion of EUA dosing	1B	8b[b]	15B	29B	91B	169B	366B	Illness/ Unsch Visit	Early Term Visit
Visit Number	00[a]	1	2	3	4	5		6	7	8	9	10	11	12		
Window (+/-)		0	1	2	3	3		0	1	2	2	7	7	28		
Informed Consent[a]	X															
Eligibility Criteria	X	X		X				X								
Medical History	X															
Vaccination		X[c]		X[c]				X[d]								
Concomitant Meds	X	X	X	X	X	X		X	X	X	X					
Interim History		X	X	X	X	X		X	X	X	X	X	X	X	X	X
Physical Exam - Targeted	X	X		X		X		X		X	X	X	X	X	X	X
Vital Signs[e]	X	X		X				X		X	X				X	
Height/Weight (BMI)[a]	X															
Urine β-HCG[f]		X		X				X								
Memory Aid, Solicited AEs		X	X	X	X			X	X	X[g]						
Unsolicited AEs		X	X	X	X	X		X	X	X	X					
SAEs, Protocol specified AESIs, MAAEs, and NOCMCs			X	X	X	X		X	X	X	X	X	X	X	X	X
Nasal or NP swab for PCR & Sequencing															X[h]	
Immunoassays																
Serum- Humoral Assays		32		32		32		32		32	32	32	32	32		32
PBMC Cellular Assays & plasma		64*		64*		64*		64		64		64	64	64		64
Daily Volume (mL)		96		96		96		96		96	32	96	96	96		96
Cumulative Volume (mL)		96		192	192	288		384		480	512	608	704	800		

[a] Optional screening visit – informed consent and height/weight only performed at screening or Day 1

[b] Telephone visit

[c] EUA-dosing with 28-day interval – new constructs may be added as EUA is awarded and vaccine available

[d] Delayed booster dose based upon assignment of variant and/or heterologous vaccine constructs added as adaptive design. If no booster administered; volunteer will not proceed to additional visits except for unscheduled illness visits

[e] Vital signs before and after vaccination. Otherwise, only as clinically indicated.

[f] For women of childbearing potential, a negative urine pregnancy test on Days 1 and 1B (delayed boost) will be performed with negative results confirmed prior to each dosing

[g] Review 7-day Memory Aid data for delayed booster dose.

[h] Collect nasal or NP swabs (x 2) for PCR. Sequencing will be performed on all Illness visit-confirmed SARS-CoV-2 specimens.

*Collection of PBMC for cellular assays is performed at the discretion of the site, based on the capacity for PBMC processing

2. INTRODUCTION

2.1 Background and Study Rationale

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first detected in Wuhan, Hubei Province, China in December 2019. The corresponding illness designation, coronavirus disease 2019 (COVID-19), was declared as a pandemic respiratory illness on March 2020.[1] As of 02 July 2021, it has infected over 182 million people worldwide and resulted in over 3.9 million deaths, including > 605,000 in the United States.[1,2]

Five Phase 3 efficacy trials of SARS-CoV-2 vaccine constructs are underway or in long-term follow-up in the U.S., through U.S. government efforts funded by the Biomedical Advanced Research and Development Authority (BARDA) and National Institutes of Health (NIH). Vaccine testing centers have prioritized research studies as part of three Phase 3, 2-dose trials in various stages of conduct (Moderna, AstraZeneca/Oxford, Novavax), one Phase 3 single-dose trial (Janssen – 2-dose testing underway internationally) and one privately funded, 2-dose trial (Pfizer/BioNTech). The ModernaTX, Inc mRNA-1273 and Pfizer/BioNTech BNT162b2 mRNA platforms encode for the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S-2P) in a prefusion conformation, derived from the Wuhan-Hu-1 strain.[3] The Janssen Pharmaceutical/Johnson & Johnson COVID-19 Vaccine (Ad26.COV.2) is composed of recombinant, replication-incompetent human adenovirus type 26, encoding a prefusion-stabilized SARS-CoV-2 spike antigen.[4] Studies of the Pfizer and Moderna mRNA vaccines demonstrated high efficacy against all symptomatic and severe disease and received Emergency Use Authorization (EUA) on December 12 and 18, 2020, respectively. Similarly, Janssen Pharmaceuticals reported 66% vaccine efficacy with a single dose and high-level protection against severe disease and death. FDA EUA was issued on February 26, 2021. AstraZeneca/Oxford's (ChAdOx-2) is expected to undergo FDA review for EUA shortly and Novavax is rapidly approaching its Phase 3 endpoint for interim analysis of vaccine efficacy. It is anticipated that the U.S. could have up to 5 different COVID-19 products under EUA by the end of second quarter 2021.

The optimization and distribution of SARS-CoV-2 vaccines is of critical public health priority. The inability to mass-vaccinate the world's population in a timely fashion is resulting in ongoing high-level transmission and accelerated emergence of variants with mutations in the S protein. Moreover, the evolution of variant strains may favor immune escape or reinfection among previously infected or vaccinated individuals. A variant first identified in South Africa (B.1.351) is associated with increased transmission, higher viral burden, and possibly increased mortality in infected persons.[5] The emergence of variant strains has raised concerns about the breadth of immunity and protection achieved by the current vaccines. Pivotal studies testing both viral vector and adjuvanted protein technologies had lower efficacy in regions where B.1.351 was known to be circulating.[6,7] Sera from individuals vaccinated with mRNA-based vaccines had a 6-to-9-fold reduction in neutralizing activity against a B.1.351-matched pseudovirion relative to a Wuhan-matched pseudovirion.[8,9] WHO SAGE and CDC ACIP have identified the safety and immunogenicity of mixed schedules as a critical and immediate research priority to inform policy on the use of mixed schedules. Vaccine manufacturers are working on variant booster candidates

to optimize efficacy against the B.1.1.7, B.1.351 and Brazilian P1 and P2 rapidly emerging variants with receptor binding domain mutations. For example, mRNA-1273.211, like mRNA-1273, encodes the prefusion stabilized S protein (S-2P) of SARS-CoV-2, but also incorporates the key mutations present in the B.1.351 viral strain (S-2P) in a 1:1 ratio with the wildtype Wuhan-Hu-1 strain. A phase 1 clinical trial to examine the immunological benefit of boosting subjects previously vaccinated with mRNA-1273 (DMID 20-0003) with the B.1.351 strain-specific S protein is underway.

Prime-boost strategies may enhance immunogenicity through complementary stimulation of humoral and T cell immune pathways. In contrast, the immune response to booster doses of certain vaccines, such as the adenovirus vector vaccines, may be limited by pre-existing antibody and/or enhanced by longer dosing intervals. Thus, the order of delivery of heterologous SARS-CoV-2 vaccine platforms may result in immune responses that are greater or less than homologous regimens of the same vaccine. In a murine model, a self-amplifying RNA vaccine followed by the adenovirus vectored vaccine (ChAdOx1-nCoV-19/AZD1222) was shown to induce high titers of neutralizing antibodies (although was not tested against a two-dose homologous regimen).[10] In humans, the Gam-COVID-Vac combined vector vaccine consisting of rAD26 carrying the full-length glycoprotein S (rAD26-S) (prime) and rAd5-S administered after 21 days as a boost, demonstrated 91.6% efficacy in adults < 60 years of age and illustrates the potential vaccine efficacy with a heterologous prime/boost strategy.[11] The United Kingdom (UK) announced plans (4 Feb 2021) to test a mix-and-match approach (at 4- and 12-week intervals) with currently UK-approved vaccines. Testing of the heterologous prime boost strategy with Pfizer/BioNTech's (BNT162b2) followed by AstraZeneca/Oxford's (ChAdOx-2) and vice versa is underway in the UK.

Knowledge of the safety, tolerability, and immunogenicity of a delayed heterologous boost vaccine incorporating a similar or variant spike administered following EUA dosing regimens might induce immunity to variant circulating strains and improve upon breadth and durability of protection. Utilizing the EUA-dosed COVID-19 vaccines available (currently mRNA-1273, -BNT162b2, and AD26.COV2.S), we propose to evaluate innate, cellular, and humoral immune responses elicited from different booster vaccines. As part of an adaptive design, we anticipate adding groups with variant-lineage spike proteins and other vaccine platforms, subject to availability.

2.1.1 Public Readiness and Emergency Preparedness Act

The study vaccines, mRNA-1273, mRNA-1273.211, BNT162b2, and Ad26.COV.2, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273, mRNA-1273.211, BNT162b2, and Ad26.COV2.S. The PREP Act provides immunity for covered persons from liability unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 10, 2020 and is retroactively effective from February 4, 2020.

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

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

If the Secretary of DHHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the initial immunization with mRNA-1273 vaccine and delayed booster inoculation of mRNA-1273, mRNA-1273.211, BNT162b2 and Ad26.COV2.S, 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.

Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, and BNT162b2)

Immediate systemic allergic reactions (e.g., anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein.[12]

Anaphylactic reactions have occurred after administration of the Moderna and the Pfizer mRNA COVID-19 vaccines in vaccination campaigns under Emergency Use Authorization (EUA) in the United States. Most of these reactions had onset within 30 minutes of vaccination, most of these events occurred in persons with a prior history of allergy, and nearly all were women. The currently estimated risk of an anaphylactic reaction to the mRNA EUA COVID-19 vaccines is about 2-5 events per million vaccinations.

As a precaution, all subjects will remain under observation at the study site for at least 30 minutes after injection.

Infrequently, people who have received dermal fillers might experience swelling at or near the site of filler injection (usually face or lips) following administration of a dose of an mRNA COVID-19 vaccine. The swelling appears to be temporary and resolves with medical treatment, including corticosteroid therapy. COVID-19 vaccines can be administered to people who have received injectable dermal fillers who have no contraindications or precautions for vaccination.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by ModernaTX, Inc. containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection. A small percentage of participants may experience late local inflammatory reactions, with onset seven or more days after, usually the first, vaccination, and characterized by redness in the deltoid area of the upper arm and/or pain or itching.[13] These reactions are self-limited and are not a contraindication to subsequent vaccinations in the vaccination series.

The majority of local and systemic solicited adverse events (AEs) observed after injection with mRNA-1273 at the 100-mcg dose level or BNT162b2 at the 30-mcg dose level have been mild to moderate in severity. The most commonly reported systemic AEs were headache, myalgia, fatigue, chills, and fever.[13-15] In the majority of cases, the reactions resolved spontaneously within several days. Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline, pre-vaccination (Day 1) values over time. The clinical significance of these observations is unknown.

There is limited experience with administration of a third dose of the mRNA COVID-19 vaccines, and it is possible that the third dose may be associated with more frequent or more severe adverse events.

Myocarditis and pericarditis have been reported following mRNA vaccines, particularly after the second dose, in a younger population (age < 30 years), and more common in males. Symptoms can include chest pain, shortness of breath, or palpitations. Typically, onset of symptoms has been within a few days following receipt of the mRNA COVID-19 vaccines. Whilst some severe cases have been reported, most cases have been associated with full resolution of symptoms in the short term; however, long-term follow-up is limited. It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of the vaccine, e.g., following a booster dose.

Further details are provided in the FDA-approved fact sheet and current IBs for mRNA-1273, mRNA-1273.211 and BNT162b2. mRNA-1273.211 has not been extensively tested clinically, but based on its similarity to mRNA-1273, the risks are expected to be similar.

Risks of Ad26.COV2.S.

Immediate systemic allergic reactions (e.g., anaphylaxis) can occur following any vaccination but no cases of anaphylaxis were noted in the Phase 3 trial. Hypersensitive reactions, not classified as anaphylaxis, are a rare occurrence within the Ad26 platform but have been reported.

The most common solicited adverse events were injection site pain, headache, fatigue and myalgia. Intramuscular injection with Ad26.COV2.S can cause local pain, erythema (redness), or swelling at the injection site, which are mostly mild to moderate in severity, transient, and usually occur within 24 hours of injection.

Pyrexia (fever defined as body temperature $\geq$ 38.0°C) was reported and generally dissipated within 24 hours of vaccination. Other solicited events systemic signs and symptoms included headache, myalgia, chills and nausea.

Grade 2 facial paralysis (Bell's Palsy) has been reported although the incidence of Bell's Palsy was not above known background prevalence rates. Tinnitus has been reported following vaccination with Ad26.COV2.S but it is unclear if these were due to vaccine or underlying medical conditions.

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. These cases occurred approximately 3 weeks following vaccination. The reporting rate of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine has been highest in females ages 18 through 49 years; some have been fatal. Thrombosis in combination with thrombocytopenia can be fatal. The exact physiology of TTS is unclear. TTS is considered an important identified risk for Ad26.COV2.S. It is unknown if this risk changes (increase or decreases) when this vaccine is used as a delayed booster vaccine. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, and skin bruising and/or petechiae beyond the site of vaccination. The medical management of thrombosis with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or

treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (e.g., from the American Society of Hematology, British Society of Haematology - Expert Haematology Panel10, and the CDC). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended. Refer to the latest version of the IB and its addenda (if applicable) for further details. Due to the possibility of the occurrence of TTS after vaccination with Ad26.COV2.S, additional reporting and data collection procedures have been included in the study for thrombotic events, thrombocytopenia, and TTS (see Section 8.3.9), which may facilitate diagnosis and clinical management of the event.

Rare cases of Guillain Barré syndrome have occurred in some people who have received the Janssen COVID-19 Vaccine. The FDA requested (12 Jul 2021) that this risk be added to the Fact Sheet. In most circumstances, symptoms began within 42 days following receipt of dosing. Reported symptoms included weakness or tingling sensations in the extremities, difficulty ambulating, difficulty with facial movements to include chewing, swallowing or speaking, diplopia or inability to move eyes, or difficulty with bowel or bladder control.

While there is a theoretical risk of vaccine-associated enhanced diseases (VAED) with SARS-CoV-2 vaccines, there has been no evidence of VAED following Ad26.COV2.S or mRNA vaccine dosing.

There is limited evidence of the effects of administering an adenovirus-vectored vaccine before or after an mRNA COVID-19 vaccine, and it is possible that a delayed booster dose may result in more frequent or more severe adverse events.

Risks to Privacy

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

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

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

Risks of Genetic Testing

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

2.2.2 Known Potential Benefits

In cohort 2, there is the potential for protection against symptomatic SARS-CoV-2 infection following receipt of an EUA vaccine. There is no known direct benefit expected to the subjects in Cohort 1 or from the booster vaccination in Cohort 2. There is potential benefit that the vaccine will boost the participant's immunity to a SARS-CoV-2 infection and the benefit to society resulting from insights gained from participation in this study due to the emerging threat of the SARS-CoV-2 outbreak. Data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 demonstrated 94.1% efficacy of the vaccine as a two-vaccination series versus placebo against symptomatic SARS-CoV-2 infection. The Phase 3 placebo-controlled trial of BNT162b2 provided 95% vaccine efficacy as a two-vaccination series versus placebo against symptomatic SARS-CoV-2 infection.[15] The Phase 3 placebo-controlled clinical trial of Ad26.COV.2 demonstrated 66% efficacy against mild-moderate SARS-CoV-2 infection and 85% against severe disease as a one-dose vaccination. The doses and vaccination strategies used in this trial may or may not alter this protection. It is unknown if the mRNA-1273.211 vaccine will provide protection against infection with the B.1.351 variant.

3. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of delayed heterologous or homologous vaccine doses after EUA dosed vaccines.	• Local and systemic solicited adverse events for 7 days following the delayed boost dose. • Adverse Events from Dose 1 to 28 days following each vaccination and delayed boost dose. • MAAEs, SAEs, NOCMCs, and AESIs from Dose 1 on study to month 12 months after last dose on study.
• To evaluate the breadth of the humoral immune responses of heterologous and homologous delayed boost regimens following EUA dosing	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization titers in serum samples as assessed via a range of assays at all timepoints.
Secondary	
• None	• None
Exploratory	
• To assess, in at least a subset of samples, the B cell immune response following EUA vaccination and delayed boost	• Magnitude, phenotype and percentage of SARS-CoV-2 specific B cells, as measured by flow cytometry and targeted B cell subset analysis at time points post-vaccination and/or delayed boost.
• To assess, in at least a subset of samples, the SARS-CoV-2 protein-specific T cell responses following EUA vaccination and delayed boost	• Magnitude, phenotype, and percentage of cytokine producing S protein T cells as measured by flow cytometry at time points post-vaccination and/or delayed boost.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• To evaluate breakthrough symptomatic SARS-CoV-2 infection and sequence strains to assess for variant spike lineage	• To perform sequence analysis on breakthrough NAAT-confirmed COVID-19 strains to assess for variant spike lineage

4. STUDY DESIGN

4.1 Overall Design

This is a phase 1/2, open-label clinical trial in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed (≥12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; -BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson). This is an adaptive design and may add arms (and increase sample size) as vaccines are awarded EUA and/or variant lineage spike vaccines are manufactured or become available. Enrollment will occur at up to twelve domestic clinical research sites.

This study includes two cohorts. Cohort 1 will provide rapid information about the safety, reactogenicity, and immunogenicity of delayed boost in a previously EUA-dosed group. This cohort can inform near term public health decisions if the variant virus becomes more widespread. Cohort 2 is an adaptive cohort that will evaluate, in a prospective fashion, the safety, reactogenicity and immunogenicity of EUA-dosed vaccine followed by delayed boost. Pools of subjects will be recruited to receive EUA-dosed vaccine and will be assigned, at a later date, to a delayed booster vaccine based on availability of vaccine product, to enable rapid implementation based on situational assessment of need. This cohort will take longer to provide information on the immunogenicity of delayed boost, but it may assume priority in enrollment as it is important to inform future public health strategies and as access to COVID-19 vaccine becomes more widespread. As Cohorts 1 and 2 are in different populations, they can be enrolled in parallel or prioritized as determined by DMID/IDCRC needs.

Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and ≥ 56 years) who received previously received COVID-19 vaccine at EUA dosing (two vaccinations of mRNA-1273 at the 100 mcg dose, two vaccinations of BNT162b2 at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the $5x10^{10}$ vp dose). Those subjects will be offered enrollment into this study ≥12 weeks after they received the last dose of their EUA vaccine. Subjects will receive an open-label delayed boost that is assigned to each of the approximately twelve domestic trial sites.

1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by:
    - Group 1E – A 100-mcg dose of mRNA-1273
    - Group 4E – A $5x10^{10}$ vp dose of Ad26.COV2.S
    - Group 7E - A 30-mcg dose of BNT162b2
    - Group 10E –A 100-mcg dose of mRNA-1273.211
    - Group 12E – A 50-mcg dose of mRNA-1273
2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by:
    - Group 2E – A 100-mcg dose of mRNA-1273
    - Group 5E – A $5x10^{10}$ vp dose of Ad26.COV2.S

- Group 8E - A 30-mcg dose of BNT162b2
  Note: There will be no boost with mRNA-1273.211 to avoid duplication of trial efforts with DMID 21-0003.
- Group 13E – A 50-mcg dose of mRNA-1273

3. Previously EUA-dosed vaccination with Pfizer/BioNTech - BNT162b2 at 30 mcg for two doses followed by:
   - Group 3E – A 100-mcg dose of mRNA-1273
   - Group 6E – A $5x10^{10}$ vp dose of Ad26.COV2.S
   - Group 9E - A 30-mcg dose of BNT162b2
   - Group 11E – A 100-mcg dose of mRNA-1273.211
   - Group 14E – A 50-mcg dose of mRNA-1273

The anticipated sample size of each group is approximately 25 subjects 18 through 55 years of age and approximately 25 subjects 56 years of age and older for a total of 50 subjects per group.

Subjects in Cohort 1 will receive a single intramuscular (IM) injection of the designated delayed booster vaccine and will be followed through 12 months after vaccination. A telephone visit will occur at Day 8 and in-person follow-up visits will occur on Days 15 and 29, as well as 3, 6, and 12 months after the vaccination.

Table 6. Cohort 1 Treatment Arms

Arm	Sample Size	Booster Vaccination Product and Dose
1E	~50	100 mcg mRNA-1273
2E	~50	100 mcg mRNA-1273
3E	~50	100 mcg mRNA-1273
4E	~50	$5x10^{10}$ vp dose Ad26.COV2.S
5E	~50	$5x10^{10}$ vp dose Ad26.COV2.S
6E	~50	$5x10^{10}$ vp dose Ad26.COV2.S
7E	~50	30 mcg BNT162b2
8E	~50	30 mcg BNT162b2
9E	~50	30 mcgBNT162b2
10E	~50	100 mcg mRNA-1273.211
11E	~50	100 mcg mRNA-1273.211
12E	~50	50 mcg mRNA-1273
13E	~50	50 mcg mRNA-1273

14E	~50	50 mcg mRNA-1273

Summary of Treatment Arms:

- 1E – Evaluates a heterologous platform booster dose of mRNA-1273 among persons who previously received an Ad26.COV2.S EUA vaccination series
- 2E- As a bridging arm evaluates a homologous platform third boosting dose of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series
- 3E – Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received a BNT162b2 EUA vaccination series
- 4E - Evaluates Ad26.COV2.S EUA vaccination series followed by a homologous platform delayed dose of Ad26.COV2.S
- 5E - Evaluates mRNA-1273 EUA vaccination series followed by a heterologous platform delayed dose of Ad26.COV2.S
- 6E - Evaluates BNT162b2 EUA vaccination series followed by a heterologous platform delayed dose of Ad26.COV2.S
- 7E - Evaluates Ad26.COV2.S EUA vaccination series followed by a heterologous platform delayed dose of BNT162b2
- 8E - Evaluates mRNA-1273 EUA vaccination series followed by a homologous platform delayed dose of BNT162b2
- 9E - Evaluates BNT162b2 EUA vaccination series followed by a homologous platform delayed dose of BNT162b2
- 10E- Evaluates Ad26.COV2.S EUA vaccination series followed by a heterologous platform delayed dose of a combined homologous and variant spike lineage mRNA-1273.211
- 11E - Evaluates BNT162b2 EUA vaccination series followed by a homologous platform delayed dose of a combined homologous and variant spike lineage mRNA-1273.211
    - Note – the homologous comparator for groups 10E and 11E (Moderna EUA vaccination with the mRNA 1273.211 variant vaccine is being conducted in another trial (NIAID DMID 21-0002) and not done here to avoid duplication.
- 12E – Evaluates a heterologous platform 50 mcg booster of mRNA-1273 among persons who previously received an Ad26.COV2.S EUA vaccination series
- 13E- Evaluates a homologous platform 50 mcg booster of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series
- 14E – Evaluates a homologous mRNA platform of mRNA-1273 50 mcg booster among persons who previously received a BNT162b2 EUA vaccination series

Cohort 2 will include approximately 250 participants per group aged $\geq$ 18 years of age who have not received a COVID-19 vaccine and have no known history of COVID-19 or SARS-CoV-2 infection. They will be assigned to receive COVID-19 vaccine under EUA dosing (as programmatically outlined in Table 7). Additional pools of subjects can be included if needed as additional COVID-19 vaccines are awarded EUA. These pools of participants will be assigned a

novel homologous or heterologous variant boost or heterologous platform boost at a minimum of 12 weeks following receipt of EUA dosing and followed through 12 months after the last vaccination. A telephone visit will occur one week after each primary EUA vaccination and one week after the booster dose. In person follow-up visits will occur on 14 days following completion of EUA vaccinations and on days 14, and 28 days after the booster dose, as well as 3, 6, and 12 months post the booster vaccination.

Table 7: Cohort 2 Treatment Arms

Group	Sample Size	First Vaccination	Second Vaccination		Booster Vaccination	
		Product and Dose	Interval	Product and Dose	Interval	Product and Dose
1	250	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273	≥ 12 weeks	Novel homologous/ heterologous variant or heterologous platform boost

For both Cohorts 1 and 2, reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays at the in-person follow-up visits.

After the IND is in effect, IRB review and approval, and site activation, the participating sites will begin recruitment outreach efforts, which can include fliers, letters, telephone calls, etc. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the participating site. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use. Screening can occur up to 28 days prior to the first dose or on Day 1 prior to administration of Dose 1.

Schedules of assessments are found in **Section 1.2, Schedule of Activities.**

4.2 Scientific Rationale for Study Design

This phase 1/2 clinical trial is designed as an open-label study, without administration of a placebo formulation. An open-label study will facilitate the need for rapid review and dissemination of study data for public health reasons.

4.3 Justification for Doses

The dosages selected are those authorized under EUA.

In the Phase 1 clinical trial, DMID 20-0003, mRNA-1273, administered as two injections 28 days apart, was investigated at dosages of 25, 50, 100 and 250 mcg in subjects 18 through 55 years of age, and at dosages of 25, 50, and 100 mcg in older cohorts (56-70 years of age and >71 years of

age).[16,17] The 100-mcg dose induced higher antibody titers than the 25-mcg dose, whereas the 250-mcg dose did not lead to significant increases. The Phase 2 trial of mRNA-1273 evaluated doses of 50 mcg and 100 mcg, administered as a two-vaccination series, in 600 adults ≥18 years of age. The safety profile of both formulations was acceptable.[18] Anti-SARS-CoV-2 S binding and neutralizing antibodies were induced by both dose levels of mRNA-1273 within 28 days after the first vaccination and rose substantially to peak titers by 14 days after the second vaccination, exceeding levels of convalescent sera from COVID-19 patients. The antibodies remained elevated through the last timepoint assessed at 57 days. Binding and neutralizing antibody responses were generally comparable in participants who received the 100-mcg mRNA-1273 and the 50-mcg dose at all time points and across the age groups of ≥18 to <55 years and ≥55 years. These findings support the evaluation of mRNA-1273 and mRNA-1273.351 at total dosages of 50 or 100 mcg per vaccination. For this reason, mRNA-1273.211 consists of a combined 50-mcg of mRNA-1273 encoding the S-2P of Wuhan-Hu-1 and 50-mcg of mRNA-1273.351 encoding the S-2P of the South African (Beta) variant strain. Further, the 50mcg dose of mRNA-1273 will be tested as a dose-sparing booster option separate from the admixture (mRNA-1273 and mRNA-1273.351) dosing. The primary efficacy analysis from the Phase 3 trial evaluating a two-dose schedule of a 100-mcg mRNA-1273 vaccine led to the issuance of the EUA and initiation of a vaccination campaign in the United States.

The Phase 1 study of BNT162b1 (which encodes the RBD) vs. BNT162b2 (which encodes the full-length spike protein) produced by Pfizer/BioNTech administered at two injections 21 days apart, was investigated at dosages of 10, 20, 30 and 100 mcg in subjects 18 through 55 years of age and 65 through 85 years of age.[14] BNT162b2 was associated with lower incidence and severity of systemic reactions compared to BNT162b1, and both produced similar levels of neutralizing antibody which superseded convalescent serum results. The lower incidence of systemic reactions was particularly apparent in older subjects. The 50% and 90% neutralizing antibody titers exceeded convalescent serum at 7 and 14 d after the second dose. Based upon these data, the 30-mcg dose was taken into Phase 2a/3 trials. The results of the Phase 2a/3 trial demonstrated thatBNT162b2 administered as two injections, 21 days apart, at a 30-mcg dose, conferred 95% protection against COVID-19 in persons ≥16 years of age.[15] The primary efficacy analysis from the Phase 3 trial led to the issuance of the EUA and initiation of a vaccination campaign in the United States.

The Phase 1/2a study of the AD26.COV2.S vaccine evaluated two dosage levels ($5x10^{10}$ vp and $1x10^{11}$ vp) based upon prior vaccine studies with the Ad26 platform.[19] Both formulations administered as a single dose had favorable safety and immunogenicity profiles,[20] yielding high and comparable humoral and cellular immune response rates. The lower dose had a more favorable reactogenicity profile and was selected for Phase 3 trial evaluation that demonstrated its protective efficacy.[19]

5. STUDY POPULATION

Two cohorts will be enrolled. For Cohort 1, approximately 700 individuals (50 subjects/group; Groups 1E-14E) 18 years of age and older, stratified into two age groups (18-55 years and ≥56 years at 1:1 ratio), who are in good health and received EUA dosed vaccinations of mRNA-1273, BNT162b2 or Ad26.COV2.S will be invited to participate in this study.

For Cohort 2, approximately 250 individuals (250 subjects/group), ≥18 years of age, who have never been vaccinated against SARS-CoV-2 or are not known to have been infected with SARS-CoV-2 and meet all eligibility criteria will be enrolled. The target population should reflect the community at large. Future groups may be added as additional EUA vaccines become available.

The estimated time from initiation of enrollment to complete enrollment in each group within this clinical trial is approximately 2-4 weeks (though could take longer). However, owing to the adaptive nature of the design, new groups may be added to Cohort 1 or 2 dependent upon manufacture of variant lineage spike protein-based vaccine constructs or vaccines newly awarded EUA. An optional screening period can occur up to 28 days prior to the first vaccination, or can be completed on Day 1, prior to dosing.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572. No exemptions are granted on Subject Inclusion or Exclusion Criteria in DMID-sponsored studies.

5.1 Inclusion Criteria

See Inclusion Criteria in Synopsis

5.2 Exclusion Criteria

See Exclusion Criteria in Synopsis.

5.2.1 Exclusion of specific populations

The effects on the fetus are not known; therefore, pregnant women will not be eligible for the trial. Children will not be included in this trial as presently there are no safety or efficacy data in adults for the variant strain. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including these populations.

5.3 Inclusion of Vulnerable Subjects

Not Applicable

5.4 Lifestyle Considerations

During this study subjects are asked to:

- Follow public health guidance on preventing SARS-CoV-2 infection.
- Subjects must avoid eating or drinking anything hot or cold within 10 minutes prior to taking oral temperature.

5.5 Screen Failures

A screening visit is optional. However, if screening assessments are performed, the participating site PI or qualified designee is to review the inclusion and exclusion criteria and determine the subject's eligibility for the study.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason for ineligibility. Subjects who are found to be ineligible will be told the reason for ineligibility.

5.6 Strategies for Recruitment and Retention

5.6.1 Recruitment

Potential subjects will learn about the study via IRB-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry and local advertisements/flyers. Screening will begin with a brief IRB-approved telephone call from study staff. Information about the study will be presented to potential subjects and questions about their health and ability to comply with the study visit schedule will be asked of potential subjects to presumptively determine eligibility. Appointments will be made at the research clinic for potential subjects who are interested in the study for further screening procedures and additional protocol-specific information.

5.6.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment/baseline visits and restriction of enrollment to persons who can attend all study visits. Participating subjects will be reminded of subsequent visits during each visit, and study staff will contact subjects prior to appointments. Study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

5.6.3 Compensation Plan for Subjects

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the amount contingent on completing study procedures.

5.6.4 Costs

There is no cost to subjects for the research tests, procedures/evaluations or 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.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Study Product Description

Product: mRNA-1273 and mRNA-1273.211

mRNA-1273 (0.2 mg/mL) is an LNP dispersion containing an mRNA that encodes for the pre fusion stabilized S protein of the Wuhan-Hu-1 strain of SARS-CoV-2. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and PEG2000 DMG.

mRNA-1273.211 (0.2 mg/mL) is formulated in the same way as the mRNA-1273 vaccine but contains 1:1 mix of mRNAs that encodes for the prefusion stabilized S protein of the B.1.351 variant SARS-CoV-2 strain and the prefusion stabilized S protein of the Wuhan-Hu-1 strain used in mRNA-1273.

Product: Ad26.COV2.S

Each 0.5 mL dose of the Ad26.COV2.S vaccine is formulated to contain $5x10^{10}$ virus particles of the Ad26 vector encoding the S glycoprotein of SARS-CoV-2. Each dose of the Ad26.COV2.S vaccine also includes the following inactive ingredients 2.19 mg sodium chloride, 0.14 mg citric acid monohydrate, 2.02 mg trisodium citrate dihydrate, 0.16 mg polysorbate-80, 25.5 mg 2-hydroxypropyl-β-cyclodextrin, 2.04 mg ethanol. Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng). The Ad26.COV2.S vaccine is a colorless to slightly yellow, clear to very opalescent suspension. Each vial contains five doses.

Product: BNT162b2

The Pfizer-BioNTech COVID-19 Vaccine (250 mcg/0.5 mL) contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose. Each vial contains up to six doses.

This vaccine requires dilution. The USP grade 0.9% NaCl or normal saline for injection is a sterile, nonpyrogenic, isotonic solution; each mL contains NaCl 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). This product should be used to dilute the BNT162b2 vaccine to the desired concentration.

6.1.2 Dosing and Administration

Product: mRNA-1273 and mRNA-1273.211

mRNA-1273 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL).

mRNA-1273 (0.2 mg/mL) will be administered in 0.25 mL doses (50 mcg/0.25 mL).

mRNA-1273.211 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL).

Product: Ad26.COV2.S

Ad26.COV2.S will be used undiluted to obtain the specified vp content in 0.5 mL doses. Each dose is 0.5 mL.

Product: BNT162b2

BNT162b2 (250 mcg/0.5 mL) will be administered in diluted 0.3 mL doses (30 mcg/0.3 mL).

For Cohort 2, the second dose of mRNA vaccine will be administered preferably in the same arm used for the first dose. For Cohort 2, the booster dose of vaccine will also be administered preferably in the same arm used for the first dose.

The pharmacist will prepare a single dose for each subject based on cohort assignment.

See the protocol-specific Manual of Procedures (MOP) for detailed information on the preparation, labeling, storage, and administration of vaccine for each cohort. Vaccine preparation will be performed by the participating site's research pharmacist on the same day of vaccine administration to the subject.

6.1.3 4.1Dose Modifications

A dose sparing 50 mcg mRNA-1273 booster (Groups 12E-14E) will be tested and compared to full dose booster dosing (Groups 1E-3E)

6.2 Accountability/Handling/Storage/Preparation

6.2.1 Acquisition and Accountability

All the vaccines (and diluents as needed) will be provided by the DMID repository:

DMID Clinical Materials Services Contract
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Phone: 240-477-1350
Fax: 240-477-1360
Email: DMID.CMS@thermofisher.com

All study products will be shipped to the clinical research site upon request and approval from DMID.

Accountability

The participating site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site PI may delegate to

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

Once all subject dosing is complete, the pharmacy staff should retain or dispose of used study products and complete study product accountability procedures in accordance with site-specific standard operating procedures (SOPs).

All used supplies noted above may either be sequestered from the unused supplies and retained until study conclusion or until study product accountability has occurred by the monitor and written notification stating retention is no longer required is received or may be destroyed in accordance with site-specific SOPs with a second pharmacy staff member's observation and verification as documented in the pharmacy log. Refer to the protocol-specific MOP for details on storing used study product vials.

Destruction

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, disposition of unused and used study product vials should occur as noted:

- Unused and used study product vials:
    - Should be destroyed on-site following applicable site procedures or by the site's selected destruction vendor. Following the site's procedure for the destruction of hazardous material or study product destruction policy/SOP when destroying used and unused items.
    - A certificate of destruction or documentation of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.
- Used syringes may be destroyed in accordance with site-specific SOPs.

6.2.2 Formulation and Appearance

Product: mRNA-1273 and mRNA-1273.211

mRNA-1273 is provided as a sterile liquid for injection, white to off-white dispersion in appearance.

mRNA-1273.211 is provided as a sterile liquid for injection, white to off-white dispersion in appearance.

Product: Ad26.COV2.S

Ad26.COV2.S is supplied as a sterile suspension in multi-dose vials. The Ad26COV2.S vaccine does not contain a preservative. The Ad26.COV2.S vaccine is a colorless to slightly yellow, clear to very opalescent suspension.

Product: BNT162b2

BNT162b2 is white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection.

Each of the study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal Law to Investigational Use."

6.2.3 Product Storage and Stability

Product: mRNA-1273

mRNA-1273 vials are stored between -50°C to -15°C (-58°F to 5°F) as per updated EUA Fact Sheet. Store in the original carton to protect from light. Do not store on dry ice or below -50ºC (-58ºF). Use of dry ice may subject vials to temperatures colder than -50°C (-58°F). Vials can be stored refrigerated between 2°C to 8°C (36° to 46°F) for up to 30 days prior to first use. Do not refreeze. Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture. Thawed vials can be handled in room light conditions. Do not refreeze once thawed.

mRNA-1273.211 vials are stored frozen between -60°C to -90°C (-76°F to -130°F). Stability and compatibility with the apparatus intended for administration for up to 8 hours after preparation were assessed. The prepared doses were stable for clinical in-use for up to 8 hours at room temperature. Store in the original carton to protect from light.

Product: Ad26.COV2.S

Storage Prior to First Puncture of the Vaccine Vial

Store unpunctured multi-dose vials of the Janssen COVID-19 Vaccine at 2°C to 8°C (36°F to 46°F) and protect from light. Do not store frozen.

Unpunctured vials of Ad26.COV2.S vaccine may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours. The Ad26.COV2.S vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If vaccine is still frozen upon receipt, thaw at 2°C to 8°C

(36°F to 46°F). If needed immediately, thaw at room temperature (maximally 25°C/77°F). At room temperature (maximally 25°C/77°F), a carton of 10 vials will take approximately 2 hours to thaw, and an individual vial will take approximately 1 hour to thaw. Do not refreeze once thawed.

Product: BNT162b2

BNT162b2 is a preservative-free, sterile dispersion of RNA formulated in LNP in aqueous cryoprotectant buffer for IM administration. The RNA drug substance is the only active ingredient in the drug product. The vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose vial. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 1 month. The vaccine must be thawed (room temperature [up to 25ºC (77ºF)] for 30 minutes or at 2ºC to 8ºC (35ºF to 46ºF) for up to 1 month.) and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration and within 2 hours of thaw. Before dilution, the vaccine vials should be inverted gently 10 times but not shaken. Do not refreeze. After dilution, the vial contains up to 6 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. During storage, minimize exposure to room light and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Note: Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in the EUA this Fact Sheet regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons. For the purposes of this study, no more than 5 doses per vial will be used.

Study Product Temperature Accountability

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

Study product must be stored in a secure area with limited access (pharmacy staff only) and must be stored as above. The storage areas should have an automated temperature recording and alert system. There must be an available back-up storage location. The storage areas 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 storage area malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any study product that was not temperature controlled during shipment or during storage to the pharmacy staff. Such product will be retained for inspection by the pharmacy staff and disposed of according to approved methods.

6.2.4 Preparation

Refer to the protocol-specific MOP for details about preparation.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Treatment Assignment Procedures

Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6: GCP, screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the electronic data capture (EDC) system that the IDCRC Statistical and Data Science Unit (SDSU) develops and manages through the Statistical Center for HIV/AIDS Research (SCHARP) at the Fred Hutchinson Cancer Research Center.

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subjects will be enrolled.

6.3.2 Randomization and Blinding

Subjects in Cohorts 1 and 2 will not be randomized to study intervention. The study will be open label and study sites will administer product to which they have been assigned.

6.3.3 Blinding and Masking Procedures

This study is unblinded.

6.4 Study Intervention Compliance

Each dose of study product will be administered by a member of the clinical research team that is qualified and licensed to administer the study product. Administration and date, time, and location of injection will be recorded on the appropriate DCF.

6.5 Concomitant Therapy

Concomitant medications include only prescription medications and vaccines received outside of the study taken by the subject at the time of enrollment through 28 days after the last vaccination. At each study visit, if there are new SAEs, Protocol Specified AESIs, MAAEs, or NOCMCs, concomitant medications should be recorded on the appropriate DCF.

6.5.1 Rescue Medicine

Not Applicable

6.5.2 Non-Research Standard of Care

Not Applicable

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Halting Criteria

The study will be halted in a given group if any of the following events occur following booster dose only:

1- Any subject experiences an SAE after administration of the vaccine that is considered related to vaccine.

2- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of vaccine that is considered related to vaccine.

3- Any subject experiences ulceration, abscess or necrosis at the injection site that is considered related to vaccine administration.

4- Two (2) or more subjects experience an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of vaccine that is considered related to vaccine.

5- Three (3) or more subjects experience a Grade 3 AE (unsolicited) related to vaccine administration, in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding.

7.1.2 Criteria for Continuation of Dosing and Redosing

In the event a halting rule is met:

- an unscheduled safety analysis by the SMC will be required for approval of further enrollment
- further administration of any study vaccine boost within the specific group, is suspended for ALL subjects within that group until an assessment by the SMC takes place.

7.1.3 Discontinuation of Study Intervention

For Cohort 2, prior to receiving the second and third vaccination, subjects will be reassessed. The following events constitute contraindications to any further administration of study vaccines. If any of these events occur during the study prior to the second vaccination, the subject must not receive the second vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination. For Cohort 2, Group 1, if any of these events occur after the second vaccination and before the third vaccination the subject must not receive the third vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination.

- Any clinically significant medical condition that, in the opinion of the participating site PI or appropriate sub-investigator, poses an additional risk to the subject if he/she continues to participate in the study.
- Confirmed SARS-CoV-2 infection.
- Anaphylaxis or unexpected systemic hypersensitivity reaction following the administration of a prior study vaccination.
- Any SAE judged to be related to vaccine.
- Pregnancy.
- New information becomes available that makes further participation unsafe or interferes with the evaluation of responses.
- Termination of this trial.

7.1.3.1 Delay of Study Vaccination

If any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date.

- Acute moderate or severe infection with or without fever at the time of vaccination.
- Fever, defined as oral temperature ≥38.0°C (100.4°F) at the time of vaccination.

Subjects with a minor illness without fever, as assessed by the participating site PI or appropriate sub-investigator, can be administered vaccines. Subjects with an oral temperature of 38.0°C (100.4°F) or higher will be re-contacted within the window specified in the SOA and re-evaluated for eligibility.

It is preferred that the vaccination still occur within the window specified in the SOA if possible but delays outside the windows are permitted (would still be a protocol deviation).

7.1.4 Follow-up for Subjects that Discontinued Study Intervention

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

7.2 Subject Withdrawal from the Study 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.
- Initial vaccine is not administered.

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

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

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

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.

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.

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

7.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-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 ASSESSMENTS AND PROCEDURES

8.1 Screening and Immunogenicity Assessments

8.1.1 Screening or Enrollment/Baseline Procedures

There is a small amount of risk to subjects who report that they are in good health but have an unknown health problem at the time of the enrollment/baseline visit. Screening assessments can occur up to 28 days before or at the subject's first vaccination visit (Day 1). At the screening (optional) or enrollment/baseline visit, and prior to any other study-related activities, the participating site PI or appropriate sub-investigator will provide the subject with detailed study information and will obtain written informed consent.

Some or all of the following assessments are performed during the screening (optional) or enrollment/baseline visit to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain medical history.
- Review pre-study medications and therapies at screening and record on the appropriate DCF. Review of adult vaccinations, including any other SARS-CoV-2 or other experimental coronavirus vaccines.
- Review any participation in investigational trials in the last 6 months.
- Measure vital signs (HR, BP, and oral temperature), and height and weight for determination of BMI.
- Targeted physical examination based upon symptoms elicited in the medical history
- Review of birth control history with female subjects of childbearing potential.
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
- Urine pregnancy test (in women of childbearing potential). If urine pregnancy is done at separate screening visit, repeat urine pregnancy test will be done within 24 hours of study vaccine administration.
- Review inclusion and exclusion criteria.

The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

Study subjects who qualify for inclusion will be contacted and scheduled for enrollment and first vaccination within the window for enrollment unless the screening and vaccination are scheduled on the same day.

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter

may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

A subject may be re-screened if there is a transient disease status (e.g., subject complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening at a later date (e.g., a medication taken within exclusionary window at the time of first screening that would not be within exclusionary window at a later rescreen).

No subjects may be screened more than twice due to a screening failure result as defined above.

Subjects will be provided the results of abnormal clinical findings necessitating follow-up at the discretion of the participating site PI or appropriate sub-investigator. Research laboratory results will not be provided to the subject.

The screening and first vaccination procedures both can be conducted at the enrollment/baseline visit.

8.1.2 Immunogenicity Evaluations

Serological Immunogenicity Assays:

The following serological immunogenicity assays may be performed:

- IgG ELISA to SARS-CoV-2 proteins.
- Neutralization assays using different strains of SARS-CoV-2 pseudovirus.
- Neutralization assay using different strains of live SARS-CoV-2.
- Quadriplex MSD assay (Nucleocapsid protein, Receptor binding domain, spike protein and variant spike protein)

Preparation of blood samples and shipping instructions for serological immunogenicity assays are outlined in the protocol-specific MOP. Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline serum for serological immunogenicity assays is collected.

Cellular Immunology Assays:

This trial may also investigate B and T cell immune responses using multiparametric flow cytometry.

Refer to the protocol-specific immune monitoring plan for details.

Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the protocol-specific MOP.

The volume of venous blood to be collected for immunogenicity evaluations is presented in Table 8 and Table 9.

8.1.3 Samples for Illness Visit

In the event that a subject develops symptoms compatible with COVID-19, the site will follow with an unscheduled Illness Visit. Wide discretion is given to sites for the assessment of COVID-19 illness. Guidance can be found at the CDC website (2020 Interim Case Definition):

https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/#:~:text=Clinical%20Criteria,of%20breath%2C%20or%20difficulty%20breathing

The following intervention will be performed in the event of an illness visit:

- Nasal or nasopharyngeal (NP) swabs for PCR and sequencing

Two nasal or NP swabs will be obtained for the purposes of 1) conducting qualitative analysis to assess for the presence of SARS-CoV-2 virus, and 2) conducting PCR quantitation/sequencing in the event that nasal or NP swab #1 is positive for SARS-CoV-2.

The first nasal or NP swab will be processed at the local level with results informing the disposition of the second nasal or NP swab. The sites will freeze and store the second swab (refer to MOP for labeling, storage, and shipping instructions) for potential shipment to the central repository for processing.

8.1.4 Samples for Genetic/Genomic Analysis

8.1.4.1 Genetic/Genomic Analysis

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

8.1.4.2 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.

8.1.4.3 Management of Results

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

8.2 Safety and Other Assessments

Study procedures are specified in the SOA. A study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator, will be responsible for all study-related medical decisions.

- Medical history:
    - A complete medical history will be obtained by interview of subjects at the screening (optional) or enrollment/baseline visit. Subjects will be queried regarding a history of significant medical disorders.
    - At all subsequent visits an interim medical history will be obtained by interview of subjects and any changes since the previous clinic visit or telephone call will be noted. The interim medical history should include an assessment to identify intercurrent Protocol Specified AESIs, MAAEs, and NOCMCs.
- Physical examination:
    - A symptom-directed (targeted) physical examination will be performed if indicated at any timepoint at the discretion of the participating site PI or appropriate sub-investigator, if necessary, to evaluate AEs.
    - Reactogenicity assessments of solicited AEs, occurring from the time of each vaccination through 7 days post vaccination, will include an assessment of injection site reactions–erythema, edema/induration and pain, as well as systemic reactions–fever, fatigue, chills, myalgia (exclusive of the injection site), arthralgia, headache, and nausea. Pre-administration reactogenicity assessments will be performed immediately prior to each vaccination to establish baseline, then the vaccination will be given.
    - Subjects will be observed in the clinic for at least 30 minutes post each vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AEs/SAEs will be recorded on the appropriate DCF prior to discharge from the clinic. The vaccination site will also be examined 7 days after vaccination.
- Vital signs: Vital sign measurements will include systolic and diastolic BP, HR, and oral temperature. Vital signs will be measured at timepoints specified in the SOA. On vaccination days, vital sign measurements will be collected prior to vaccine administration. Vital signs assessed on Day 1 prior to the first vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
    - Urine pregnancy test: Urine pregnancy test will be performed locally by the site laboratory within 24 hours prior to each vaccination, and as needed at interim or unscheduled visits for all women of childbearing potential. Results must be confirmed as negative prior to enrollment on Day 1 and administration of each vaccination as applicable.

- Memory aid:
    - All subjects will complete a Memory Aid from the time of each vaccination through 7 days post each vaccination. Memory Aids will be reviewed with the subjects for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs and concomitant medications during telephone calls 7 days after each vaccination. Based on the information collected, subjects may be asked to return to the clinic for evaluation. Memory Aids will be reviewed again, and subjects will be assessed for delayed onset local reactions 14 days after booster vaccination (initial vaccination in Cohort 1, delayed vaccination in Cohort 2). Memory aids will be reviewed 7 days after each vaccination in the initial part of Cohort 2.

Table 8: Venipuncture Volumes for Cohort 1 (One Vaccination – EUA Dosed Cohort)

Study Day	-28 to -1	1	8	15	29	91	169	366	Early Termination Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05	06	07		
Vaccination		X								
Serum for Serological Immunogenicity Assays[1]		16		16	16	16	16	16	16[2]	96
PBMCs (and Plasma) for Cellular Immunology Assays		64		64			64	64	64[2]	256
Serum for Secondary Research		16		16	16	16	16	16	16[2]	96
Per Visit Blood Volume Total (mL)		96		96	32	32	96	96	96[2]	448
Cumulative Blood Volume (mL) (prior 56 days)		96	96	192	224	32	96	96		
Running Blood Volume Total (mL)		96	96	192	224	256	352	448		

[1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected. Refer to the Blood Collection Summary Table in the MOP for the minimum number of expected aliquots for this blood draw volume and minimum aliquots required to completed testing under the protocol

[2] These blood volumes are not included in the blood volume totals.

Table 9: Venipuncture Volumes for Cohort 2: (Up to Three Vaccinations)

Study Day	**-28 to -1**	**1**	**8**	**29**	**36**	**43**	Delayed Boost to occur ≥12 weeks from completion of EUA dosing.	**1B**	**8B**	**15B**	**29B**	**91B**	**169B**	**366B**	**Early Termination Visit**	**Total Volume of Blood Drawn (mL)**
Visit Window (±number of days)		0	1	2	3	3		0	1	2	2	7	7	28		
Study Visit	Screening (optional) 00	01	02	3	04[3]	05[3]		06[3]	07[3]	08[4]	09[4]	10[4]	11[4]	12[4]		
Vaccination		X		X												
Serum for Serological Immunogenicity Assays[1]		16		16		16		16		16	16	16	16	16	16[2]	144
PBMCs (and Plasma) for Cellular Immunology Assays		64		64		64		64		64		64	64	64	64[2]	512
Serum for Secondary Research		16		16		16		16		16	16	16	16	16	16[2]	144
Per Visit Blood Volume Total (mL)		96		96		96		96		96	32	96	96	96	96[2]	800
Cumulative Blood Volume (mL) (prior 56 days)		96	96	192	192	288		96	96	192	224	96	96	96		
Running Blood Volume Total (mL)		96	96	192	192	288		384	384	480	512	608	704	800		

[1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected. Refer to the Blood Collection Summary Table in the MOP for the minimum number of expected aliquots for this blood draw volume and minimum aliquots required to completed testing under the protocol

[2] These blood volumes are not included in the blood volume totals.
[3] Visits 05-07 windows should be based off the actual Visit 03 date.
[4] Visits 08-12 windows should be based off the actual Visit 06 date.

8.2.1 Procedures to be Followed in the Event of Abnormal Clinical Findings

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

All abnormal clinical findings that occur post vaccination will be considered AEs.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related [21 CFR 312.32 (a)]. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

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

All AEs will be assessed for severity and relationship to study intervention (Section 8.3.3). Reporting of all AEs, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after each vaccination. After 28 days post last vaccination through the end of study, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be reported as AEs.

All AEs, solicited and unsolicited, will be captured on the appropriate DCF. Solicited AEs will be regarded as related to the study product and will not require separate entry into the AE log. Information to be collected for unsolicited AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator), date of resolution, seriousness, and outcome. AEs occurring during the study-collection and reporting period will be documented appropriately regardless of relationship.

AEs will be followed to resolution or stabilization.

8.3.1.1 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.

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

For this study, solicited AEs will be:

- Injection site Pain
- Injection site Erythema
- Injection site Edema/Induration
- Headache
- Fatigue
- Myalgia
- Arthralgia
- Nausea
- Fever
- Chills

Subjects will also be assessed for delayed onset local reactions through 14 days post each vaccination.

8.3.1.2 Unsolicited Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from study staff or revealed by observation, physical examination or other diagnostic procedures must be recorded on the appropriate DCF.

Unsolicited AEs of all severities will be reported from the time of study product administration through 28 days post each vaccination.

After 28 days post last vaccination through the end of study, only SAEs, AESIs, MAAEs, and NOCMCs (as detailed in Section 8.3.2) will be reported as AEs.

8.3.1.3 Special Reporting of Adverse Events

Not Applicable

8.3.2 Definition of Serious Adverse Event (SAE)

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

- Death,
- a life-threatening AE,
- inpatient hospitalization or prolongation of existing hospitalization,

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

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

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

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

All SAEs will be recorded on the appropriate SAE DCF.

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

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

8.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

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

8.3.4 Classification of an Adverse Event

The determination of seriousness, severity and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs and classify AEs based upon medical judgment. This includes, but is not limited to, physicians, physician assistants and nurse practitioners.

8.3.4.1 Severity of Adverse Events

All AEs and SAEs will be assessed for severity, according to the toxicity grading scales in the FDA "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 specific 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.
- Potentially Life Threatening (Grade 4): Events that lead to an ER visit or hospitalization. (recorded on Adverse Event log as a Serious Adverse Event (SAE) and to be reviewed by Medical Monitor). Death (Grade 5): Events that lead to death (recorded on Adverse Event log as a Serious Adverse Event (SAE) and to be reviewed by Medical Monitor). 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.

8.3.4.2 Relationship to Study Intervention

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

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Solicited adverse events reported in the 7 days after each vaccination are considered related to study product unless they are also recorded as an unsolicited event, in which case the relationship to study product will be determined by the PI or qualified designee.

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

For this study:

- solicited AEs will be collected for 7 days post each vaccination.
- unsolicited AEs will be collected until 28 days after each vaccination.
- SAEs, AESIs, MAAEs, and NOCMCs will be collected from Day 1 through the end of the study.

8.3.6 Adverse Event Reporting

8.3.6.1 Investigators Reporting of AEs

Information on all AEs should be recorded on the appropriate DCF. All clearly related signs, symptoms and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a clinical laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual clinical laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.3.7 Serious Adverse Event Reporting

8.3.7.1 Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as an SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

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

SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the SCHARP's EDC system. Refer to the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID Medical Monitor 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 participating site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the participating site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

8.3.7.2 Regulatory Reporting of SAEs

Following notification from the participating site PI or appropriate sub-investigator, DMID, as the IND sponsor, will report any SUSAR in an IND safety report to the FDA and will notify all participating site PIs (i.e., all PIs to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for

reporting as specified in 21 CFR Part 312.32. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

8.3.8 Reporting Events to Subjects

Subjects will be informed of any AEs or SAEs that occur as part of their participation in this trial.

8.3.9 Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest (AESIs) represent any events for which additional data (besides the standard AE data) are desired. 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 is required. Such an event may require 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) may also be required. These may be at the request of the regulatory agency, industry partner or DMID, and driven by a regulatory requirement, or known or potential risk from the product or class. Non-structured data similar to SAEs will be collected for AESIs. AESIs encompass the following terms:

- Protocol Specified AESIs: See Section 12, APPENDIX A: Adverse Events of Special Interest (AESIs) Terms.
    - All suspected cases of anaphylaxis should be recorded. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis should be reported as a potential case of anaphylaxis.
    - Thrombosis with Thrombocytopenia Syndrome (TTS) has been observed very rarely following vaccination with Ad26.COV2.S and is considered an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia. Because this syndrome is rare and not completely understood, all cases of thrombosis and/or thrombocytopenia will be considered a suspected case of TTS until further adjudication can be performed. The investigator shall be responsible for reporting any suspected AESI of TTS using the SAE form. A suspected TTS case is defined as:
        - Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 12, APPENDIX A: Adverse Events of Special Interest (AESIs) Terms
        - Thrombocytopenia, defined as platelet count below 150,000/μL

      Symptoms, signs, or conditions suggestive of a thrombotic event should be recorded and reported as a suspected AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated

or shown to be less likely. Follow-up information and final diagnoses, if applicable, should be submitted to the sponsor as soon as they become available.

In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used.

For either a thrombotic event or thrombocytopenia, testing for anti-PF4 should be performed at the local laboratory or substitute local laboratory; repeat testing may be requested for confirmation upon sponsor discretion.

- All suspected cases of myocarditis and pericarditis must be reported as AESI. Symptoms of chest pain, shortness of breath or palpitations may represent myocarditis or pericarditis. Typically, onset of symptoms has been within a few days following receipt of the mRNA COVID-19 vaccines.

- Guillain Barré Syndrome has occurred in some people who have received the Janssen COVID-19 Vaccine and will be recorded as an AESI in this study. In most circumstances, symptoms began within 42 days following receipt of dosing.

- 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 a hospitalization, emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason; and considered related to study product.

All AESIs are assessed, recorded, and followed as described above under AEs. AESIs that meet SAE criteria will be reported on an SAE form within 24 hours to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

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

SAE Email Address: PVG@dmidcroms.com

In addition, 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 DMID Pharmacovigilance Group; however, the narrative will indicate that the AESI did not meet SAE criteria.

8.3.10 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs following the booster dose (through three months after booster dose or through 12 months after the mRNA-1272.211

booster dose) should be reported to the sponsor on the appropriate DCF Pregnancy form and pregnancy should be followed to outcome.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UPs)

The Department of Health and Human Services (DHHS) OHRP considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the SDSU/study sponsor within 24 hours of the participating site PI or appropriate sub-investigator becoming aware of the event per the above-described SAE reporting process.
- UPs that are SAEs will be collected from Day 1 through the end of the study.
- Any other UP will be reported to the IRB and to the SDSU/study sponsor within 3 days of the participating site PI or appropriate sub-investigator becoming aware of the problem.
- UPs that are not SAEs will be collected from Day 1 through 28 days after last vaccination.

8.4.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this trial.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

This is a phase 1/2, open-label, multi-site clinical trial that is not designed to test a specific hypothesis. Rather, it is intended to obtain preliminary estimates in healthy adults of the safety, reactogenicity, and immunogenicity of delayed heterologous SARS-CoV-2 vaccine dosing (boost) after receipt of EUA vaccines.

9.2 Sample Size Determination

9.2.1 Sample Size Calculation for the Safety Endpoint

Rare AEs are not demonstrable in a clinical study of this size; however, the probabilities of observing one or more AEs given various true event rates are presented in Table 10. With the assumption that all enrolled subjects will likely complete immunizations and safety visits in this relatively short duration study, the following statistical considerations apply. With approximately 50 subjects in each group there is a 99.5% chance of observing at least one AE of probability 10%. Similarly, with approximately 25 subjects in each of the age subgroups, there is a 92.8% chance of observing at least one AE of probability 10%. Therefore, if no AEs of a given type occur in a Cohort 1group, we can be relatively confident that they will occur in fewer than 10% of people once the vaccine is implemented.

Probabilities of observing one or more AEs, assuming an attrition rate of approximately 10% (N = 45, N = 22), are also shown in Table 10.

9.2.2 Sample Size Calculation for the Immunogenicity Endpoints

A co-primary objective of this study is to evaluate the magnitude of SARS-CoV-2 specific antibody titers in serum samples. This objective is descriptive in nature and will be accomplished by estimating 95% confidence intervals (CI) for the geometric mean titer (GMT) at each timepoint when samples are collected.

Table 10: Probability of Observing an Adverse Event for Various Event Rates in one vaccine schedule group (or age subgroup), assuming no attrition (N = 50 or N = 25) or approximately 10% attrition (N = 45 or N = 22).

N	"True" Event Rate	Probability of Observing ≥ 1 events (%)	N	"True" Event Rate	Probability of Observing ≥ 1 events (%)
50	0.1%	4.9	45	0.1%	4.4
	0.5%	22.2		0.5%	20.2
	1.0%	39.5		1.0%	36.4
	2.0%	63.6		2.0%	59.7
	3.0%	78.2		3.0%	74.6
	4.0%	87.0		4.0%	84.1
	5.0%	92.3		5.0%	90.1
	10.0%	99.5		10.0%	99.1
	15.0%	>99.9		15.0%	99.9
	20.0%	>99.9		20.0%	>99.9
	30.0%	>99.9		30.0%	>99.9
N	**"True" Event Rate**	**Probability of Observing ≥ 1 events (%)**	**N**	**"True" Event Rate**	**Probability of Observing ≥ 1 events (%)**
25	0.1%	2.5	22	0.1%	2.2
	0.5%	11.8		0.5%	10.4
	1.0%	22.2		1.0%	19.8
	2.0%	39.7		2.0%	35.9
	3.0%	53.3		3.0%	48.8
	4.0%	64.0		4.0%	59.3
	5.0%	72.3		5.0%	67.6
	10.0%	92.8		10.0%	90.2
	15.0%	98.3		15.0%	97.2
	20.0%	99.6		20.0%	99.3
	30.0%	>99.9		30.0%	>99.9

The precision with which the GMT can be estimated from observed data depends on the standard deviation (SD) of the measurements, on the logarithmic scale, and the sample size. Table 11 displays two-sided 95% confidence intervals for the GMT for several values of the observed antibody titer. Table 11 also shows results assuming up to 10% attrition.

Table 11: Two-sided 95% confidence intervals based on observing a particular average loge-antibody titer in subjects' vaccine groups and age subgroups.

Observed average $\log_e$ antibody titer	SD of $\log_e$ antibody titer	95% confidence interval of GMT in vaccine group		95% confidence interval of GMT in age subgroup	
		N = 50	N = 45*	N = 25	N = 22*
$\log_e$ (5)	0.5	(4.3, 5.8)	(4.3, 5.8)	(4.1, 6.1)	(4, 6.2)
$\log_e$ (20)		(17.4, 23.1)	(17.2, 23.2)	(16.3, 24.6)	(16, 25)
$\log_e$ (50)		(43.4, 57.6)	(43, 58.1)	(40.7, 61.5)	(40.1, 62.4)
$\log_e$ (100)		(86.8, 115.3)	(86.1, 116.2)	(81.4, 122.9)	(80.1, 124.8)
$\log_e$ (250)		(216.9, 288.2)	(215.1, 290.5)	(203.4, 307.3)	(200.3, 312)
$\log_e$ (500)		(433.8, 576.3)	(430.3, 581)	(406.8, 614.6)	(400.6, 624.1)
$\log_e$ (1000)		(867.5, 1152.7)	(860.5, 1162.1)	(813.5, 1229.2)	(801.2, 1248.2)
$\log_e$ (5)	1.0	(3.8, 6.6)	(3.7, 6.8)	(3.3, 7.6)	(3.2, 7.8)
$\log_e$ (20)		(15.1, 26.6)	(14.8, 27)	(13.2, 30.2)	(12.8, 31.2)
$\log_e$ (50)		(37.6, 66.4)	(37, 67.5)	(33.1, 75.6)	(32.1, 77.9)
$\log_e$ (100)		(75.3, 132.9)	(74, 135)	(66.2, 151.1)	(64.2, 155.8)
$\log_e$ (250)		(188.2, 332.2)	(185.1, 337.6)	(165.5, 377.8)	(160.5, 389.5)
$\log_e$ (500)		(376.3, 664.3)	(370.2, 675.2)	(330.9, 755.5)	(320.9, 779)
$\log_e$ (1000)		(752.6, 1328.7)	(740.5, 1350.4)	(661.8, 1511)	(641.9, 1558)

* Assumes approximately 10% attrition.

9.3 Populations for Analyses

The safety analysis population includes all enrolled subjects who received at least one dose of study vaccine. Analyses for the safety population will include safety reported through the end of the study. The modified intent-to-treat (mITT) population includes all subjects who received at least one dose of vaccine and contributed both pre- and at least one post-vaccination venous blood sample for immunogenicity testing for which valid results were reported.

In the final analysis, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis. The per protocol (PP) population will then be defined – and this includes all subjects in the mITT subset with the following exclusions:

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

9.4 Statistical Analyses

Interim analyses of safety, reactogenicity, and immunologic response data will be done, as needed.

The final analysis will be performed after the final data lock and clinical study report (CSR) completed when all primary safety endpoint data and all secondary immunogenicity endpoint data are available and received by the SDSU. Any available data from the exploratory immunogenicity endpoints may also be included in the CSR. Remaining exploratory immunogenicity endpoint data may be included in an addendum to the CSR, publication of manuscript(s), or other report(s). Abbreviated analysis plans that describe planned analyses to facilitate dissemination of study data for public health reasons, including manuscript publication(s), will be developed by the SDSU. A full statistical analysis plan (SAP) will be developed by the SDSU and finalized prior to the primary data lock.

9.4.1 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.

9.4.2 Analysis of the Primary Endpoint(s)

Section 9.4.4 describes the analyses of Safety Endpoints, which is one of the co-primary endpoints of this protocol.

9.4.3 Analysis of the Co-Primary Endpoint(s)

Descriptive summaries of immunogenicity data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a per-protocol (PP) analysis may also be performed.

Geometric Mean Titers (GMT) and Geometric Mean Fold Rise (GMFR) from baseline of SARS-CoV-2 specific antibody binding and neutralization titers will be calculated, along with 95% CIs, for all groups, at each timepoint. Summaries will also be displayed graphically. Rates of seroconversion, defined as a 4-fold increase in antibody titer over baseline, will also be reported for all groups, at each timepoint, along with 95% CIs.

9.4.4 Safety Analyses

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

Solicited AEs will be summarized by severity for each day post vaccination (Days 1-8) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed using standard techniques, such as exact confidence intervals (CI), to summarize the proportion of subjects reporting each symptom, any application site symptom, and any systemic symptom.

Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after the last vaccination. Unsolicited AEs will be coded by MedDRA for preferred term and system organ class (SOC). SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first vaccination through the end of the study. The numbers of SAEs, AESIs, NOCMCs and MAAEs will be reported by detailed listings showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA categories will be computed.

9.4.5 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 arm and cohort.

9.4.6 Planned Interim and Early Analyses

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community. Early analyses will include safety and immunogenicity as described in Sections 9.4.6.1, 9.4.6.2 and 9.4.6.3. Further, the protocol team will review data periodically to confirm no halting criteria have been met as described in Section 10.1.6.1.

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

9.4.6.1 Interim Safety Analyses

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

The SMC will review separate cumulative AE data reports after all subjects within each booster product group have been dosed and completed Day 29 within Cohort 1. Given the safety database known for EUA vaccines, there is no routine mandatory review by the SMC during the EUA dosing in cohort 2 unless halting rules are triggered.

9.4.6.2 Interim Immunogenicity Review

Interim data review of immunogenicity will be performed as often as needed to inform public health decisions.

Statistical analyses of secondary immunogenicity endpoints, by vaccine schedule group, may be performed when subjects have completed key immunogenicity visits. Immunogenicity reviews may be shared with the SMC, as determined by DMID.

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

9.4.6.3 Interim Immunogenicity and Safety Review

Interim analyses of safety, reactogenicity, and immunologic response data may be done, as needed.

9.4.7 Sub-Group Analyses

Subgroup analyses, by age group, may be performed. Detailed information will be provided in the Statistical Analysis Plan.

9.4.8 Tabulation of Individual Subject Data

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

9.4.9 Exploratory Analyses

Summaries and analysis of cellular assay data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a PP analysis may also be performed.

The magnitude, phenotype and percentage of innate immune cells and SARS-CoV-2 specific B cells will be summarized at each timepoint by arm.

The magnitude, phenotype and percentage of cytokine producing S protein-specific T cells will be summarized at each timepoint by arm.

Breakthrough NAAT-confirmed, SARS-CoV-2 infections will be sequenced to assess for the presence of variant spike lineage proteins.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

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

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

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

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

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

10.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a subject's informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed. The participating site PI or other study staff may obtain oral or written information for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject if the process is approved by the IRB.

At the first study visit, informed consent will be obtained and documented before any study procedures are performed. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study interventions/products, risks and discomforts, the expected duration of the subject's participation in the trial, any expected benefits to the subject, and alternative treatments and procedures that may be available to the subject. The explanation will be organized and presented

in lay terminology and language that facilitates understanding why one might or might not want to participate.

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

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

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

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

New information will be communicated by the participating site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

10.1.1.1 Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

Not Applicable

10.1.1.2 Other Informed Consent Procedures

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, nasal or NP swabs, the use of residual specimens, and the sharing of genetic information and samples for secondary research. This extra/residual blood and corresponding serum, plasma and PBMCs will be used as back-up specimens for PP defined assays or designated for secondary research use and stored indefinitely at a designated storage facility.

Subjects will be asked to consent specifically to genetic testing on primary and secondary research samples, including but not limited to transcriptomics and DNA sequencing. DNA sequencing data will be kept private. DNA data may be used to produce commercial antibody-based therapeutics. Subjects will not share in profits or commercial rights to those products.

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

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

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

Samples designated for secondary research use may be used for additional immunological assessments that may include but are not limited to antibody epitope mapping, B and T cell repertoire determination, non-traditional immune assay development, determination of innate immune factors and the ability of vaccine-induced antibodies to cross-react to different proteins and virus strains. These blood samples might be used in new or different immunological laboratory tests, to provide information for the development of new vaccines or therapeutics, or for the studies of SARS-CoV-2 or other infections. Secondary research using DNA may also be warranted to understand genetic factors involved in vaccination failures.

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

There are no direct benefits to the subject for extra specimens collected or from 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 additional volume of blood collected, such as anemia. Risks for loss of privacy and confidentiality are described below.

Subjects may withdraw permission to use samples for secondary use at any time. They will need to contact the participating site and the samples will be removed from the study repository after

this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples. Subjects who withdraw consent before the last visit will not have the extra blood drawn for secondary use.

Human Genetic Testing

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

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

10.1.2 Study Termination and Closure

In Section 7, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

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

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

If the study is prematurely terminated, the PI will promptly inform study subjects and the IRB as applicable. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule. The PI will assure appropriate follow-up for the subjects, as necessary.

The sponsor will notify regulatory authorities as applicable.

10.1.3 Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples and genetic tests, and all other information generated during participation in the study. No identifiable information concerning subjects in the study will

be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the participating site PI, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The participating site will permit access to such records.

All source records, including electronic data, will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the participating site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the participating site. Names or readily identifying information will not be released unless DMID approves and it aligns with the consent form, or according to laws for required reporting.

Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and re-identified data could potentially be used to discriminate against or stigmatize subjects, their families, or groups. In addition, there may be unknown risks.

As this research is funded by the NIH, it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality (COC). By this policy, researchers cannot be forced to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

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

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

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

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

10.1.4 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ‘‘primary’’ or ‘‘initial’’ activity, such as the data and samples collected in this protocol. This section will detail the samples and data available for secondary research. Any use of the secondary sample or data, however, will be presented in a separate protocol and require separate IRB approval.

10.1.4.1 Samples for Secondary Research

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

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

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

Residual/Repository Research Samples, upon written request and approval from DMID and any approvals required by the site or network, may be shared for secondary research with investigators at the participating site, with researchers at other Infectious Disease Clinical Research Consortium (IDCRC) sites or other institutions, or company-designated research laboratories. The samples will not be sold or used directly for production of any commercial product. DMID will authorize shipment from the DMID CMS.

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

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

10.1.4.2 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All of the individual subject data collected during this study will be made available after de-identification. The SAP and Analytic Code will also be made available. Data will be available immediately following publication, with no end date. Upon written request, with provision of a methodologically sound proposal, and approval from DMID and any approvals required by the site or network, data may be shared for secondary research with investigators/researchers. The data will be available for only the purpose outlined in the approved proposal.

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

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

10.1.5 Key Roles and Study Governance

This study is sponsored by DMID. Decisions related to this study will be made by the protocol team, which includes representatives from the participating site (PI), DMID (sponsor), VRC, and ModernaTX, Inc. Key Roles are noted in the protocol-specific MOP.

10.1.6 Safety Oversight

10.1.6.1 Safety Monitoring Committee (SMC)

The SMC is an independent group of at least 2-3 experts that monitors subject safety and advises DMID. SMC members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The SMC will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

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

Given the frequency and urgency to review data, the SMC will not need to meet (unless halting rules are met), and materials will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

The SMC will review separate cumulative AE data reports after all subjects within each product booster group have been dosed and completed Day 29 within Cohort 1. The SMC will also review cumulative AE data after all subjects in Cohort 2 have been dosed and prior to the second vaccination (preferably after all subjects have completed Day 8).

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

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

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

10.1.7 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 is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are documented in a 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, electronic case report forms (eCRFs), ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study staff and all study documentation according to the DMID-approved CMP. Study monitors will meet with all participating site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

10.1.8 Quality Control (QC) and Quality Assurance (QA)

To ensure the reliability of study data, the participating site will develop a Clinical Quality Management Plan (CQMP). The CQMP will describe:

- routine internal quality control (QC) and QA activities
    - for the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
    - independent of sponsor site monitoring.
- a process for addressing data quality issues (i.e., collecting, recording), and reporting findings in a timely manner); systemic issues (i.e., protocol conduct, non-compliance, human subject protections), and implementation and evaluation of Corrective and Preventative Action Plan (CAPA) procedures.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the participating site under the supervision of the participating site PI. The participating site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation, including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory data, will be entered by the participating site into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by SCHARP. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent,

incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The IDCRC SDSU and SCHARP will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to DMID.

10.1.9.2 Study Record Retention

Study-related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records, should be maintained for a period of 2 years following the date a marketing application is approved for the investigational 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 such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research.

10.1.9.3 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. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Study data will be collected on paper CRFs and entered the eCRF or data will be entered directly into the eCRF. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents. Data entered directly into the eCRFS will be considered the source document.

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

10.1.9.4 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific MOP or GCP requirements, or

any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

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

It is the responsibility of the participating site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The participating site PI and study staff are responsible for knowing and adhering to their IRB requirements. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

10.1.9.5 Publication and Data Sharing Policy

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

10.1.9.6 Human Data Sharing Plan

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

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

10.1.9.7 Genomic Data Sharing (GDS) Plan

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

10.1.9.8 Publication

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

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

10.1.9.9 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

10.2.1 Research Related Injuries

For any potential research related injury, the participating site PI or designee will assess the subject. Study staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the vaccine. As needed, referrals to appropriate health care facilities will be provided to the subject. The participating site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial.

If it is determined by the participating site 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 staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the vaccine. No financial compensation will be provided to the subject by NIAID, NIH, the vaccine manufacturer, or the participating site for any injury suffered due to participation in this trial.

For this protocol, the study vaccines are covered under the PREP Act, as described in Section 2.1.1.

10.3 Abbreviations

Table 12: Abbreviations

ACIP	Advisory Committee on Immunization Practices
Ad	Adenovirus
AE	Adverse Event
AESI	Adverse Event of Special Interest

AIDS	Acquired Immunodeficiency Syndrome
PBMC	Peripheral Blood Mononuclear Cell
BMI	Body Mass Index
BP	Blood Pressure
°C	Degrees Celsius
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
COC	Certificate of Confidentiality
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
CQMP	Clinical Quality Management Plan
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay

EUA	Emergency Use Authorization
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GWAS	Genome-Wide Association Studies
HEENT	Head, Ears, Eyes, Nose, and Throat
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HR	Heart Rate
HRSA	Health Resources and Services Administration
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDCRC	Infectious Disease Clinical Research Consortium
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LNP	Lipid Nanoparticle
m	Meter

MAAE	Medically Attended Adverse Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mg	Milligrams
MI	Myocardial Infarction
min	Minute
mITT	Modified Intent-To-Treat
mL	Milliliter
mm Hg	Millimeter of Mercury
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
N	Number (typically refers to subjects)
NAAT	Nucleic Acid Amplification Test
NaCl	Sodium Chloride
NDA	New Drug Application
NEUT	Neutralizing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Condition
NP	Nasopharyngeal
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
OWS	Operation Warp Speed
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PREP Act	Public Readiness and Emergency Preparedness Act

QA	Quality Assurance
QC	Quality Control
RBD	Receptor Binding Domain
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	SARS Coronavirus
SARS-CoV-2	SARS Coronavirus 2
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SD	Standard Deviation
SDSP	Study Data Standardization Plan
SDSU	Statistical and Data Science Unit
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th	T helper
TTS	Thrombosis with Thrombocytopenia Syndrome
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
vp	Viral Particles
VRC	Vaccine Research Center
WBC	White Blood Cell
WHO	World Health Organization
WIV1	Chinese Horseshoe Bat Coronavirus WIV1

10.4 Protocol Amendment History

Table 13: Protocol Amendment History

Version 2.0 of the protocol was amended 22 June 2021.

Version 3.0 of the protocol was amended 15 July 2021

Version 4.0 of the protocol was amended 20 August 2021

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12. APPENDIX A: Adverse Events of Special Interest (AESIs) Terms

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in the protocol. The following AESIs are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of a COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies

	• Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc.) • Include all cases that meet the following criteria: o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; o OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days o OR Urine volume ≤0.5 ml/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc.) • Include all cases that meet the following criteria o > 3-fold elevation above the upper normal limit for ALT or AST o OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia and/or Thrombosis with Thrombocytopenia Syndrome (TTS)	• Platelet counts < 150 x10^9 • Thrombotic events: Suspected deep vessel venous or arterial thrombotic events • Including but not limited to TTS (default operative diagnosis if boosted with Ad26.COV2.S), immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura,

	thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (e.g., gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: o Guillain-Barre Syndrome o Acute disseminated encephalomyelitis (ADEM) o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by: o sudden onset AND o rapid progression of signs and symptoms AND o involving two or more organ systems, as follows: o Skin/ mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes o Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation o Respiratory: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea o Gastrointestinal: diarrhea, abdominal pain, nausea, vomiting

	• Follow reporting procedures in protocol.
Myocarditis and/or pericarditis	Symptoms and diagnostic findings include but are not limited to: • Chest pain • Dyspnea • ST or T wave changes on ECG • Elevated cardiac enzymes • Abnormal echocardiography or other cardiac imaging.
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) • Myasthenia gravis

DMID Protocol #21-0012 Protocol Version 1.0, 14 April 2021
Updated in
DMID Protocol #21-0012 Protocol Version 2.0, 22 June 2021

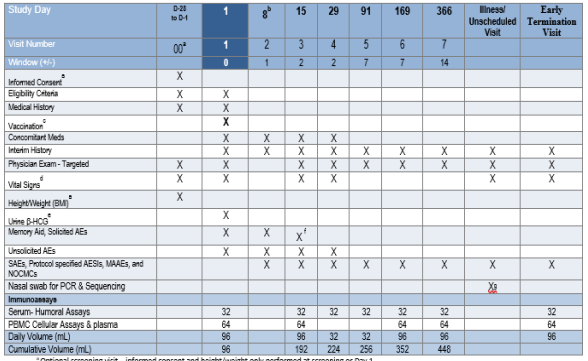
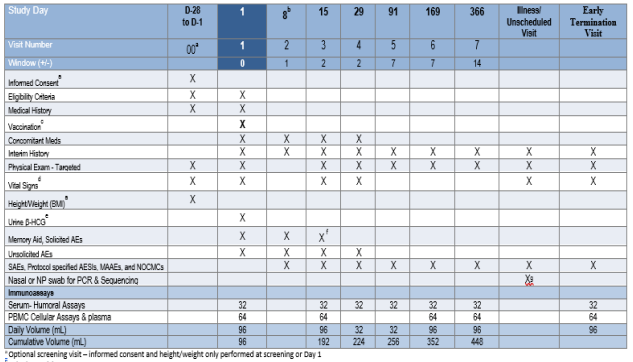
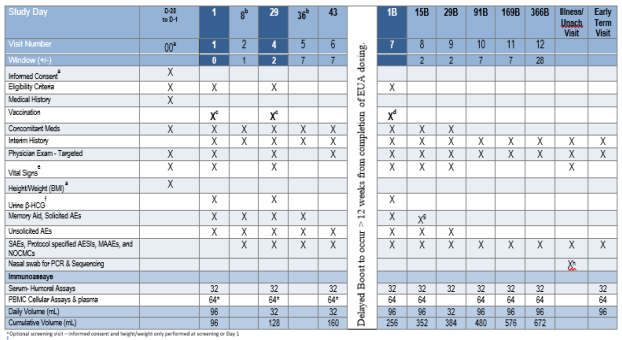
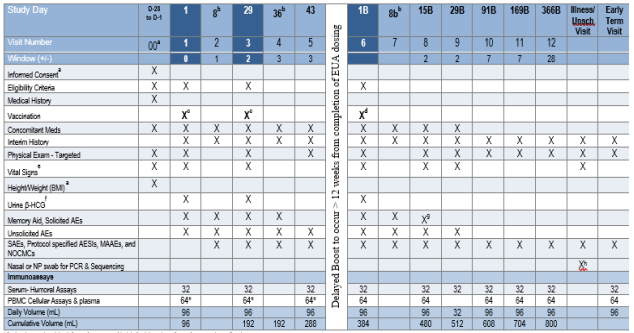
Protocol:

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
1	All pages, Header	Version 1.0 14 April 2021	Version 2.0 22 June 2021	Update to the protocol version and date.
2	Page 1, Title Page	Version Number: 1.0 14 April 2021	Version Number: 2.0 22 June 2021	Update to the protocol version and date.
3	Page 8, Section 1.1 Synopsis	**Population:** Approximately -400 healthy individuals aged ≥ 18 years"	**Population:** Approximately -550 healthy individuals aged ≥ 18 years"	Updated the population size to account for additional cohort 1 arms.
4	Page 9, Section 1.1 Synopsis, Objectives, Primary: #1, Bullet 1	• Adverse Events from Dose 1 to 28 days following boost dose.	• Adverse Events from Dose 1 to 28 days following each vaccination and delayed boost dose.	Added text to clarify AEs followed vaccines as well as delayed boost.
5	Page 9, Section 1.1 Synopsis, Objectives, Primary: #1, Bullet 2	• Related MAAEs, SAEs, AESI from Dose 1 on study to month 12 months after last dose on study	• MAAEs, SAEs, NOCMCs, and AESIs from Dose 1 on study to month 12 months after last dose on study	Added NOCMs. Removed related from AEs.
6	Page 9, Section 1.1 Synopsis, Objectives, Exploratory: 3	1. To assess, in at least a subset of samples, the B cell immune response following EUA vaccination and delayed boost;	1. …….. 2. ……..	Added a new exploratory objective

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
		2. To assess, in at least a subset of samples, the SARS-CoV-2 protein-specific T cell responses following EUA vaccination and delayed boost;	3. To evaluate breakthrough symptomatic SARS-CoV-2 infection and sequence strains to assess for variant spike lineage.	
7	Page 9, Section 1.1 Synopsis, Study Design: Bottom paragraph, first three sentences	***EUA-dosed Cohort:*** Cohort 1 will recruit persons who have previously received COVID-19 vaccine under EUA dosing guidelines, in the prior 12-20 weeks. Eligible individuals will be stratified by age (18-55 years or ≥ 56 years) in a 1:1 ratio (N = 25/group). Subjects will be sequentially enrolled to receive one of the available delayed boost options (Table 1). A total of 50 per group will be recruited for the EUA-dosed Cohort 1.	***EUA-dosed Cohort:*** Cohort 1 will recruit persons who have previously received COVID-19 vaccine under EUA dosing guidelines, completing their regimen at least 12 weeks prior to enrollment. Eligible individuals will be stratified by age group (18-55 years or ≥ 56 years) in a 1:1 ratio (N = 25/group). Subjects will be sequentially enrolled to receive one of the available delayed boost options (Table 1). A total of approximately 50 per group will be recruited for each group (combination of EUA primary vaccination plus booster) in Cohort 1.	Added clarifying language on the treatment regime and removed the upper limit for enrollment (changed from 12-20 weeks to at least 12 weeks). Changed number of subjects/groups to an approximate number.

<table>
<tr><th>#</th><th>Page and Section</th><th>Originally in Version 1.0</th><th>Updated in Version 2.0</th><th>Rationale for change</th></tr>
<tr><td>8</td><td>Page 10, Section 1.1 Synopsis, Table 1</td><td>
Table 1: EUA-dosed Cohort 1
<table>
<tr><th>Group</th><th>Sample Size*</th><th>EUA Dosing Scheme</th><th>Interval (weeks)</th><th>Delayed Booster Vaccination</th><th>Strategy Tested</th></tr>
<tr><td>1E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>12-20</td><td>Moderna- mRNA-1273</td><td>Same Strain
Heterologous platform</td></tr>
<tr><td>2E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>12-20</td><td>Moderna- mRNA-1273</td><td>Control - Same Strain
& platform</td></tr>
<tr><td>3E</td><td>50</td><td>Previously dosed Pfizer/BioNTech – mRNA- BNT162b2</td><td>12-20</td><td>Moderna- mRNA-1273</td><td>Same Strain
Similar platform</td></tr>
</table>
*Sample cohort size, N = 50, two age strata: 18-55 years (n = 25), 56+ years (n = 25)
</td><td>
Table 1: EUA-dosed Cohort 1
<table>
<tr><th>Group</th><th>Sample Size*</th><th>EUA Dosing Scheme</th><th>Interval (weeks)</th><th>Delayed Booster Vaccination</th><th>Strategy Tested</th></tr>
<tr><td>1E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Same Strain
Heterologous platform</td></tr>
<tr><td>2E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Control - Same Strain
& platform</td></tr>
<tr><td>3E</td><td>50</td><td>Previously dosed Pfizer/BioNTech – mRNA- BNT162b2</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Same Strain
Similar platform</td></tr>
<tr><td>4E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Control - Same Strain
& platform</td></tr>
<tr><td>5E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Same Strain
Heterologous platform</td></tr>
<tr><td>6E</td><td>50</td><td>Previously dosed Pfizer/BioNTech – mRNA- BNT162b2</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Same Strain
Heterologous platform</td></tr>
</table>
*Sample cohort size, N = 50, two age strata: 18-55 years (n = 25), ≥56 years (n = 25)
</td><td>Added three new arms (4E-6E) for the Janssen booster vaccine. The interval was updated to ≥12. The age group was corrected to ≥56.</td></tr>
<tr><td>9</td><td>Page 10, Section 1.1 Synopsis, Prospective Cohort</td><td>Prospective Cohort: Cohort 2 will recruit persons who are naïve to COVID-19 vaccine and infection (by history). These individuals will be given a vaccine as part of the study that matches the vaccine/dose available under an EUA. Currently, this includes the Moderna mRNA-1273 vaccine only, but it could include other vaccines in the future.</td><td>Prospective Cohort: Cohort 2 will recruit persons who are naïve to COVID-19 vaccine and infection (by history). These individuals will be given a vaccine as part of the study that matches the vaccine/dose available under an EUA.</td><td>Removed what types of vaccines could be available.</td></tr>
<tr><td>10</td><td>Page 11, Section 1.1 Synopsis, Table 2</td><td>
Table 2: Prospective Cohort 2
<table>
<tr><th>Group</th><th>Sample Size*</th><th>First Vaccination**</th><th>Interval</th><th>Second Vaccination88</th><th>Interval (Weeks)</th><th>Delayed Booster Vaccination</th></tr>
<tr><td>1</td><td>250</td><td>Moderna- mRNA-1273</td><td>28d</td><td>Modern- mRNA-1273</td><td>>12</td><td>Novel homologous or heterologous variant or heterologous platform boost</td></tr>
</table>
*Aged ≥ 18 years
** As part of an adaptive design, products newly awarded EUA can be added (e.g., Janssen Ad26.COV2.S and Novavax NVX-CoV2373)
</td><td>
Table 2: Prospective Cohort 2
<table>
<tr><th>Group</th><th>Sample Size*</th><th>First Vaccination**</th><th>Interval</th><th>Second Vaccination**</th><th>Interval (Weeks)</th><th>Delayed Booster Vaccination</th></tr>
<tr><td>1</td><td>250</td><td>Moderna- mRNA-1273</td><td>28d</td><td>Moderna- mRNA-1273</td><td>≥12</td><td>Novel homologous or heterologous variant or heterologous platform boost</td></tr>
</table>
*Aged ≥ 18 years
** As part of an adaptive design, products newly awarded EUA can be added as programmatically needed.
</td><td>Column 4, row 1 heading was updated from ‘88” to “**”. Column 4 row 2 – Moderna spelling was corrected. In the footer, reference to</td></tr>
</table>

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
				types of vaccines was generalized.
11	Page 11, Section 1.1 Synopsis, Criteria for Inclusion/Exclusion. Inclusion Criteria, #2	2. Received and completed COVID-19 vaccine under EUA dosing guidelines at least 12 weeks and no more than 20 weeks prior to enrollment (Cohort 1 only).	2. Received and completed COVID-19 vaccine under EUA dosing guidelines at least 12 weeks prior to enrollment (Cohort 1 only).	Removed the upper limit for enrollment (changed from 12-20 weeks to at least 12 weeks).
12	Page 11, Section 1.1 Synopsis, Criteria for Inclusion/Exclusion. Inclusion Criteria, #4	4. Determined by medical history, targeted physician examination and clinical judgement of the investigator to be in good health.	4. Determined by medical history, targeted physical examination and clinical judgement of the investigator to be in good health.	Corrected the text from physician to physical.
13	Page 12, Section 1.1 Synopsis, Criteria for Inclusion/Exclusion. Inclusion Criteria, #5, Bullet 3	• Has a negative pregnancy test at screening and on the day of the first vaccine dose (Day 1),	• Has a negative pregnancy test at screening and on the day of the first study vaccine dose (Day 1),	Clarified that Day 1 was the first **study** vaccine dose
14	Page 12, Section 1.1 Synopsis, Criteria for Inclusion/Exclusion. Exclusion Criteria #7	7. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with intramuscular injections or blood draws.	7. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with intramuscular injections or blood draws, or previously experienced thrombosis with thrombocytopenia (TTS) or heparin-induced thrombocytopenia.	Updated exclusion criteria to include TTS or heparin-induced thrombocytopenia.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
15	Page 14, Section 12, Schedule of Activities (SOA), Table 3: SOA for EUA-dosed Cohort 1	**1.2 Schedule of Activities (SOA)** **Table 3: SOA for EUA-dosed Cohort 1** 	**1.2 Schedule of Activities (SOA)** **Table 3: SOA for EUA-dosed Cohort 1** 	Corrected the text from physician to physical. Add NP to the illness/unscheduled visit and in the footer. Removed assessment for the memory aid.
16	Page 15, Section 12, Schedule of Activities (SOA), Table 4: SOA for Prospective Cohort 2	**Table 4: SOA for Prospective Cohort 2:** 	**Table 4: SOA for Prospective Cohort 2:** 	Added visit 8b to match the description in the protocol. Corrected the visit numbers, visit windows and daily and cumulative volumes. Corrected the text from physician to physical. Add NP to the illness/unscheduled visit and in the footer. Removed assessment for the memory aid.
17	Page 16, Section 2.1 Background and Study	The corresponding illness designation, coronavirus disease 2019 (COVID-19), was	The corresponding illness designation, coronavirus disease 2019 (COVID-19), was	Updated the start date of the pandemic.

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	Rational, 1st paragraph, 2nd sentence	declared as a pandemic respiratory illness on 11 May 2020.[1]	declared as a pandemic respiratory illness on March 2020.[1]	
18	Page 17, Section 2.1 Background and Study Rational, 3rd paragraph, last sentence	Testing of the Pfizer/BioNTech's (BNT162b2) followed by AstraZeneca/Oxford's (ChAdOx-2) and vice versa is underway in the UK.	Testing of the heterologous prime boost strategy with Pfizer/BioNTech's (BNT162b2) followed by AstraZeneca/Oxford's (ChAdOx-2) and vice versa is underway in the UK.	Added text on the vaccine strategy.
19	Page 17, Section 2.1 Background and Study Rational, last paragraph, last two sentences	Utilizing the EUA-dosed COVID-19 vaccines available (currently mRNA-1273, mRNA-BNT162b2, and AD26.COV2.S), we propose to evaluate innate, cellular, and humoral immune responses elicited from multiple prime boost combinations, utilizing the mRNA with homologous spike protein as a boost while seeking to avoid duplicating trial designs currently in planning stages or in process. As part of an adaptive design, we anticipate adding groups with variant-lineage spike proteins and other vaccine platforms such as the adenovirus vectored platforms as booster doses, subject to availability.	Utilizing the EUA-dosed COVID-19 vaccines available (currently mRNA-1273, mRNA-BNT162b2, and AD26.COV2.S), we propose to evaluate innate, cellular, and humoral immune responses elicited from different booster vaccines. As part of an adaptive design, we anticipate adding groups with variant-lineage spike proteins and other vaccine platforms, subject to availability.	Simplified the booster vaccine language.
20	Page 17, Section 2.1.1 Public Readiness and Emergency Preparedness Act, 1st paragraph, 2nd sentence	Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273	Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273 and Ad26.COV2.S.	Added the Ad26.COV2.S vaccine.
21	Page 18, Section 2.2.1 Known	The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the initial	The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the initial	Added the Ad26.COV2.S vaccine.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
	Potential Risks , 1st paragraph,	immunization with mRNA-1273 vaccine and delayed booster inoculation of mRNA-1273, and breach of confidentiality.	immunization with mRNA-1273 vaccine and delayed booster inoculation of mRNA-1273 and Ad26.COV2.S, and breach of confidentiality.	
22	Page 21, Section 2.2.1 Known Potential Risks , last paragraph	Further details are provided in the current IB for mRNA-1273.	Further details are provided in the FDA-approved fact sheet and current IB for mRNA-1273.	Added additional reference for mRNA-1273
23	Page 20-21, Section 2.2.1 Known Potential Risks	New	**Risks of Ad26.COV2.S.** Immediate systemic allergic reactions (e.g., anaphylaxis) can occur following any vaccination but no cases of anaphylaxis were noted in the Phase 3 trial. Hypersensitive reactions, not classified as anaphylaxis, are a rare occurrence within the Ad26 platform but have been reported. The most common solicited adverse events were injection site pain, headache, fatigue and myalgia. Intramuscular injection with Ad26.COV2.S can cause local pain, erythema (redness), or swelling at the injection site, which are mostly mild to moderate in severity, transient, and usually occur within 24 hours of injection. Pyrexia (fever defined as body temperature ≥ 38.0°C) was reported and generally dissipated within 24 hours of vaccination. Other solicited events systemic signs and symptoms included headache, myalgia, chills and nausea. Grade 2 facial paralysis (Bell's Palsy) has been reported although the incidence of Bell's Palsy was not above known background prevalence	Added potential risks for Ad26.COV2.S

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
			rates. Tinnitus has been reported following vaccination with Ad26.COV2.S but it is unclear if these were due to vaccine or underlying medical conditions. Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. These cases occurred approximately 3 weeks following vaccination, mostly in women under 60 years of age. Thrombosis in combination with thrombocytopenia can be fatal. The exact physiology of TTS is unclear. TTS is considered an important identified risk for Ad26.COV2.S. It is unknown if this risk changes (increase or decreases) when this vaccine is used as a delayed booster vaccine. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, and skin bruising and/or petechiae beyond the site of vaccination. The medical management of thrombosis with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow	

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
			available guidelines for treatment of thrombotic thrombocytopenia (eg, from the American Society of Hematology, British Society of Haematology - Expert Haematology Panel10, and the CDC). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended. Refer to the latest version of the IB and its addenda (if applicable) for further details. Due to the possibility of the occurrence of TTS after vaccination with Ad26.COV2.S, additional reporting and data collection procedures have been included in the study for thrombotic events, thrombocytopenia, and TTS (see Section **Error! Reference source not found.**), which may facilitate diagnosis and clinical management of the event. While there is a theoretical risk of vaccine-associated enhanced diseases (VAED) with SARS-CoV-2 vaccines, there has been no evidence of VAED following Ad26.COV2.S or mRNA vaccine dosing. There is limited evidence of the effects of administering an adenovirus-vectored vaccine before or after an mRNA COVID-19 vaccine, and it is possible that a delayed booster dose may result in more frequent or more severe adverse events.	
24	Page 21, Section 2.2.2 Known Potential Benefits	In cohort 2, there is the potential for protection against symptomatic SARS-CoV-2 infection following receipt of an EUA vaccine. There is no direct benefit to the subjects in Cohort 1 or from	In cohort 2, there is the potential for protection against symptomatic SARS-CoV-2 infection following receipt of an EUA vaccine. There is no known direct benefit expected to the subjects in	Added language to clarify benefits from booster vaccines and from

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
		the booster vaccination in Cohort 2. There is potential benefit society resulting from insights gained from participation in this study due to the emerging threat of the SARS-CoV-2 outbreak. Data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 demonstrated 94.1% efficacy of the vaccine as a two-vaccination series versus placebo against SARS-CoV-2 infection. The doses and vaccination strategies used in this trial may or may not alter this protection.	Cohort 1 or from the booster vaccination in Cohort 2. There is potential benefit that the vaccine will boost the participant's immunity to a SARS-CoV-2 infection and the benefit to society resulting from insights gained from participation in this study due to the emerging threat of the SARS-CoV-2 outbreak. Data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 demonstrated 94.1% efficacy of the vaccine as a two-vaccination series versus placebo against symptomatic SARS-CoV-2 infection. The Phase 3 placebo-controlled clinical trial of Ad26.COV.2 demonstrated 66% efficacy against mild-moderate SARS-CoV-2 infection and 85% against severe disease as a one-dose vaccination. The doses and vaccination strategies used in this trial may or may not alter this protection.	the Ad26.COV.2.S vaccine.
25	Page 22, Section 3, Objectives and Endpoints, Table 5, Endpoints (Outcome Measures), Bullets 2 and 3	• Adverse Events from Dose 1 to 28 days following delayed boost dose • Related MAAEs, SAEs, from Dose 1 on study to month 12 months after last dose on study.	• Adverse Events from Dose 1 to 28 days following each vaccination and delayed boost dose. • MAAEs, SAEs, NOCMCs, and AESIs from Dose 1 on study to month 12 months after last dose on study.	• Added that that AEs follow each vaccine boost • Added NOCMs. Removed related from AEs
26	Page 24, Section 4 Study Design,	This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed	This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed	The interval was updated to ≥12.

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	Overall Design, 1st paragraph, Second Sentence	(>12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.;	(≥12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.;	
27	Page 24, Section 4, Study Design, Overall Design, 1st paragraph, last sentence	Enrollment will occur at approximately twelve domestic clinical research sites.	Enrollment will occur at up to twelve domestic clinical research sites.	Number of sites was capped at twelve
28	Page 24, Section 4, Study Design, Overall Design, 1st paragraph	Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and > 56 years) who received previously COVID-19 vaccine at EUA dosing (two vaccinations of mRNA-1273 at the 100 mcg dose, two vaccinations of mRNA-BNT162b2 at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the $5x10^{10}$ vp dose). Those subjects will be offered enrollment into this study 12-20 weeks after they received the last dose of their EUA vaccine. Subjects will receive an open-label delayed boost that is assigned to each of the approximately twelve domestic trial sites.	Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and ≥ 56 years) who received previously received COVID-19 vaccine at EUA dosing (two vaccinations of mRNA-1273 at the 100 mcg dose, two vaccinations of mRNA-BNT162b2 at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the $5x10^{10}$ vp dose). Those subjects will be offered enrollment into this study ≥12 weeks after they received the last dose of their EUA vaccine. Subjects will receive an open-label delayed boost that is assigned to each of the approximately twelve domestic trial sites.	Added received to the first sentence. Removed the upper limit for enrollment (changed from 12-20 weeks to at least 12 weeks) in the third sentence.
29	Page 24-25 Section 4, Study Design, Overall Design,#1-3	1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by: • Group 1E – A 100-mcg dose of mRNA-1273 2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by: • Group 2E – A 100-mcg dose of mRNA-1273	1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by: • Group 1E – A 100-mcg dose of mRNA-1273 • Group 4E – A $5x10^{10}$ vp dose of Ad26.COV2.S 2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by:	Added arms 4E-6E to include the boost with Ad26.COV2.S

<table>
<tr><th>#</th><th>Page and Section</th><th>Originally in Version 1.0</th><th>Updated in Version 2.0</th><th>Rationale for change</th></tr>
<tr><td></td><td></td><td>3. Previously EUA-dosed vaccination with Pfizer/BioNTech - mRNA-BNT162b2 at 30 mcg for two doses followed by:
Group 3E – A 100-mcg dose of mRNA-1273</td><td>Group 2E – A 100-mcg dose of mRNA-1273
Group 5E – A 5x10^{10} vp dose of Ad26.COV2.S
3. Previously EUA-dosed vaccination with Pfizer/BioNTech - mRNA-BNT162b2 at 30 mcg for two doses followed by:
Group 3E – A 100-mcg dose of mRNA-1273
Group 6E – A 5x10^{10} vp dose of Ad26.COV2.S</td><td></td></tr>
<tr><td>30</td><td>Page 25, Section 4, Study Design, Overall Design, Table 6 Cohort 1 Treatment Arms</td><td>Table 6. Cohort 1 Treatment Arms<table><tr><th>Arm</th><th>Sample Size</th><th>Booster Vaccination Product and Dose</th></tr><tr><td>1E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>2E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>3E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr></table></td><td>Table 6. Cohort 1 Treatment Arms<table><tr><th>Arm</th><th>Sample Size</th><th>Booster Vaccination Product and Dose</th></tr><tr><td>1E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>2E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>3E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>4E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2.S</td></tr><tr><td>5E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2.S</td></tr><tr><td>6E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2.S</td></tr></table></td><td>Added arms 4E-6E to include the boost with Ad26.COV2.S</td></tr>
<tr><td>31</td><td>Page 25, Section 4, Study Design, Overall Design, Summary of Treatment Arms</td><td>1E – Evaluates a heterologous platform booster dose of mRNA-1273 among persons who previously received an Ad26.COV2.S EUA vaccination series
2E- As a bridging arm evaluates a homologous platform third boosting dose of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series
3E – Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received</td><td>1E – Evaluates a heterologous platform booster dose of mRNA-1273 among persons who previously received an Ad26.COV2.S EUA vaccination series
2E- As a bridging arm evaluates a homologous platform third boosting dose of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series
3E – Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received</td><td>Added arms 4E-6E to include the boost with Ad26.COV2.S</td></tr>
</table>

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		a mRNA-BNT162b2 EUA vaccination series	a mRNA-BNT162b2 EUA vaccination series • 4E - Evaluates Ad26.COV2.S EUA vaccination series followed by a homologous platform delayed dose of Ad26.COV2.S • 5E - Evaluates mRNA-1273 EUA vaccination series followed by a heterologous platform delayed dose of Ad26.COV2.S • 6E - Evaluates mRNA-BNT162b2 EUA vaccination series followed by a heterologous platform delayed dose of Ad26.COV2.S	
32	Page 25-26, Section 4, Study Design, Overall Design, last paragraph, 2nd sentence	Cohort 2 will include approximately 250 participants per group aged ≥ 18 years of age who have not received a COVID-19 vaccine and have no known history of COVID-19 or SARS-CoV-2 infection. They will be assigned to receive COVID-19 vaccine under EUA dosing (as outlined in Table 7).	Cohort 2 will include approximately 250 participants per group aged ≥ 18 years of age who have not received a COVID-19 vaccine and have no known history of COVID-19 or SARS-CoV-2 infection. They will be assigned to receive COVID-19 vaccine under EUA dosing (as programmatically outlined in Table 7).	Added 'programmatically'.
33	Page 25-26, Section 4, Study Design, Overall Design, last paragraph, 3rd sentence	Additional pools of subjects can be included as additional COVID-19 vaccines are awarded EUA (e.g., Janssen – Ad26.COV2.S or Novavax- NVX-CoV2373).	Additional pools of subjects can be included if needed as additional COVID-19 vaccines are awarded EUA.	Removed specific vaccine names
34	Page 25-26, Section 4, Study Design, Overall Design, last	A telephone visit will occur one week after each primary EUA vaccination.	A telephone visit will occur one week after each primary EUA vaccination and one week after the booster dose.	Added telephone call at one week after primary boost which conforms to the SOA.

<table>
<tr><th>#</th><th>Page and Section</th><th>Originally in Version 1.0</th><th>Updated in Version 2.0</th><th>Rationale for change</th></tr>
<tr><td></td><td>paragraph, 5th sentence</td><td></td><td></td><td></td></tr>
<tr><td>35</td><td>Page 26, Section 4, Study Design, Overall Design, Table 7 Cohort 2 Treatment Arms</td><td>Table 7: Cohort 2 Treatment Arms<table><tr><th rowspan="2">Group</th><th rowspan="2">Sample Size</th><th>First Vaccination</th><th colspan="2">Second Vaccination</th><th colspan="2">Booster Vaccination</th></tr><tr><th>Product and Dose</th><th>Interval</th><th>Product and Dose</th><th>Interval</th><th>Product and Dose</th></tr><tr><td>1</td><td>250</td><td>100 mcg mRNA-1273</td><td>28 days</td><td>100 mcg mRNA-1273</td><td>> 12 weeks</td><td>Novel homologous/ heterologous variant or heterologous platform boost</td></tr></table></td><td>Table 7: Cohort 2 Treatment Arms<table><tr><th rowspan="2">Group</th><th rowspan="2">Sample Size</th><th>First Vaccination</th><th colspan="2">Second Vaccination</th><th colspan="2">Booster Vaccination</th></tr><tr><th>Product and Dose</th><th>Interval</th><th>Product and Dose</th><th>Interval</th><th>Product and Dose</th></tr><tr><td>1</td><td>250</td><td>100 mcg mRNA-1273</td><td>28 days</td><td>100 mcg mRNA-1273</td><td>≥ 12 weeks</td><td>Novel homologous/ heterologous variant or heterologous platform boost</td></tr></table></td><td>Update Interval to ≥ 12 weeks</td></tr>
<tr><td>36</td><td>Page 26, Section 4, Study Design, Overall Design, 2nd paragraph</td><td>For both Cohorts 1 and 2, reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays.</td><td>For both Cohorts 1 and 2, reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays at the in-person follow-up visits.</td><td>Added clarification on timing of immunogenicity assays</td></tr>
<tr><td>37</td><td>Page 26, Section 4, Study Design, Overall Design, 3rd paragraph, last sentence</td><td>Screening can occur up to 28 days prior to the first dose and is optional prior to Dose 1.</td><td>Screening can occur up to 28 days prior to the first dose. Screening can occur up to 28 days prior to the first dose or on Day 1 prior to administration of Dose 1.</td><td>Added additional time when screening can occur.</td></tr>
<tr><td>38</td><td>Page 26, Section 4, Study Design, Overall Design, last paragraph</td><td>Schedule of assessments are found in Section Error! Reference source not found., Schedule of Activities.</td><td>Schedules of assessments are found in Section Error! Reference source not found., Schedule of Activities.</td><td>Added “s” to schedule</td></tr>
<tr><td>39</td><td>Page 28, Section 5, Study Population, 1st paragraph</td><td>Two cohorts will be enrolled. For Cohort 1, approximately 150 individuals (50 subjects/group; Groups 1E-3E) 18 years of age and older, stratified into two age groups (18-55 years and >56 years at 1:1 ratio), who are in good health and received EUA dosed vaccinations of mRNA-1273, BNT162b2 or Ad26.COV2.S will be invited to participate in this study.</td><td>Two cohorts will be enrolled. For Cohort 1, approximately 300 individuals (50 subjects/group; Groups 1E-6E) 18 years of age and older, stratified into two age groups (18-55 years and ≥56 years at 1:1 ratio), who are in good health and received EUA dosed vaccinations of mRNA-1273, BNT162b2 or Ad26.COV2.S will be invited to participate in this study.</td><td>Updated Cohort study population to 300 and updated groups to include arms 4E-6E.</td></tr>
</table>

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
40	Page 28, Section 5, Study Population, 3rd paragraph, first and last sentence	The estimated time from initiation of enrollment to complete enrollment in this clinical trial is approximately 4 weeks (though could take longer). However, owing to the adaptive nature of the design, new groups may be added to Cohort 1 or 2 dependent upon manufacture of variant lineage spike protein-based vaccine constructs or vaccines newly awarded EUA. An optional screening period can occur up to 28 days prior to the first vaccination.	The estimated time from initiation of enrollment to complete enrollment in each group within this clinical trial is approximately 2-4 weeks (though could take longer). However, owing to the adaptive nature of the design, new groups may be added to Cohort 1 or 2 dependent upon manufacture of variant lineage spike protein-based vaccine constructs or vaccines newly awarded EUA. An optional screening period can occur up to 28 days prior to the first vaccination, or can be completed on Day 1, prior to dosing.	Updated text to say that enrollment could be in each group. Updated options for the screening period to match the SOA.
41	Page 28, Section 5.4 Lifestyle Considerations, last bullet	• Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.	• Subjects must avoid eating or drinking anything hot or cold within 10 minutes prior to taking oral temperature.	Updated language on Lifestyle Considerations
42	Page 30, Section 6.1.1 Study Product Description	New	**Product 2: Ad26.COV2.S** Each 0.5 mL dose of the Ad26.COV2.S vaccine is formulated to contain $5x10^{10}$ virus particles of the Ad26 vector encoding the S glycoprotein of SARS-CoV-2. Each dose of the Ad26.COV2.S vaccine also includes the following inactive ingredients 2.19 mg sodium chloride, 0.14 mg citric acid monohydrate, 2.02 mg trisodium citrate dihydrate, 0.16 mg polysorbate-80, 25.5 mg 2-hydroxypropyl-β-cyclodextrin, 2.04 mg ethanol. Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng). The Ad26.COV2.S vaccine is a colorless to slightly yellow, clear to	Added a description of Ad26.COV2.S

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			very opalescent suspension. Each vial contains five doses.	
43	Page 30, Section 6.1.2 Dosing and Administration, 2nd Paragraph	New	Ad26.COV2.S will be used undiluted to obtain the specified vp content in 0.5 mL doses. Each dose is 0.5 mL.	Added dosing and administration information for 41Ad26.COV2.S
44	Page 30, Section 6.1.2 Dosing and Administration, 6th paragraph	The expiration time of the dosing syringe containing the prepared mRNA study vaccines is 8 hours at room temperature after the solution is drawn into the dosing syringe.	[Deleted]	Removed specific Dosing and Administration reference to mRNA. Site refer to the MOP.
45	Page 31, Section 6.2.1 Acquisition and Accountability, 1st paragraph,	Product: mRNA-1273 Will be provided by HHS-OWS Research Allocation via the DMID repository: DMID Clinical Materials Services Contract Fisher BioServices 20439 Seneca Meadows Parkway Germantown, MD 20876 Phone: 240-477-1350 Fax: 240-477-1360 Email: DMID.CMS@thermofisher.com	The mRNA-1273 , and Ad26.COV2.S will be provided by HHS-OWS Research Allocation via the DMID repository: DMID Clinical Materials Services Contract Fisher BioServices 20439 Seneca Meadows Parkway Germantown, MD 20876 Phone: 240-477-1350 Fax: 240-477-1360 Email: DMID.CMS@thermofisher.com	Added Ad26.COV2.S

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46	Page 31, Section 6.2.1 Acquisition and Accountability, Accountability, 1st paragraph, 2nd sentence from the bottom	All study product(s), including the amount of study product, diluent (0.9% NaCl for injection, USP), and vial admixtures, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.	All study product(s), including the amount of study product, and vial admixtures, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.	Removed diluent (0.9% NaCl for injection, USP) from the study product list.
47	Page 31, Section 6.2.1 Acquisition and Accountability, Accountability, 2nd paragraph from the bottom	Once all subject dosing is complete, the pharmacy staff should retain or dispose of used study products and complete study product accountability procedures in accordance with site-specific standard operating procedures (SOPs). This applies to: used and unused mRNA-1273 vials mRNA-1273 cartons	Once all subject dosing is complete, the pharmacy staff should retain or dispose of used study products and complete study product accountability procedures in accordance with site-specific standard operating procedures (SOPs).	Removed text on used and unused study product as the site will follow their SOPs.
48	Page 32, Section 6.2.2 Formulation and Appearance	New	**Product: Ad26.COV2.S** Ad26.COV2.S is supplied as a sterile suspension in multi-dose vials. The Ad26COV2.S vaccine does not contain a preservative. The Ad26.COV2.S vaccine is a colorless to slightly yellow, clear to very opalescent suspension	Added Ad26.COV2.S
49	Page 32, Section 6.2.3 Product Storage and Stability	New	**Product: Ad26.COV2.S** Storage Prior to First Puncture of the Vaccine Vial Store unpunctured multi-dose vials of the Janssen COVID-19 Vaccine at 2°C to 8°C (36°F to 46°F) and protect from light. Do not store frozen.	Added Ad26.COV2.S

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
			Unpunctured vials of Ad26.COV2.S vaccine may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours. The Ad26.COV2.S vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If vaccine is still frozen upon receipt, thaw at 2°C to 8°C (36°F to 46°F). If needed immediately, thaw at room temperature (maximally 25°C/77°F). At room temperature (maximally 25°C/77°F), a carton of 10 vials will take approximately 2 hours to thaw, and an individual vial will take approximately 1 hour to thaw. Do not refreeze once thawed.	
50	Page 33, Section 6.2.3 Product Storage and Stability	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 trial per site-specific SOPs, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). The participating site's research pharmacist must alert the participating site PI and study coordinator, if the temperature fluctuates outside of the required range.	Study Product Temperature Accountability 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 trial per site-specific SOPs, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). The participating site's research pharmacist must alert the participating site PI, study coordinator, and the DMID Product Support Team if the temperature fluctuates outside of the required range.	Added a header prior to this paragraph. Added in the 3rd sentence that the DMID Product Support Team must also be alerted for temperature excursions.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
51	Page 33, Section 6.2.3 Product Storage and Stability, last paragraph	mRNA-1273 must be stored in a secure area with limited access (pharmacy staff only) and must be stored frozen. The freezer should have an automated temperature recording and alert system. There must be an available back-up freezer. The freezers must be connected to a back-up generator, or alternate plan in the event of a power failure. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any mRNA-1273 that was not temperature controlled during shipment or during storage to the pharmacy staff. Such mRNA-1273 will be retained for inspection by the pharmacy staff and disposed of according to approved methods.	Study product must be stored in a secure area with limited access (pharmacy staff only) and must be stored frozen. The freezer should have an automated temperature recording and alert system. There must be an available back-up freezer. The freezers must be connected to a back-up generator, or alternate plan in the event of a power failure. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any study product that was not temperature controlled during shipment or during storage to the pharmacy staff. Such product will be retained for inspection by the pharmacy staff and disposed of according to approved methods.	Replaced 'mRNA' with 'study product' to make this section applicable to all study products.
52	Page 40, Section 8.1.1 Screening or Enrollment Baseline Procedures, 8th bullet	• Urine pregnancy test (in women of childbearing potential).	• Urine pregnancy test (in women of childbearing potential). If urine pregnancy is done at separate screening visit, repeat urine pregnancy test will be done within 24 hours of study vaccine administration.	Added clarification on urine pregnancy testing.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
53	Page 39-40, Section 8.1.3 Samples for Illness Visit	New	**8.1.3 Samples for Illness Visit** In the event that a subject develops symptoms compatible with COVID-19, the site will follow with an unscheduled Illness Visit. Wide discretion is given to sites for the assessment of COVID-19 illness. Guidance can be found at the CDC website (2020 Interim Case Definition): https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/#:~:text=Clinical%20Criteria,of%20breath%2C%20or%20difficulty%20breathing The following intervention will be performed in the event of an illness visit: • Nasal or nasopharyngeal (NP) swabs for PCR and sequencing Two nasal or NP swabs will be obtained for the purposes of 1) conducting qualitative analysis to assess for the presence of SARS-CoV-2 virus, and 2) conducting PCR quantitation/sequencing in the event that nasal or NP swab #1 is positive for SARS-CoV-2. The first nasal or NP swab will be processed at the local level with results informing the disposition of the second nasal or NP swab. The sites will freeze and store the second swab (refer to MOP for labeling, storage, and shipping instructions) for potential shipment to the central repository for processing.	Added details on the collection and processing of Nasal or nasopharyngeal (NP) swabs for PCR and sequencing. The collection of these swabs for unscheduled Illness Visits are included in the SOA for Table 3 – Cohort 1 and Table 4 – Cohort 2.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
54	Page 40, Sections 8.1.3 Samples for Genetic Testing and sections 8.1.4.1 - 8.1.4.3	**8.1.3 Samples for Genetic/Genomic Analysis** **8.1.3.1 Genetic/Genomic Analysis** **8.1.3.2 Genetic Privacy and Confidentiality** **8.1.3.3 Management of Results** .	**8.1.4 Samples for Genetic/Genomic Analysis** **8.1.4.1 Genetic/Genomic Analysis** **8.1.4.2 Genetic Privacy and Confidentiality** **8.1.4.3 Management of Results**	Updated section #s after the addition of section 8.1.3 Sample for Illness Visit.
55	Page 43, Section 8.2, Safety and Other Assessments, Table 8 Venipuncture Volumes for Cohort 1 (One Vaccination – EUA Dosed Cohort)	**Table 8: Venipuncture Volumes for Cohort 1 (One Vaccination – EUA Dosed Cohort)** [1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected. [2] These blood volumes are not included in the blood volume totals.	**Table 8: Venipuncture Volumes for Cohort 1 (One Vaccination – EUA Dosed Cohort)** [1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected. Refer to the Blood Collection Summary Table in the MOP for the minimum number of expected aliquots for this blood draw volume and minimum aliquots required to completed testing under the protocol [2] These blood volumes are not included in the blood volume totals.	Added a reference to the Blood Collection Summary Table in Footer #1
56	Page 44, Section 8.2, Safety and Other Assessments, Table 9, Venipuncture Volumes for Cohort 2 (Up to Three Vaccinations)	**Table 9: Venipuncture Volumes for Cohort 2: (Up to Three Vaccinations)** [1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected. [2] These blood volumes are not included in the blood volume totals. [3] Visits 05-07 windows should be based off the actual Visit 04 date.	**Table 9: Venipuncture Volumes for Cohort 2: (Up to Three Vaccinations)** [1] Inability (e.g., failure of venipuncture) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline blood volume is collected. Refer to the Blood Collection Summary Table in the MOP for the minimum number of expected aliquots for this blood draw volume and minimum aliquots required to completed testing under the protocol [2] These blood volumes are not included in the blood volume totals. [3] Visits 05-07 windows should be based off the actual Visit 03 date. [4] Visits 08-12 windows should be based off the actual Visit 06 date.	Added visit 8B to match the description in the protocol. Corrected the visit numbers, visit windows and daily, cumulative and total blood volumes. Updated the Delayed Boost Banner to

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
				≥12.Added a reference to the Blood Collection Summary Table in Footer #1
57	Page 45, Section 8.3.1 Definition of Adverse Event (AE), 4th paragraph, 2nd sentence	All AEs will be assessed for severity and relationship to study intervention (Section **Error! Reference source not found.**). Reporting of all AEs, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after the last vaccination.	All AEs will be assessed for severity and relationship to study intervention (Section **Error! Reference source not found.**). Reporting of all AEs, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after each vaccination.	Update reporting of AEs to occur after **each** vaccination.
58	Page 45, Section 8.3.1 Definition of Adverse Event (AE), 5th paragraph, added sentence between 1st and 2nd sentence	All AEs, solicited and unsolicited, will be captured on the appropriate DCF.	All AEs, solicited and unsolicited, will be captured on the appropriate DCF. Solicited AEs will be regarded as related to the study product and will not require separate entry into the AE log.	Add clarification on Solicited AEs
59	Page 45, Section 8.3.1 Definition of Adverse Event (AE), 5th paragraph, 3rd sentence	Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator), date of resolution, seriousness, and outcome.	Information to be collected for unsolicited AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator), date of resolution, seriousness, and outcome.	Added the clarification that the information is to be collected for '**unsolicited**

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
60	Page 46, Section 8.3.1.2 Unsolicited Adverse Events, 3rd paragraph	Unsolicited AEs of all severities will be reported from the time of study product administration through 28 days post last vaccination.	Unsolicited AEs of all severities will be reported from the time of study product administration through 28 days post each vaccination.	Update reporting of unsolicited AEs to occur after **each** vaccination.
61	Page 46, Section 8.3.1.2 Unsolicited Adverse Events, 4th paragraph	After 28 days post last vaccination through the end of study, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs (as detailed in Section **Error! Reference source not found.**) will be reported as AEs.	After 28 days post last vaccination through the end of study, only SAEs, AESIs, MAAEs, and NOCMCs (as detailed in Section **Error! Reference source not found.**) will be reported as AEs.	Removed '**Protocol Specified'** for AEs.
62	Page 48, Section 8.3.4.1. Severity of Adverse Events, added two more bullets after Severe (Grade 3)	• 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.	• 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. • Potentially Life Threatening (Grade 4): Events that lead to an ER visit or hospitalization. (recorded on Adverse Event log as a Serious Adverse Event (SAE) and to be reviewed by Medical Monitor). • Death (Grade 5): Events that lead to death (recorded on Adverse Event log as a Serious Adverse Event (SAE) and to be reviewed by Medical Monitor).	Added additional AE grades to conform with the FDA grading scale.
63	Page 48, Section 8.3.4.2 Relationship to Study Intervention:	• Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and	• Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or	Added clarifying information on how solicited/unsolicited events should be

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	added a new paragraph after the bullets	event onset, or an alternate etiology has been established.	an alternate etiology has been established. Solicited adverse events reported in the 7 days after each vaccination are considered related to study product unless they are also recorded as an unsolicited event, in which case the relationship to study product will be determined by the PI or qualified designee.	recorded as related.
64	Page 50, Section 8.3.5 Time Period and Frequency for Event Assessment and Follow-Up, 2nd List Item	• unsolicited AEs will be collected until 28 days post last vaccination.	• unsolicited AEs will be collected until 28 days after each vaccination.	Updated AEs collect after each vaccination.
65	Page 50, Section 8.3.9 Adverse Events of Special Interest (AESIs), Protocol Specified AESIs: added new bullet	○ All suspected cases of anaphylaxis should be recorded. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis should be reported as a potential case of anaphylaxis.	○ All suspected cases of anaphylaxis should be recorded. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis should be reported as a potential case of anaphylaxis. ○ Thrombosis with Thrombocytopenia Syndrome (TTS) has been observed very rarely following vaccination with Ad26.COV2.S and is considered an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and	Added reporting requirements for new adverse events of TTS

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			thrombocytopenia. Because this syndrome is rare and not completely understood, all cases of thrombosis and/or thrombocytopenia will be considered a suspected case of TTS until further adjudication can be performed. The investigator shall be responsible for reporting any suspected AESI of TTS using the SAE form. A suspected TTS case is defined as: • Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 12, Appendix A • Thrombocytopenia, defined as platelet count below 150,000/µL Symptoms, signs, or conditions suggestive of a thrombotic event should be recorded and reported as a suspected AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely. Follow-up information and final diagnoses, if applicable, should be submitted to the	

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			sponsor as soon as they become available. In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used. For either a thrombotic event or thrombocytopenia, testing for anti-PF4 should be performed at the local laboratory or substitute local laboratory; repeat testing may be requested for confirmation upon sponsor discretion.	
66	Page 56, Section 9.3 Population for Analyses, 1st paragraph, 1st sentence	The safety analysis population includes all enrolled subjects who received one dose of study vaccine.	The safety analysis population includes all enrolled subjects who received at least one dose of study vaccine.	Updated to say "at least" one…
67	Page 56, Section 9.4.3 Analyses of the Co-Primary Endpoint(s)	**9.4.3 Analysis of the Secondary Endpoint(s)**	**9.4.3 Analysis of the Co-Primary Endpoint(s)**	Title was updated to include the primary and co-primary endpoints listed in Table 5
68	Page 57, Section 9.4.4 Safety Analyses, 2nd paragraph , 3rd sentence	Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after the last vaccination…….The numbers of SAEs, Protocol Specified AESIs and MAAEs will be reported by detailed	Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after the last vaccination. …….The numbers of SAEs, AESIs, NOCMCs and MAAEs will be reported by detailed listings	Added clarification on unsolicited AEs

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		listings showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event.	showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event.	
69	Page 61, Section 10.1.1.2 Other Informed Consent Procedures, 2nd paragraph , 1st sentence	Subjects will be asked for consent to collect additional blood, the use of residual specimens, and the sharing of genetic information and samples for secondary research.	Subjects will be asked for consent to collect additional blood, nasal or NP swabs, the use of residual specimens, and the sharing of genetic information and samples for secondary research.	Added nasal or NP swabs to the consent form
70	Page 64, Section 10.1.4 Secondary Use of Stored Specimens and Data, 1st paragraph , 3rd sentence	Any use of the sample or data, however, will be presented in a separate protocol and require separate IRB approval.	Any use of the secondary sample or data, however, will be presented in a separate protocol and require separate IRB approval.	Added 'secondary' to conform with the section title.
71	Page 66, Section 10.1.6.1 Safety Monitoring Committee, 2nd paragraph	The SMC will hold an organizational meeting prior to enrollment. At this meeting, the SMC will review the charter, protocol, ICF, IB, and safety report templates.	The SMC will hold an organizational meeting or electronic review prior to enrollment. At this meeting, the SMC will review the charter, protocol, ICF, IB, and safety report templates.	Added electronic review option for SMC
72	Page 68, Section 10.1.9.3 Source Records, 1st Paragraph, 3rd and 4th sentence	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. Each participating site will maintain appropriate medical and research records for this	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. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH	Added language on types of source.

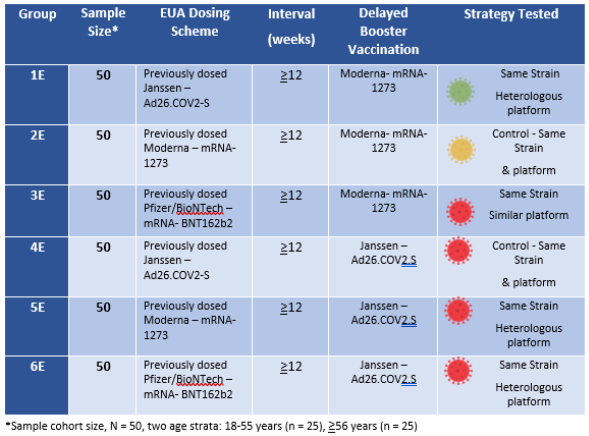
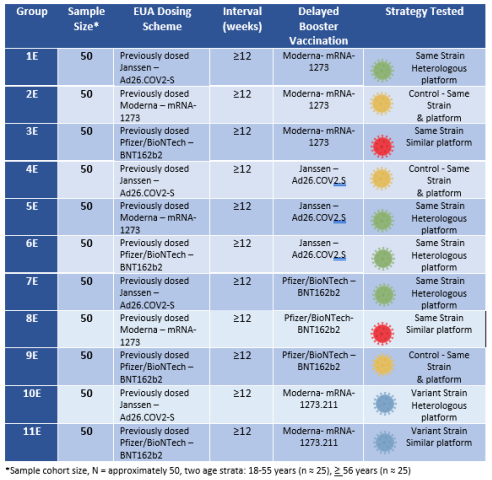
#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
		trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.	GCP, regulatory, and institutional requirements. Study data will be collected on paper CRFs and entered the eCRF or data will be entered directly into the eCRF. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents. Data entered directly into the eCRFS will be considered the source document.	
73	Page 70, Section 10.3 Abbreviations. Table 12: Abbreviations	New	Ad Adenovirus	Updated abbreviation table.
74	Page 73, Section 10.3 Abbreviations. Table 12: Abbreviations	New	NP Nasopharyngeal	Updated abbreviation table.
75	Page 74, Section 10.3 Abbreviations. Table 12: Abbreviations	New	TTS Thrombosis with Thrombocytopenia Syndrome	Updated abbreviation table.
76	Page 74, Section 10.4 Protocol Amendment History, Table 13 Protocol Amendment History,	This is the initial protocol with no amendment history at this time.	This is version 2.0 of the protocol and the first amendment at this time.	Updated amendment history.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for change
77	Page 81, Section 12. Appendix A: Adverse Events of Special Interest (AESISs)	**Thrombocytopenia** • Platelet counts < 150 x10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome	**Thrombocytopenia and/or Thrombosis with Thrombocytopenia Syndrome (TTS)** • Platelet counts < 150 x10^9 • Thrombotic events: Suspected deep vessel venous or arterial thrombotic events • Including but not limited to TTS (default operative diagnosis if boosted with Ad26.COV2.S), immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome	Added "and/or Thrombosis with Thrombocytopenia Syndrome (TTS)" and included Thrombotic events and other events.

DMID Protocol #21-0012 Protocol Version 2.0, 22 June 2021
Updated in
DMID Protocol #21-0012 Protocol Version 3.0, 15 July 2021

Protocol:

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
1	All pages, Header	Version 2.0 22 June 2021	Version 3.0 15 July 2021	Update to the protocol version and date.
2	Page 1, Title Page	Version Number: 2.0 22 June 2021	Version Number: 3.0 15 July 2021	Update to the protocol version and date.
3	Page 9, Section 1.1 Population	"**Population:** Approximately -550 healthy individuals aged ≥ 18 years"	**"Population:** Approximately -800 healthy individuals aged ≥ 18 years"	The protocol version added 5 additional cohort arms of 50 participants per arm therefore increasing the population size.
4	Page 9, Section 1.1 Rational	The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causative agent of the coronavirus disease of 2019 (COVID-19) pandemic, has infected over 126 million people worldwide and resulted in over 2.7 million deaths, including > 548,000 in the United States (March 27, 2021, WHO; www.who.int).	The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causative agent of the coronavirus disease of 2019 (COVID-19) pandemic, has infected over 182 million people worldwide and resulted in over 3.9 million deaths, including > 605,000 in the United States (July 02, 2021, WHO; www.who.int).	Update the number of infections and deaths.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
5	Page 11, Section 1.1 Table 5	 *Sample cohort size, N = 50, two age strata: 18-55 years (n = 25), ≥56 years (n = 25)	 *Sample cohort size, N = approximately 50, two age strata: 18-55 years (n ≈ 25), ≥ 56 years (n ≈ 25)	Added additional arms to cohort 1 to boost with additional study product.
6	Page 15, Section 1.2 Table 3 SOA Note f	[f] Collect 7-day Memory Aid.	[f] Review 7-day Memory Aid data.	Clarification on what to do with memory aid.
7	Page 16, Section 1.2 Table 4 SOA	Delayed Boost to occur > 12 weeks from completion of EUA dosing	Delayed Boost to occur ≥12 weeks from completion of EUA dosing	Updated to reflect minimum window for boosting post EUA dosing.
8	Page 16, Section 1.2 Table 4 SOA Visit 1B and 8b[b]	Window (+/-) is missing	0 was added to Visit 1B 1 was added to Visit 8b[b]	Visit windows needed to be defined.
9	Page 16, Section 1.2 Table 4 SOA Note g	[g] Collect 7-day Memory Aid for delayed booster dose.	[g] Review 7-day Memory Aid data for delayed booster dose.	Clarification on what to do with the memory aid.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
10	Page 17, Section 2.1 Background and Study Rationale, 1st Paragraph	The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first detected in Wuhan, Hubei Province, China in December 2019. The corresponding illness designation, coronavirus disease 2019 (COVID-19), was declared as a pandemic respiratory illness on March 2020.[1] As of 3 April 2021, it has infected over 130 million people worldwide and resulted in over 2.8 million deaths, including > 554,000 in the United States.[1,2]	The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first detected in Wuhan, Hubei Province, China in December 2019. The corresponding illness designation, coronavirus disease 2019 (COVID-19), was declared as a pandemic respiratory illness on March 2020.[1] As of 02 July 2021, it has infected over 182 million people worldwide and resulted in over 3.9 million deaths, including > 605,000 in the United States.[1,2]	Updated numbers of infected and global deaths.
11	Page 18, Section 2.1 Background and Study Rationale, 3rd Paragraph	For example, mRNA-1273.211, like mRNA-1273, encodes the prefusion stabilized S protein of SARS-CoV-2, but incorporates the key mutations present in the B.1.351 viral strain.	For example, mRNA-1273.211, like mRNA-1273, encodes the prefusion stabilized S protein (S-2P) of SARS-CoV-2, but also incorporates the key mutations present in the B.1.351 viral strain (S-2P) in a 1:1 ratio with the wildtype Wuhan-Hu-1 strain.	Updated information on the content of the mRNA-1272.211
12	Page 18, Section 2.1 Background and Study Rationale, 5th Paragraph	Utilizing the EUA-dosed COVID-19 vaccines available (currently mRNA-1273, mRNA-BNT162b2, and AD26.COV2.S), we propose to evaluate innate, cellular, and humoral immune responses elicited from different booster vaccines.	Utilizing the EUA-dosed COVID-19 vaccines available (currently mRNA-1273, -BNT162b2, and AD26.COV2.S), we propose to evaluate innate, cellular, and humoral immune responses elicited from different booster vaccines.	Updated the Pfizer vaccine product name
13	Page 18, Section 2.1.1 Public Readiness and Emergency Preparedness Act, 1st Paragraph	The study vaccines, mRNA-1273, mRNA-BNT162b2, and Ad26.COV.2, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S.	The study vaccines, mRNA-1273, mRNA-1273.211, BNT162b2, and Ad26.COV.2, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the	Added in the mRNA-1273.211 vaccine and updated the Pfizer product name.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
		Department of Health and Human Services under that Act.	Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act.	
14	Page 18, Section 2.1.1 Public Readiness and Emergency Preparedness Act, 1st Paragraph	Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273 and Ad26.COV2.S.	Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273, mRNA-1273.211, BNT162b2, and Ad26.COV2.S.	Added in the mRNA-1273.211 vaccine and BNT162b2.
15	Page 19, Section 2.2.1 Known Potential Risks, 1st Paragraph	The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the initial immunization with mRNA-1273 vaccine and delayed booster inoculation of mRNA-1273 and Ad26.COV2.S, and breach of confidentiality.	The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the initial immunization with mRNA-1273 vaccine and delayed booster inoculation of mRNA-1273, mRNA-1273.211, BNT162b2 and Ad26.COV2.S, and breach of confidentiality.	Added in the additional study products.
16	Page 20, Section 2.2.1 Known Potential Risks, Subheading	**Risks of mRNA-1273**	**Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, and BNT162b2)**	Updated the sub header with study product.
17	Page 20, Section 2.2.1 Known Potential Risks, Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211,	The currently estimated risk of an anaphylactic reaction to the Moderna EUA COVID-19 vaccine is about 3 events per million vaccinations.	The currently estimated risk of an anaphylactic reaction to the mRNA EUA COVID-19 vaccines is about 2-5 events per million vaccinations.	Risks were revised with the current information for mRNA vaccines

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	and BNT162b2), 2nd Paragraph			
18	Page 20, Section 2.2.1 Known Potential Risks, Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, and BNT162b2), 6th paragraph	Intramuscular injection with other mRNA vaccines manufactured by ModernaTX Inc containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction.	Intramuscular injection with other mRNA vaccines manufactured by ModernaTX, Inc. containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction.	Grammatical update
19	Page 20, Section 2.2.1 Known Potential Risks, Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, and BNT162b2), 7th paragraph	The majority of local and systemic solicited adverse events (AEs) observed after injection with mRNA-1273 at the 100-mcg dose level have been mild to moderate in severity.	The majority of local and systemic solicited adverse events (AEs) observed after injection with mRNA-1273 at the 100-mcg dose level or BNT162b2 at the 30-mcg dose level have been mild to moderate in severity.	Updated language for additional study product.
20	Page 21, Section 2.2.1 Known Potential Risks, Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, and BNT162b2), 9th Paragraph	New	Myocarditis and pericarditis have been reported following mRNA vaccines, particularly after the second dose, in a younger population (age < 30 years), and more common in males. Symptoms can include chest pain, shortness of breath, or palpitations. Typically, onset of symptoms has been within a few days following receipt of the mRNA COVID-19 vaccines. Whilst some severe cases have been reported, most cases have been associated with full resolution of symptoms in the short term; however, long-term follow-up is limited. It is not known whether the risk of myocarditis or pericarditis is increased	Update the risks for mRNA vaccines to include myocarditis and pericarditis as reported by the FDA.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
			following additional doses of the vaccine, e.g. following a booster dose.	
21	Page 21, Section 2.2.1 Known Potential Risks, Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, and BNT162b2), 10th Paragraph	Further details are provided in the FDA-approved fact sheet and current IB for mRNA-1273.	Further details are provided in the FDA-approved fact sheet and current IBs for mRNA-1273, mRNA-1273.211 and BNT162b2. mRNA-1273.211 has not been extensively tested clinically, but based on its similarity to mRNA-1273, the risks are expected to be similar.	Include a reference to the updated IBs and FDA fact sheet information for the added study product.
22	Page 21, Section 2.2.1 Known Potential Risks, Risks of Ad26.COV2.S, 5th Paragraph	These cases occurred approximately 3 weeks following vaccination, mostly in women under 60 years of age.	These cases occurred approximately 3 weeks following vaccination. The reporting rate of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine has been highest in females ages 18 through 49 years; some have been fatal.	Updated risk of Janssen study product to include the reporting rate of thrombosis and population affected by this risk.
23	Page 22, Section 2.2.1 Known Potential Risks, Risks of Ad26.COV2.S, 5th Paragraph	Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, from the American Society of Hematology, British Society of Haematology - Expert Haematology Panel10, and the CDC).	Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (e.g., from the American Society of Hematology, British Society of Haematology - Expert Haematology Panel10, and the CDC)	Grammatical update.
24	Page 22, Section 2.2.1 Known Potential Risks, Risks of Ad26.COV2.S, 6th Paragraph	New	Rare cases of Guillain Barré syndrome have occurred in some people who have received the Janssen COVID-19 Vaccine. The FDA requested (12 Jul 2021) that this risk be added to the Fact Sheet. In most circumstances, symptoms began within 42 days following receipt of dosing. Reported symptoms included weakness or	Update the risk of the Janssen product to include Guillain Barré syndrome as stated in the

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
			tingling sensations in the extremities, difficulty ambulating, difficulty with facial movements to include chewing, swallowing or speaking, diplopia or inability to move eyes, or difficulty with bowel or bladder control.	product FDA fact sheet and IB.
25	Page 23, Section 2.2.2 Known Potential Benefits	Data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 demonstrated 94.1% efficacy of the vaccine as a two-vaccination series versus placebo against symptomatic SARS-CoV-2 infection. The Phase 3 placebo-controlled clinical trial of Ad26.COV.2 demonstrated 66% efficacy against mild-moderate SARS-CoV-2 infection and 85% against severe disease as a one-dose vaccination. The doses and vaccination strategies used in this trial may or may not alter this protection.	The Phase 3 placebo-controlled trial of BNT162b2 provided 95% vaccine efficacy as a two-vaccination series versus placebo against symptomatic SARS-CoV-2 infection.[15] The Phase 3 placebo-controlled clinical trial of Ad26.COV.2 demonstrated 66% efficacy against mild-moderate SARS-CoV-2 infection and 85% against severe disease as a one-dose vaccination. The doses and vaccination strategies used in this trial may or may not alter this protection. It is unknown if the mRNA-1273.211 vaccine will provide protection against infection with the B.1.351 variant.	Updated the potential benefits to include vaccine efficacy for Pfizer BNT162b2.Also mentioned the unknown benefit of the mRNA 1273.211 vaccine.
26	Page 26, Section 4.1, Overall Design, 1st Paragraph	This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed (≥12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; mRNA-BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).	This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed (≥12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273 manufactured by ModernaTX, Inc.; -BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).	Updated the Pfizer study product name to not include mRNA.
27	Page 26, Section 4.1, Overall Design, 3rd Paragraph	Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and ≥ 56 years) who	Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and ≥ 56 years) who	Updated the Pfizer study product name to

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
		received previously received COVID-19 vaccine at EUA dosing (two vaccinations of mRNA-1273 at the 100 mcg dose, two vaccinations of mRNA-BNT162b2 at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the $5x10^{10}$ vp dose).	received previously received COVID-19 vaccine at EUA dosing (two vaccinations of mRNA-1273 at the 100 mcg dose, two vaccinations of BNT162b2 at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the $5x10^{10}$ vp dose).	not include mRNA.
28	Page 26, Section 4.1, Overall Design, 3rd Paragraph, List item 1	1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by: • Group 1E – A 100-mcg dose of mRNA-1273 • Group 4E – A $5x10^{10}$ vp dose of Ad26.COV2.S	1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by: • Group 1E – A 100-mcg dose of mRNA-1273 • Group 4E – A $5x10^{10}$ vp dose of Ad26.COV2.S • Group 7E - A 30-mcg dose of BNT162b2 • Group 10E –A 100-mcg dose of mRNA-1273.211	Updated to include the additional cohort arms added.
29	Page 26-27, Section 4.1, Overall Design, 3rd Paragraph, List item 2	2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by: • Group 2E – A 100-mcg dose of mRNA-1273 • Group 5E – A $5x10^{10}$ vp dose of Ad26.COV2.S	2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by: • Group 2E – A 100-mcg dose of mRNA-1273 • Group 5E – A $5x10^{10}$ vp dose of Ad26.COV2.S • Group 8E - A 30-mcg dose of BNT162b2 *Note: There will be no boost with mRNA-1273.211 to avoid duplication of trial efforts with DMID 21-0003.*	Updated to include the additional cohort arms added.

<table>
<tr><th>#</th><th>Page and Section of V3.0</th><th>Originally in Version 2.0</th><th>Updated in Version 3.0</th><th>Rationale for change</th></tr>
<tr><td>30</td><td>Page 27, Section 4.1, Overall Design, 3rd Paragraph, List item 3</td><td>3. Previously EUA-dosed vaccination with Pfizer/BioNTech - mRNA-BNT162b2 at 30 mcg for two doses followed by:
Group 3E – A 100-mcg dose of mRNA-1273
Group 6E – A 5x10^{10} vp dose of Ad26.COV2.S</td><td>3. Previously EUA-dosed vaccination with Pfizer/BioNTech - BNT162b2 at 30 mcg for two doses followed by:
Group 3E – A 100-mcg dose of mRNA-1273
Group 6E – A 5x10^{10} vp dose of Ad26.COV2.S
Group 9E - A 30-mcg dose of BNT162b2
Group 11E – A 100-mcg dose of mRNA-1273.211</td><td>Updated to include the additional cohort arms added. Updated the Pfizer study product name to not include mRNA.</td></tr>
<tr><td>31</td><td>Page 27, Section 4.1, Overall Design, 3rd Paragraph, Table 6</td><td>Table 6. Cohort 1 Treatment Arms<table><tr><th>Arm</th><th>Sample Size</th><th>Booster Vaccination Product and Dose</th></tr><tr><td>1E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>2E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>3E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>4E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2</td></tr><tr><td>5E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2</td></tr><tr><td>6E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2</td></tr></table></td><td>Table 6. Cohort 1 Treatment Arms<table><tr><th>Arm</th><th>Sample Size</th><th>Booster Vaccination Product and Dose</th></tr><tr><td>1E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>2E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>3E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr><tr><td>4E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2.S</td></tr><tr><td>5E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2.S</td></tr><tr><td>6E</td><td>~50</td><td>5x10^{10} vp dose Ad26.COV2.S</td></tr><tr><td>7E</td><td>~50</td><td>30 mcg BNT162b2</td></tr><tr><td>8E</td><td>~50</td><td>30 mcg BNT162b2</td></tr><tr><td>9E</td><td>~50</td><td>30 mcgBNT162b2</td></tr><tr><td>10E</td><td>~50</td><td>100 mcg mRNA-1273.211</td></tr><tr><td>11E</td><td>~50</td><td>100 mcg mRNA-1273.211</td></tr></table></td><td>Added 5 arms to cohort 1 for additional study product.</td></tr>
<tr><td>32</td><td>Page 28, Section 4.1, Overall Design, Summary of Treatment Arms</td><td>3E – Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received a mRNA-BNT162b2 EUA vaccination series
6E - Evaluates mRNA-BNT162b2 EUA vaccination series followed by a heterologous platform delayed dose of Ad26.COV2.S</td><td>3E – Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received a BNT162b2 EUA vaccination series
6E - Evaluates BNT162b2 EUA vaccination series followed by a heterologous platform delayed dose of Ad26.COV2.S</td><td>Updated the Pfizer study product name to not include mRNA.</td></tr>
</table>

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
33	Page 28, Section 4.1, Overall Design, Summary of Treatment Arms	New	Added • 7E - Evaluates Ad26.COV2.S EUA vaccination series followed by a heterologous platform delayed dose of BNT162b2 • 8E - Evaluates mRNA-1273 EUA vaccination series followed by a homologous platform delayed dose of BNT162b2 • 9E - Evaluates BNT162b2 EUA vaccination series followed by a homologous platform delayed dose of BNT162b2 • 10E- Evaluates Ad26.COV2.S EUA vaccination series followed by a heterologous platform delayed dose of a combined homologous and variant spike lineage mRNA-1273.211 • 11E - Evaluates BNT162b2 EUA vaccination series followed by a homologous platform delayed dose of a combined homologous and variant spike lineage mRNA-1273.211 o Note – the homologous comparator for groups 10E and 11E (Moderna EUA vaccination with the mRNA 1273.211 variant vaccine is being conducted in another trial (NIAID DMID 21-0002) and not done here to avoid duplication.	Updated list to include additional cohort arms and the reason for not including the homologous comparator.
34	Page 29, Section 4.3, Justification for Doses, 2nd Paragraph	Binding and neutralizing antibody responses were generally comparable in participants who received the 100 mcg mRNA-1273 and the 50	Binding and neutralizing antibody responses were generally comparable in participants who received the 100-mcg mRNA-1273 and the 50-	Grammatical update.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
		mcg dose at all time points and across the age groups of ≥18 to <55 years and ≥55 years.	mcg dose at all time points and across the age groups of ≥18 to <55 years and ≥55 years	
35	Page 29, Section 4.3, Justification for Doses, 2nd Paragraph	New	For this reason, mRNA-1273.211 consists of a combined 50-mcg of mRNA-1273 encoding the S-2P of Wuhan-Hu-1 and 50-mcg of mRNA-1273.351 encoding the S-2P of the South African (Beta) variant strain.	Provided justification for the dose of Moderna mRNA-1273.211.
36	Page 31, Section 5, Study Population, 1st Paragraph	For Cohort 1, approximately 300 individuals (50 subjects/group; Groups 1E-6E) 18 years of age and older, stratified into two age groups (18-55 years and ≥56 years at 1:1 ratio), who are in good health and received EUA dosed vaccinations of mRNA-1273, BNT162b2 or Ad26.COV2.S will be invited to participate in this study.	For Cohort 1, approximately 550 individuals (50 subjects/group; Groups 1E-11E) 18 years of age and older, stratified into two age groups (18-55 years and ≥56 years at 1:1 ratio), who are in good health and received EUA dosed vaccinations of mRNA-1273, BNT162b2 or Ad26.COV2.S will be invited to participate in this study.	Study population size and group number was updated for the new cohort arms.
37	Page 33, Section 6.1.1, Study Product Description, Subheading	**Product 1: mRNA-1273**	**Product: mRNA-1273 and mRNA-1273.211**	Update the header to include the additional study product and removed the product #.
38	Page 33, Section 6.1.1, Study Product Description, Product: mRHNA-1273 and mRNA-1273.211, 2nd Paragraph	New	**mRNA-1273.211 (0.2 mg/mL)** is formulated in the same way as the mRNA-1273 vaccine but contains 1:1 mix of mRNAs that encodes for the prefusion stabilized S protein of the B.1.351 variant SARS-CoV-2 strain and the prefusion stabilized S protein of the Wuhan-Hu-1 strain used in mRNA-1273.	Included study product description for Moderna mRNA-1273.211.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
39	Page 33, Section 6.1.1, Study Product Description, Product: mRHNA-1273 and mRNA-1273.211, 3rd Paragraph heading	**Product 2: Ad26.COV2.S**	**Product: Ad26.COV2.S**	Removed the product #. Products will not be numbered.
40	Page 33, Section 6.1.1, Study Product Description, Product: BNT162b2	New	**Product: BNT162b2** The Pfizer-BioNTech COVID-19 Vaccine (250 mcg/0.5 mL) contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose. Each vial contains up to six doses. This vaccine requires dilution. The USP grade 0.9% NaCl or normal saline for injection is a sterile, nonpyrogenic, isotonic solution; each mL contains NaCl 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). This product should be used to dilute the BNT162b2 vaccine to the desired concentration.	Included the study product description for the additional study product: Pfizer BNT162b2.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
41	Page 34, Section 6.1.2, Dosing and Administration, Subheading	New	**Product: mRNA-1273 and mRNA-1273.211**	Includes subheading for study products.
42	Page 34, Section 6.1.2 Dosing and Administration, Product: mRNA-1273 and mRNA-1273.211	New	mRNA-1273.211 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL).	Includes the dosing and administration information for the additional study product: Moderna mRNA-1273.211.
43	Page 34, Section 6.1.2 Dosing and Administration, Subheading	New	**Product: Ad26.COV2.S**	Includes subheading for study products.
44	Page 34, Section 6.1.2 Dosing and Administration, Subheading	New	**Product: BNT162b2**	Includes subheading for study products.
45	Page 34, Section 6.1.2 Dosing and Administration, Product: BNT162b2, 1st Paragraph	New	BNT162b2 (250 mcg/0.5 mL) will be administered in diluted 0.3 mL doses (30 mcg/0.3 mL).	Includes the dosing and administration information for the additional study product: Pfizer BNT162b2.
46	Page 34, Section 6.2.1 Acquisition and	The mRNA-1273 , and Ad26.COV2.Swill be provided by HHS-OWS Research Allocation via the DMID repository:	All the vaccines (and diluents as needed) will be provided by the DMID repository:	Updated the language to include all the

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
	Accountability, 1st Paragraph			vaccines used in this study.
47	Page 36, Section 6.2.2 Formulation and Appearance, Subheading	**Product: mRNA-1273**	**Product: mRNA-1273 and mRNA-1273.211**	Updated the subheading to include mRNA-1273.211.
48	Page 36, Section 6.2.2 Formulation and Appearance, Product: mRNA-1273 and mRNA-1273.211, 2nd Paragraph	New	**mRNA-1273.211** is provided as a sterile liquid for injection, white to off-white dispersion in appearance.	Provided the formulation and appearance of mRNA-1273.211.
49	Page 36, Section 6.2.2 Formulation and Appearance, 3rd subheading and 1st Paragraph	New	**Product: BNT162b2** BNT162b2 is white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection.	Updated the subheading to include Pfizer BNT162b2. Provided the formulation and appearance of Pfizer BNT162b2.
50	Page 36, Section 6.2.3 Product Storage and Stability, Product: mRNA-1273, 2nd Paragraph	New	**mRNA-1273.211** vials are stored frozen between -60°C to -90°C (-76°F to -130°F). Stability and compatibility with the apparatus intended for administration for up to 8 hours after preparation were assessed. The prepared doses were stable for clinical in-use for up to 8 hours at room temperature. Store in the original carton to protect from light.	Provided the product storage and stability for the Moderna mRNA-1273.211 product.
51	Page 37, Section 6.2.3 Product Storage	New	Product: BNT162b2	Provided the product storage and stability for

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
	and Stability, 3rd subheading and 1st paragraph		BNT162b2 is a preservative-free, sterile dispersion of RNA formulated in LNP in aqueous cryoprotectant buffer for IM administration. The RNA drug substance is the only active ingredient in the drug product. The vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose vial. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 1 month. The vaccine must be thawed (room temperature [up to 25ºC (77ºF)] for 30 minutes or at 2ºC to 8ºC (35ºF to 46ºF) for up to 1 month.) and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration and within 2 hours of thaw. Before dilution, the vaccine vials should be inverted gently 10 times but not shaken. Do not refreeze. After dilution, the vial contains up to 6 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. During storage, minimize exposure to room light and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Note: Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in the EUA this Fact Sheet regarding the number of doses per vial after dilution supersedes the number of doses stated	the Pfizer BNT162b2 product.

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
			on vial labels and cartons. For the purposes of this study, no more than 5 doses per vial will be used.	
52	Page 38, Section 6.2.3 Product Storage and Stability, Study Product Temperature Accountability, 2nd Paragraph	Study product must be stored in a secure area with limited access (pharmacy staff only) and must be stored frozen. 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.	Study product must be stored in a secure area with limited access (pharmacy staff only) and must be stored as above. The storage areas should have an automated temperature recording and alert system. There must be an available back-up storage locations. The storage areas 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 storage area malfunctioning.	Adjusted language for product to be stored in the "storage area" rather than freezer.
53	Page 47, Section 8.2 Safety and Other Assessments, List Item: Memory Aid, 1st bullet	Memory Aids will be collected, and subjects will be assessed for delayed onset local reactions 14 days after booster vaccination (initial vaccination in Cohort 1, delayed vaccination in Cohort 2). Memory aids will be collected 7 days after each vaccination in the initial part of Cohort 2.	Memory Aids will be reviewed again, and subjects will be assessed for delayed onset local reactions 14 days after booster vaccination (initial vaccination in Cohort 1, delayed vaccination in Cohort 2). Memory aids will be reviewed 7 days after each vaccination in the initial part of Cohort 2.	Clarified language on memory aid activity.
54	Page 56, Section 8.3.9 Adverse Events of Special Interests (AESIs), List Item: Protocol	New	○ All suspected cases of myocarditis and pericarditis must be reported as AESI. Symptoms of chest pain, shortness of breath or palpitations may represent myocarditis or pericarditis. Typically, onset of symptoms has been within a few days following receipt of the mRNA COVID-19 vaccines.	Added reporting requirements for new adverse events of myocarditis and Guillain Barré Syndrome

#	Page and Section of V3.0	Originally in Version 2.0	Updated in Version 3.0	Rationale for change
	Specified AESIs: See Section 12, Appendix A		○ Guillain Barré Syndrome has occurred in some people who have received the Janssen COVID-19 Vaccine and will be recorded as an AESI in this study. In most circumstances, symptoms began within 42 days following receipt of dosing.	
55	Page 75, Section 10.2.1 Research Related Injuries, 3rd Paragraph	For this protocol, the study vaccines, mRNA-1273, manufactured by ModernaTX, Inc. are covered under the PREP Act, as described in Section 2.1.1	For this protocol, the study vaccines are covered under the PREP Act, as described in Section **Error! Reference source not found.**	Language was updated to include all vaccines.
56	Page 79-80, Section 10.4 Protocol Amendment History, Table 13	This is version 2.0 of the protocol and the first amendment at this time.	Version 2.0 of the protocol was amended 22 June, 2021. V3.0 of the protocol was amended 14 July 2021	Updated the version history table with the version and dates of the protocol amendments.
57	Page 84, Section 12 APPENDIX A: Adverse Events of Special Interest (AESIs) Terms	New	**Myocarditis and/or pericarditis** — Symptoms and diagnostic findings include but are not limited to: • Chest pain • Dyspnea • ST or T wave changes on ECG • Elevated cardiac enzymes • Abnormal echocardiography or other cardiac imaging.	Updated the AESIs to include the myocarditis risk for mRNA vaccines.

DMID Protocol #21-0012 Protocol Version 3.0, 15 July 2021
Updated in
DMID Protocol #21-0012 Protocol Version 4.0, 20 August 2021

Protocol:

#	Page and Section	Originally in Version 3.0	Updated in Version 4.0	Rationale for change
1	All pages, Headers	Version 3.0 15 July 2021	Version 4.0 20 August 2021	Updated to the protocol version and date.
2	Title page	**Version Number: 3.0** **15 July 2021**	**Version Number: 4.0** **20 Aug 2021**	Updated to the protocol version and date.
3	Page 11, Section 1: Protocol Summary	**Population:** Approximately -800 healthy individuals aged ≥ 18 years	**Population:** Approximately 950 healthy individuals aged ≥ 18 years	The protocol version added 3 additional groups of 50 participants per group. Therefore, increasing the population size of the study.

<table>
<tr><th>#</th><th>Page and Section</th><th>Originally in Version 3.0</th><th>Updated in Version 4.0</th><th>Rationale for change</th></tr>
<tr><td>4</td><td>Page 11, Table 1: EUA-doses Cohort 1</td><td>
Table 1: EUA-dosed Cohort 1
<table>
<tr><th>Group</th><th>Sample Size*</th><th>EUA Dosing Scheme</th><th>Interval (weeks)</th><th>Delayed Booster Vaccination</th><th>Strategy Tested</th></tr>
<tr><td>1E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Same Strain Heterologous platform</td></tr>
<tr><td>2E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Control - Same Strain & platform</td></tr>
<tr><td>3E</td><td>50</td><td>Previously dosed Pfizer/BioNTech – BNT162b2</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Same Strain Similar platform</td></tr>
<tr><td>4E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Control - Same Strain & platform</td></tr>
<tr><td>5E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Same Strain Heterologous platform</td></tr>
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<tr><td>2E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Control - Same Strain & platform</td></tr>
<tr><td>3E</td><td>50</td><td>Previously dosed Pfizer/BioNTech – BNT162b2</td><td>≥12</td><td>Moderna- mRNA-1273</td><td>Same Strain Similar platform</td></tr>
<tr><td>4E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Control - Same Strain & platform</td></tr>
<tr><td>5E</td><td>50</td><td>Previously dosed Moderna – mRNA-1273</td><td>≥12</td><td>Janssen – Ad26.COV2.S</td><td>Same Strain Heterologous platform</td></tr>
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<tr><td>12E</td><td>50</td><td>Previously dosed Janssen – Ad26.COV2-S</td><td>≥12</td><td>Moderna- mRNA-1273 50 mcg</td><td>Same Strain Heterologous platform</td></tr>
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*Sample cohort size, N = approximately 50, two age strata: 18-55 years (n ≈ 25), ≥ 56 years (n ≈ 25)
</td><td>Added additional; arms to cohort 1 for the groups.</td></tr>
<tr><td>5</td><td>Page 26, Section 4.1 Overall Design, 3rd Paragraph, 1st List, Bullet Item 5</td><td>1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by:
[Bulleted List]</td><td>1. Previously EUA-dosed vaccination with Janssen – Ad26.COV.2.S at $5x10^{10}$ vp followed by:
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• Group 12E – A 50-mcg dose of mRNA-1273</td><td>Updated to include the additional cohort group.</td></tr>
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<tr><td>6</td><td>Page 27, Section 4.1, 3rd Paragraph, 2nd List, Bullet Item 4</td><td>2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by:
[Bulleted List]</td><td>2. Previously EUA-dosed vaccination with Moderna – mRNA-1273 at 100 mcg for two doses followed by:
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<tr><td>7</td><td>Page 27, Section 4.1 Overall Design, 3rd Paragraph, 3rd List, Bullet Item 5</td><td>3. Previously EUA-dosed vaccination with Pfizer/BioNTech - BNT162b2 at 30 mcg for two doses followed by:
[Bulleted List]</td><td>4. Previously EUA-dosed vaccination with Pfizer/BioNTech - BNT162b2 at 30 mcg for two doses followed by:
[Bulleted List]
• Group 14E – A 50-mcg dose of mRNA-1273</td><td>Updated to include the additional cohort group.</td></tr>
<tr><td>8</td><td>Page 27-28, Section 4.1 Overall Design, Table 6</td><td>Table 6. Cohort 1 Treatment Arms
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<tr><th>Arm</th><th>Sample Size</th><th>Booster Vaccination Product and Dose</th></tr>
<tr><td>1E</td><td>~50</td><td>100 mcg mRNA-1273</td></tr>
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</table></td><td>Updated to include the additional cohort group.</td></tr>
<tr><td>9</td><td>Page 28, Section 4.1 Overall Design,</td><td>New</td><td>• 12E – Evaluates a heterologous platform 50 mcg booster of mRNA-1273 among persons</td><td>Updated list to include additional</td></tr>
</table>

#	Page and Section	Originally in Version 3.0	Updated in Version 4.0	Rationale for change
	Summary of Treatment Arms, Bullet Item 12-14		who previously received an Ad26.COV2.S EUA vaccination series • 13E- Evaluates a homologous platform 50 mcg booster of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series • 14E – Evaluates a homologous mRNA platform of mRNA-1273 50 mcg booster among persons who previously received a BNT162b2 EUA vaccination series	cohort groups.
10	Page 30, Section 4.3 Justification for Doses, 2nd Paragraph	[Last sentence in the paragraph] The primary efficacy analysis from the Phase 3 trial evaluating a two-dose schedule of a 100-mcg mRNA-1273 vaccine led to the issuance of the EUA and initiation of a vaccination campaign in the United States.	[2nd to last sentence in the paragraph] Further, the 50-mcg dose of mRNA-1273 will be tested as a dose-sparing booster option separate from the admixture (mRNA-1273 and mRNA-1273.351) dosing. The primary efficacy analysis from the Phase 3 trial evaluating a two-dose schedule of a 100-mcg mRNA-1273 vaccine led to the issuance of the EUA and initiation of a vaccination campaign in the United States.	Update to include the additional groups.
11	Page 31, Section 5 Study Population, 1st paragraph	For Cohort 1, approximately 550 individuals (50 subjects/group; Groups 1E-11E) 18 years of age and older, stratified into two age groups (18-55 years and ≥56 years at 1:1 ratio) ….	For Cohort 1, approximately 700 individuals (50 subjects/group; Groups 1E-14E) 18 years of age and older, stratified into two age groups (18-55 years and ≥56 years at 1:1 ratio) ….	Updated the study population description for cohort 1.

#	Page and Section	Originally in Version 3.0	Updated in Version 4.0	Rationale for change
12	Page 34 Section 6.1.2 Dosing and Administration **Product: mRNA-1273 and mRNA-1273.211**	mRNA-1273 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL). mRNA-1273.211 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL).	mRNA-1273 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL). mRNA-1273 (0.2 mg/mL) will be administered in 0.25 mL doses (50 mcg/0.25 mL). mRNA-1273.211 (0.2 mg/mL) will be administered in 0.5 mL doses (100 mcg/0.5 mL).	Added mRNA-1272 50 mcg
13	Page 34, Section 6.1.3 Dose Modification, 1st Paragraph	No dose modifications.	A dose sparing 50 mcg mRNA-1273 booster (Groups 12E-14E) will be tested and compared to full dose booster dosing (Groups 1E-3E)	Updated to include the dose modification for Moderna mRNA-1273 (50 mcg).
14	Page 38, 1st paragraph, 3rd sentence	There must be an available back-up storage locations.	There must be an available back-up storage location.	Grammatical correction.
15	Page 56-57 Section 8.3.10 Reporting of Pregnancy	Pregnancy is not an AE. However, any pregnancy that occurs following the booster dose (through three months after boost) should be reported to the sponsor on the appropriate DCF Pregnancy and followed to outcome.	Pregnancy is not an AE. However, any pregnancy that occurs following the booster dose (through three months after booster dose or through 12 months after the mRNA-1272.211 booster dose) should be reported to the sponsor on the appropriate DCF Pregnancy form and pregnancy should be followed to outcome.	Adds language on pregnancy follow-up for mRNA-1272.211
16	Page 63, Section 9.4.6.1	…The SMC will not need to meet (unless halting rules are met), and materials will be provided	… The SMC may not need to meet (unless halting rules are met), and materials will be provided	Updated the SMC report

#	Page and Section	Originally in Version 3.0	Updated in Version 4.0	Rationale for change
	Interim Safety Analyses, 1st and 2nd Paragraph	electronically. Documentation of review and any concerns noted will be solicited electronically. The SMC will review cumulative AE data after all subjects for each group in Cohort 1 have been dosed and completed Day 8. The SMC will also review cumulative AE data after all subjects in a given booster group have been dosed and completed Day 8.	electronically. Documentation of review and any concerns noted will be solicited electronically. The SMC will review separate cumulative AE data reports after all subjects within each booster product group have been dosed and completed Day 29 within Cohort 1….	to include data report for participants that were dosed and completed day 29.
17	Page 71, Section 10.1.6.1 Safety Monitoring Committee (SMC), 4th Paragraph	The SMC will review cumulative AE data after all subjects in Cohort 1 have been dosed and completed Day 8**.**	The SMC will review separate cumulative AE data reports after all subjects within each product booster group have been dosed and completed Day 29 within Cohort 1….	Updated the SMC report to include data report for participants that were dosed and completed day 29
18	Page 80, Section 10.4 Protocol Amendment History, Table 13: Protocol Amendment History	**Table 1: Protocol Amendment History** Version 2.0 of the protocol was amended 22 June, 2021. V3.0 of the protocol was amended 14 July 2021	**Table 2: Protocol Amendment History** Version 2.0 of the protocol was amended 22 June, 2021. Version 3.0 of the protocol was amended 15 July 2021 Version 4.0 of the protocol was amended 20 August 2021	Updated the version history table with the version and dates of the protocol amendments.

<table>
<tr><th>#</th><th>Page and Section</th><th>Originally in Version 3.0</th><th>Updated in Version 4.0</th><th>Rationale for change</th></tr>
<tr><td>19</td><td>Page 86
Appendix A: Adverse Events of Special Interest (AESIs) Terms</td><td><table><tr><td>Other syndromes</td><td>• Fibromyalgia
• Postural Orthostatic Tachycardia Syndrome
• Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome)</td></tr></table></td><td><table><tr><td>Other syndromes</td><td>• Fibromyalgia
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• Myasthenia gravis</td></tr></table></td><td>Updated the AESIs to include myasthenia gravis</td></tr>
</table>

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STATISTICAL ANALYSIS PLAN

A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines

DMID Protocol Number: 21-0012

Effective Date: 31/08/2021

Version: 1.0

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STATISTICAL ANALYSIS PLAN

Protocol Name:	A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines.
Protocol Number:	DMID Protocol Number: 21-0012
Author(s):	Clara Dominguez Islas, Lead Statistician Elizabeth Brown, Lead Statistician
Version:	1.0

Author(s):

Clara Dominguez Islas Lead Statistician	Signature	Date: DD/MM/YYYY
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The effective date of this document is the date of the latest signature.

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1. LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
DMID	Division of Microbiology and Infectious Diseases
EUA	emergency use authorization
FSR	Final Study Report
GM	geometric mean
GMFR	geometric mean fold rise
MAAE	medically attended adverse event
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
NOCMC	new-onset chronic medical condition
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	SARS coronavirus
SARS-CoV-2	SARS coronavirus 2
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDSU	Statistical and Data Science Unit
SMC	Safety Monitoring Committee
SOC	system organ class
TLFs	tables, listings, and figures

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2. INTRODUCTION

2.1 Purpose

The purpose of this Statistical Analysis Plan (SAP) is to define the analyses planned DMID 21-0012 study. DMID 21-0012 is a Phase 1/2 study that will evaluate the safety, tolerability, and immunogenicity of different SARS-CoV-2 vaccine delayed boosts at >12 weeks.

This SAP is based on Version 4.0 of the Study Protocol (20 August 2021) and describes the planned analyses for reports prepared for the Final Study Report (FSR). Subsets of the analyses described here will be included in reports for Safety Monitoring Committee (SMC) Meetings or in reports for early Immunogenicity Reviews.

2.2 General Design Considerations

This study will be composed of two different cohorts:

1. A cohort of persons previously vaccinated with an EUA vaccine who will be boosted with a homologous or heterologous vaccine strain on a homologous or a heterologous platform (Table 1). This cohort is referred to as “Cohort 1” throughout this document.
2. A cohort of persons who are prospectively vaccinated with EUA standard dosing and who will be available for rapid assessment of a heterologous boost at some point in the future (Table 2). This cohort is referred to as “Cohort 2” throughout this document.

EUA-dosed Cohort: Cohort 1 will recruit persons who have previously received COVID-19 vaccine under EUA dosing guidelines at least 12 weeks earlier. Eligible individuals will be stratified by age (18-55 years or $\geq$ 56 years) in a 1:1 ratio (N = 25/group). Subjects will be sequentially enrolled to receive one of the available delayed boost options (Table 1). A total of ~50 per group will be recruited for each group in the EUA-dosed Cohort 1. This study is has an adaptive design, and as more vaccines become available under EUA or new variants of available EUA vaccine become available, the number of groups may be expanded. Participants will be assessed for safety and tolerability endpoints following administration of a delayed boost.

Prospective Cohort: Cohort 2 will recruit persons who are naïve to COVID-19 vaccine and infection (by history). These individuals will be given a vaccine as part of the study that matches the vaccine/dose available under an EUA. Cohorts from this pool will then be available to be boosted with a novel homologous or heterologous variant lineage spike proteins or heterologous platform delayed boost as part of an adaptive design meant to respond quickly to circulating SARS-CoV-2 variants. As new vaccines are manufactured to emerging variant lineages, these dosed “pools” of study participants will enable rapid deployment of delayed booster constructs.

Prioritization of Cohort 1 versus Cohort 2 enrollment will be determined by availability of EUA-dosed vaccines, status of distribution, and current epidemiology. Cohorts 1 and 2 may enroll simultaneously.

Duration of Study: Approximately 4 years

Duration of participation per subject: Up to 2 years (approximately 12 months after delay boost inoculation)

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Table 1: EUA-dosed Cohort 1

Group	Sample Size*	EUA Dosing Scheme	Interval (weeks)	Delayed Booster Vaccination	Strategy Tested
1E	50	Previously dosed Janssen – Ad26.COV2-S	≥12	Moderna- mRNA-1273	Same Strain Heterologous platform
2E	50	Previously dosed Moderna – mRNA-1273	≥12	Moderna- mRNA-1273	Control - Same Strain & platform
3E	50	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Moderna- mRNA-1273	Same Strain Similar platform
4E	50	Previously dosed Janssen – Ad26.COV2-S	≥12	Janssen – Ad26.COV2.S	Control - Same Strain & platform
5E	50	Previously dosed Moderna – mRNA-1273	≥12	Janssen – Ad26.COV2.S	Same Strain Heterologous platform
6E	50	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Janssen – Ad26.COV2.S	Same Strain Heterologous platform
7E	50	Previously dosed Janssen – Ad26.COV2-S	≥12	Pfizer/BioNTech – BNT162b2	Same Strain Heterologous platform
8E	50	Previously dosed Moderna – mRNA-1273	≥12	Pfizer/BioNTech-BNT162b2	Same Strain Similar platform
9E	50	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Pfizer/BioNTech – BNT162b2	Control - Same Strain & platform
10E	50	Previously dosed Janssen – Ad26.COV2-S	≥12	Moderna- mRNA-1273.211	Variant Strain Heterologous platform
11E	50	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Moderna- mRNA-1273.211	Variant Strain Similar platform
12E	50	Previously dosed Janssen – Ad26.COV2-S	≥12	Moderna- mRNA-1273 50 mcg	Same Strain Heterologous platform
13E	50	Previously dosed Moderna – mRNA-1273	≥12	Moderna- mRNA-1273 50 mcg	Control - Same Strain & platform
14E	50	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	Moderna- mRNA-1273 50 mcg	Same Strain Similar platform

*Sample cohort size, N = approximately 50, two age strata: 18-55 years (n ≈ 25), ≥ 56 years (n ≈ 25)

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Table 2: Prospective Cohort 2

Group	Sample Size*	First Vaccination**	Interval	Second Vaccination88	Interval (Weeks)	Delayed Booster Vaccination
1	**250**	Moderna-mRNA-1273	28d	Modern- mRNA-1273	>12	Novel homologous or heterologous variant or heterologous platform boost

*Aged ≥ 18 years
** As part of an adaptive design, products newly awarded EUA can be added (e.g., Janssen Ad26.COV2.S and Novavax NVX-CoV2373)

2.3 Study Objectives and Endpoints

Table 3: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of delayed heterologous or homologous vaccine doses after EUA dosed vaccines.	• Local and systemic solicited adverse events for 7 days following the delayed boost dose. • Adverse Events from Dose 1 to 28 days following delayed boost dose Related MAAEs, SAEs, and AESI from Dose 1 on study to month 12 months after last dose on study.
• To evaluate the breadth of the humoral immune responses of heterologous and homologous delayed boost regimens following EUA dosing	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization titers in serum samples as assessed via a range of assays at all clinic visits.
Secondary	
• None	• None

2.4 Randomization

Subjects in Cohorts 1 and 2 will not be randomized to study intervention. The study will be open label and study sites will administer product to which they have been assigned

2.5 Blinding

This study is unblinded.

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2.6 Sample Size and Power

This is a phase 1/2, open-label, multi-site clinical trial that is not designed to test a specific hypothesis. Rather, it is intended to obtain preliminary estimates in healthy adults of the safety, reactogenicity, and immunogenicity of delayed heterologous SARS-CoV-2 vaccine dosing (boost) after receipt of EUA vaccines.

Although rare AEs are not demonstrable in a clinical study of this size, there is a good chance of observing AEs of relatively low frequency. With approximately 50 subjects in each group there is a 99.5% chance of observing at least one AE of probability 10%. Similarly, with approximately 25 subjects in each of the age subgroups, there is a 92.8% chance of observing at least one AE of probability 10%. Therefore, if no AEs of a given type occur in a Cohort 1 group, we can be relatively confident that they will occur in fewer than 10% of people once the vaccine is implemented.

Additional information on the probability of observing AEs, as well as the precision with which immunogenicity endpoints can be estimated (width of 95% Confidence Intervals) with the proposed sample size, is provided in the Section 9.2 of the Study Protocol.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

3.1.1 Analysis Sets for Cohort 1

The Cohort 1 safety analysis set includes all subjects enrolled in Cohort 1 who received the study vaccine delayed boost (≥12 weeks after receipt of EUA vaccines). Final analyses of the Safety Primary Endpoints for Cohort 1 will be conducted on the safety analysis set and will include safety data reported through the end of the study. Analyses of the Safety Primary Endpoints for scheduled or unscheduled SMC reports will be conducted in the safety population and will include safety data accumulated up to that time. Events triggering SMC Safety Reports are described in Section 4.1.

The Cohort 1 modified intent-to-treat (mITT) analysis sets, specific to each primary immunogenicity endpoint, will include all enrolled subjects who received the study vaccine delayed boost and contributed both pre- and at least one post-vaccination boost venous blood sample for the corresponding immunogenicity endpoint testing and for which valid results were reported. Final and early statistical analyses of the immunogenicity endpoints will be conducted in this population.

For the final analysis of immunogenicity endpoints, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis. The Cohort 1 specific per protocol (PP) analysis set will then be defined as a subset of the mITT analysis set. Exclusions may include, for example:

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

3.1.2 Analysis Sets for Cohort 2

As of Version 4.0 of the protocol (20 August 2021), Cohort 2 consists of a pool of participants receiving a EUA vaccine (Moderna mRNA-1273) and who will potentially receive a delayed boost vaccination with a yet to be determined vaccine in the future. Given that the delayed boost is the intervention of interest for this Cohort, safety data collected after the receipt of the EUA vaccine but before receipt of the delayed boost is not part of the primary objective or endpoints of interest. Following future amendments to the

Protocol to include timing and type of delayed boost, this SAP would be amended to define corresponding Safety and mITT populations.

3.2 Statistical Analysis Issues

In general, summaries of safety and immunogenicity data for Cohort 1 will be presented by Group, as defined in the protocol and given by combination of EUA vaccine previously received and the delayed boost received as part of the study. From this point forward, these will be referred to as Study Groups. Following the stratified enrollment into two main age groups (18-55 years old and ≥56 years old), summaries may also be shown by Study Groups and Age Group.

Statistical analyses of primary endpoints are planned to be descriptive. No formal statistical tests to compare safety or immunogenicity endpoints between Study Groups or between Age Groups are planned.

Immunogenicity data collected outside of the allowable visit windows will be included in analyses of the mITT population. After further evaluation it will be determined if any observations should be excluded from the per-protocol analysis set (see Section 3.1.1).

4. INTERIM ANALYSIS AND SAFETY MONITORING COMMITTEE

No formal interim analyses will be conducted, understanding by this the sequential testing of a statistical hypothesis for which adjustment of type I error probability is required.

However, given the need for rapid review and dissemination of study data for formulating public health policies, early reports summarizing safety and immunogenicity endpoints and from data cumulated up to pre-defined timepoints, will be produced. These reports may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community. None of the analyses included in these reports will include any formal statistical hypothesis testing; therefore, no adjustment of the significance level will be done.

4.1 Safety Monitoring Committee Reports

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

Following Protocol Version 4.0, the SMC will review separate cumulative AE data reports after all subjects within a Study Group in Cohort 1 have been dosed and completed Day 29. Study Groups that are concurrently enrolled and planned to receive the same delayed boost can be included in a single report.

Prior to Version 4.0, scheduled SMC reviews were targeted after subjects within a Study Group have completed Day 8. At the time of the writing of this SAP, a SMC report after Day 8 has only been produced only for Groups 1E, 2E and 3E. For the remainder groups, SMC reports for a given boost will be produced after participants in the corresponding groups have completed Day 29.

Given the safety database known for EUA vaccines, there is no routine mandatory review by the SMC during the EUA dosing in Cohort 2 unless halting rules are triggered.

4.2 Immunogenicity Review

Data review of immunogenicity endpoints will be performed as often as needed to inform public health decisions. These reviews may be performed when subjects have completed key immunogenicity visits and the data is available. The analyses will be conducted on the mITT analysis set.

Study Groups that are concurrently enrolled and planned to receive the same delayed boost can be included in a single report. The planned summaries and analyses for immunogenicity reports are

described in detail in Section 10. The timing of the reports, along with key milestone visits determining the cumulative data to be included in the reports, will be informed by the Central Assay Plan and/or determined by DMID.

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

5. GENERAL ANALYSIS METHODS

The following descriptive statistics will be used to summarize continuous outcomes: number of non-missing values, mean and standard deviation, median, interquartile range, and range (minimum and maximum). Descriptive statistics for categorical endpoints may include number of non-missing values, frequencies, relative frequencies, and percentages.

Additionally, descriptive summaries of immunogenicity data may include Geometric Means (GM), Geometric Mean Fold Rise (GMFR) from baseline, and proportion of participants achieving a pre-specified increase from baseline.

For selected binary endpoints, 95% exact binomial Confidence Intervals (CI), calculated using the Clopper-Pearson method. For GM and GMR, corresponding 95% CIs will be based on a t-distribution of the log-transformed endpoint.

Graphical summaries of the data, including bar plots, boxplots and line plots will also be presented.

6. STUDY PARTICIPANT DISPOSITION

6.1 Study Screening and Enrollment

For each Cohort, and for each boosting stage (i.e. study enrollment stages in which a particular boost is planned to be administered), the numbers of participant screened, screened out (with reasons for exclusion) and enrolled will be tabulated by Study Group.

6.2 Disposition of Participants

For each Cohort, the disposition of participants enrolled in the study will be described as follows, by boosting group: number of participants enrolled, and from these number and percentage of participants who received the study boost (Cohort 1) or the number and percentage of participants who received the first/second vaccination (Cohort 2), the number and percentage of participants with early termination from the Study (along with the reason for early termination), the number and percentage of participants remaining in study (for reports produced with partial follow-up) and number and percentage of participants who completed the study.

6.3 Treatment Compliance

The number and proportion of enrolled participants receiving study vaccinations will be presented, by Study Group. For Participants in Cohort 1, only one study vaccination is expected (delayed boost at least 12 weeks after EUA vaccination). For participants in Cohort 2, up to three study vaccinations are expected (two vaccination as part of the EUA immunization and a delayed boost). These summaries may be included in tables describing disposition of participants.

6.4 Retention (Visit Completion)

The number and proportion of participants expected to complete and who completed each visit (regardless of whether the visit was completed within the allowable visit window) will be tabulated, by visit

and by Study Group. The number and proportion of completed visits that were completed inside the window and outside the window will also be tabulated. These summaries, presented by visit and by Study Group, may be included in tables describing disposition of participants.

6.5 Protocol Deviations

Protocol deviations, as collected in the protocol deviations log eCRF will be reported. The number and type of protocol deviations will be tabulated by boosting group. A listing with all the recorded protocol deviations will be presented, including the description of the deviation, the plans and/or actions taken to address the deviation and the pans or/actions taken to prevent future occurrences.

7 BASELINE DATA

7.1 Demographics characteristics

Demographic characteristics collected at baseline include age in years, sex, ethnicity, and race. Height (cm) and weight (kg) were also collected. Summary statistics for each baseline characteristic, including BMI (calculated as weight divided by height squared, expressed in kg/m^2 units) will be presented in tables by Study Group. No formal comparison or statistical testing will be performed.

7.2 BMI and Vital signs

Height (cm), weight (kg) and BMI (cm/kg) were collected at screening, along with vital signs: body temperature (C), systolic blood pressure (mmHG), diastolic blood pressure (mmHG) and pulse (beats/minute). Summary statistics will be presented in tables by Study Group. A subset of these (e.g. height, weight and BMI) may be included as part of the Demographic Characteristics table in some early reports. No formal comparison or statistical testing will be performed.

7.3 Prior SARS-CoV-2 Vaccination

For participants in Cohort 1, time from last SARS-CoV-2 vaccination (administered under EUA) will be calculated as the number of weeks from the date the participant received a Janssen vaccination (prior to enrollment into the study) or date of the second Moderna or Pfizer/Biotech vaccination (prior to enrollment into the study) to the date when participants receive the study delayed boost (Day 1 visit). The time from last SARS-CoV-2 vaccination will be presented in tables by Study Group, and it may be included as part of the Demographic Characteristics table in some reports. No formal comparison or statistical testing will be performed.

7.4 Prior and concurrent Medical Conditions

Individual subject listings will be presented for all reported medical conditions current or prior to participant's boost vaccination date.

7.5 Prior and Concurrent Medications

Individual subject listings will be presented for all reported medications concurrent or prior to participant's boost vaccination date.

8 EFFICACY/EFFECTIVENESS ANALYSES

See Section 9 for the planned analyses of the co-primary safety endpoint related to safety, and Section 10 for the planned analyses of the co-primary endpoint related to immune response.

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9 SAFETY ANALYSES

Summaries and analyses of all safety data will be conducted on the Safety Analysis Set.

For Cohort 1, safety data will be summarized after the study delayed boost. For Cohort 2, data will be summarized after each of the EUA vaccines and after the delayed boost.

9.1 Solicited Local and Systemic Adverse Events (Reactogenicity)

Solicited adverse events (systemic and local signs/symptoms) were collected pre-vaccination, 30 minutes post-vaccination and then daily for 7 days after each vaccination. Severity grade for solicited AEs is recorded as none, mild, moderate, Severe and Potentially Life Threatening. Systemic AEs include malaise and/or fatigue, myalgia, headache, nausea, chills, arthralgia and fever. Local AEs include erythema/redness (severity and largest diameter in cm), induration/swelling (severity grade and largest diameter in cm), and pain and/or tenderness.

For each systemic and local solicited AE, the maximum severity reported by participants over 7 days after vaccination/boost will be summarized. The number and percentage of subjects reporting each AE will be presented in tables by Symptom, Maximum Severity and Study Group. For calculation of percentages, the denominator is the number of subjects in the safety analysis set (excluding those missing all post-boost assessments for the symptom). For local AEs that report largest diameter, summary statistics (mean and SD, median and IQR, range) will be presented. Overall result for all Study Groups sharing the same boost will also be included.

For each systemic and local solicited AE, bar plots describing the classification (proportion) of participants by the maximum severity of the AE reported, by Study Group, will be produced.

All systemic and local solicited AEs will be summarized by Symptom, Severity, and collection time (Day 1 early assessment and Days 1-8 post-vaccination), for participants in each Study Group. For calculation of percentages, the denominator is the number of subjects in the safety analysis set (excluding those missing assessments for the day and symptom) Summary statistics for largest diameter of local AEs, as appropriate, will also be reported.

For the final analysis, the proportion of participants with at least one solicited adverse event, along with 95% CI, will be reported for: (i) each solicited adverse event, (ii) any systemic symptom, (iii) any local symptom, and (iv) any symptoms.

9.2 Unsolicited Adverse Events

Unsolicited (non-serious) AEs will be collected from the time of first vaccination through 28 days after the last vaccination. Severity grade for unsolicited AEs is recorded as mild, moderate, severe, potentially life-threatening and death. Unsolicited AEs will be coded by MedDRA for preferred term and corresponding system organ class (SOC). Unsolicited AEs will also be classified as related or not related to study product.

All Unsolicited AEs will be cross tabulated by severity and relationship to study product, for each Study Group.

The number and percentage of subjects reporting at least one (unsolicited) AE related to study product, overall and for each MedDRA preferred term, will be presented in tables by MedDRA SOC, preferred term, Severity and Study Group. For participants reporting multiple events within the same MedDRA term, the maximum severity grade is counted. Percentages are calculated as the number of participants reporting an event of a specific severity grade divided by the number of participants in the safety analysis set.

For graphical display of results, a bar chart showing unsolicited AEs by MedDRA SOC and severity, as well as a bar chart showing AEs by MedDRA SOC and relationship to study product, will be produced.

Incidence of related AEs over time (based on the date of onset relative to the date of the study boost) will be presented as the number and percentage of participants reporting related AEs by day post vaccination (Day 1 to Day 8, and Day 9-29).

For the final analysis, the proportion of participants (along with 95% CI) who reported at least one related unsolicited AE will be reported for (i) any mild or higher related AE, (ii) any moderate or higher related AE, and (iii) any severe or higher related AE. Similar estimates will be obtained for AEs regardless of relationship to study product.

All adverse events graded as Moderate or above, will be listed. The listing will include Group, Site, Subject ID, MeDRA Preferred Term and AE description verbatim, Severity, Relationship to Study Product, Study Visit where the AE was reported, Onset Date, Outcome Date, Duration Days, Treatment, Outcome and if the AE qualifies as SAE.

9.3 Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events (SAEs) Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first vaccination through the end of the study (1 year after delayed boost vaccination).

Serious Adverse Events (SAE), as collected in the Adverse Event log eCRF, will be reported in listings, by Study Group. The listing will include Group, Site, Subject ID, MeDRA Preferred Term and AE description verbatim, Severity, Relationship to Study Product, Study Visit where the AE was reported, Onset Date, Outcome Date, Duration Days, Treatment, Outcome, and if the AE meets the criteria for triggering a halting rule.

Adverse Events of Special Interest, including NOCMCs and MAAEs, as collected in the Adverse Event log eCRF, will be reported in listings, by Study Group. The listing will include Group, Site, Subject ID, MeDRA Preferred Term and AE description verbatim, Severity, Relationship to Study Product, Study Visit where the AE was reported, Onset Date, Outcome Date, Duration Days, Treatment, Outcome, if the AE qualifies as SAE and if the AE meets the criteria for halting rules.

9.4 Pregnancies

For participates who become pregnant during the study, follow-up and collection of information will be targeted until completion of pregnancy, whenever possible. Detailed listings with information about the pregnancies reported in the study (including date when pregnancy is fist reported and estimated delivery time), the pregnancy history of participants who become pregnant and the pregnancy outcomes will be produced. The total number of pregnancies and the outcomes of these pregnancies (full term live birth, premature live birth, stillbirth/intrauterine fetal demise, spontaneous abortion, ectopic pregnancy, therapeutic/elective abortion, other) will be presented in a table.

9.5 Clinical Laboratory Evaluations

For this study, no local clinical laboratory data is collected during follow-up.

9.6 Other Safety Measures

The number of specimens collected for SARS-CoV-2 tests will be reported, along with the number and percentage of positive, negative and indetermined tests by Study Group and Age Group. The number and proportions of participants with at least one positive SARS-CoV-2 test result will be tabulated by Study Group and Age Group. A listing of specimens with a positive SARS-CoV-2 Test will be produced, including date in which the participant received the study vaccinations/boost and the date when the specimen was collected.

9.7 SMC reports

Reports produced for SMC review will include a selection of the descriptive analyses described in Section 7 and this section. A mock report including shell TLFs with the planned content for SMC reports is included in Appendix I.

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10 IMMUNOGENICITY ANALYSES

As per the most current version of the DMID 21-0012 Central Assay Plan (Version 1.4, dated 2021), the endpoints associated to this co-primary objective include the following:

- SARS-CoV-2 IgG binding antibody (bAbs) levels, as obtained by the MSD® 384-well Custom Serology Assay Electrochemiluminescence Immunoassay (4-plex ECLIA) Version 2.
- SARS-CoV-2 pseudovirus neutralizing titers (ID50 and ID80).
- SARS-CoV-2 live-virus neutralizing titers (ID50 and ID80), by Focus Reduction Neutralization Test (FRNT).

Here, we describe the planned approaches for analysis of these primary endpoints.

10.1 SARS-CoV-2 IgG Binding Antibody (bAb) Levels

For antigens tested with via a 4-plex ECLIA V.2, the results reported from the Laboratory will be in Arbitrary Units per milliliter (AU/mL). The Laboratory is expected to provide Lower and Upper Limits of Quantification (LLOQ, ULOQ) for each of the antigens tested by this method. The Lower Limit of Detection will be considered equivalent to the LLOQ. Values of the bAb are below the LLOQ are expected to be reported by the Laboratory as numeric value equivalent to LLOQ/2. If no numeric values are provided (i.e., observations reported as "<<LLOQ" or "BLQ"), numeric values equivalent to LLOQ/2 will be assigned before and for all descriptive reporting.

Values that are greater than the upper limit of quantification (ULOQ) will be kept when actual values are reported from the corresponding Laboratory. If actual values above the ULOQ are not provided, observations will be replaced with a value equivalent to the ULOQ

Selected summaries of IgG bAb levels, as bridged to the WHO standard Binding Antibody Units per milliliter (BAU/mL) may be presented (when appropriate), in addition or as supplemental material to relevant reports or manuscripts. Conversion from AU/mL to BAU/mL units will be done using conversion factors provided by the Laboratory. Specific to the SARS-CoV-2 WA-1 variant, a conversion factor of 0.0090 for the SARS-CoV-2 Spike antigen, a conversion factor of 0.0024 for the SARS-CoV-2 N antigen and a conversion factor of 0.0272 for the SARS-CoV-2 RBD antigen will be applied.

10.2 SARS-CoV-2 Pseudovirus Neutralizing titers (ID50 and ID80)

These endpoints are based on the Duke assay from the Montefiori Laboratory. As reported elsewhere [1], the process for validating the assay defined the LLOD, LLOQ, and ULOQ for ID50 and ID80 as follows:

• ID50:
–LLOD = 10
–LLOQ = 18.5
–ULOQ = 4511815

•ID80:
–LLOD = 10
–LLOQ = 14.3
–ULOQ = 10232

Values below the Lower Limit of Detection (LLOD), which are expected to be reported by the Laboratory as "<< 10", will be assigned a value equivalent to LLOD/2 = 10/2 = 5. Levels that are reported as above the LLOD but below the Lower Limit of Quantification (LLOQ) will be kept as reported by the corresponding Laboratory if actual numerical values are provided. If actual values below the LLOQ are not provided, the observations will be replaced with a value equivalent LLOQ/2. Values that are greater than the upper limit of quantification (ULOQ) will be kept when actual values are reported from the corresponding Laboratory.

If actual values above the ULOQ are not provided, observations will be replaced with a value equivalent to the ULOQ.

Selected summaries of neutralizing titers calibrated to the WHO standard International Units (IU50 and IU80), may be presented (when appropriate) in addition or as supplemental material to relevant reports or manuscripts. Conversion will be done using calibration factors provided by the Laboratory. Specifically for the SARS-CoV-2 D614G Pseudovirus, a calibration factor of 0.242 for ID50 and a calibration factor of 1.502 for ID80 will be applied.

10.3 SARS-CoV-2 live-virus neutralizing titers (ID50 and ID80)

Values below the Lower Limit of Detection (LLOD) will be assigned a value equivalent to LLOD. Levels of Abs that are reported as above the LLOD but below the Lower Limit of Quantification (LLOQ) will be kept as reported by the corresponding Laboratory if actual numerical values are provided. If actual values below the LLOQ are not provided, the observations will be replaced with a value equivalent LLOQ/2. Values that are greater than the upper limit of quantification (ULOQ) will be kept when actual values are reported from the corresponding Laboratory. If actual values above the ULOQ are not provided, observations will be replaced with a value equivalent to the ULOQ.

10.4 Descriptive Statistics

To describe binding antibody IgG levels and neutralizing titers for each of the groups and at different visits, the following statistics will be reported:

- number of participants with non-missing measurements at that visit
- median, with 25th and 75th percentiles
- range (minimum and maximum)
- Geometric Mean Concentration (GMC) or Geometric Mean Titer (GMT), with 95% Confidence Interval (CI). The GMC/GMT and 95% CIs are obtained by exponentiating the mean (and corresponding 95% CI) of the log-transformed outcomes, where the CI is based on a t-distribution.

Additionally, for specimens obtained at post-boost visits (Day 15, Day 29, Day 91, Day169 and Day 366 visits), the following statistics will be reported:

- number of participants with non-missing observations at both the pre-boost (Day 1) and the post-boost visit
- proportion of participants with at least a 2-fold increase relative to pre-boost (Day 1) levels, among participants with non-missing observations at both visits, with 95% CIs obtained using the Clopper-Pearson method.
- proportion of participants with at least a 4-fold increase relative to pre-boost (Day 1) levels, among participants with non-missing observations at both visits, with 95% CIs obtained using the Clopper-Pearson method.
- Geometric Mean Fold Rise (GMFR) with 95% Confidence intervals: The Geometric Mean of participants fold-rise (relative to pre-boost, Day 1, levels) and 95% CIs will be obtained by exponentiating the mean (and corresponding 95% CI) of the log-transformed fold-rises, where the CI is based on a t-distribution.

Information on the specific assay LLOQ and ULOQ, when available, will be included as footnote to corresponding table/figures.

For graphic illustration of the distribution of the outcomes, boxplots showing Median and Quartiles will be produced by (i) Group and visit and (ii) Age Groups within Study Groups and visit. Also, line plots showing GMs and GMTs with 95% CI over time will be produced for graphic illustration over multiple timepoints.

10.5 Early Immunogenicity Reports

To be responsive to urgent needs for data to inform public health policy, immunogenicity reports may be produced and disseminated as soon as participants reach key milestones, and their specimens are processed. Reports for immunogenicity review will consist of a narrative describing the assay (as provided by the corresponding Laboratory) and TLFs summarizing key study data. Mock immunogenicity reports with shell TLFs are available in Appendix II.

11 EXPLORATORY IMMUNOGENICTY ENDPOINTS

Additional to the primary immunogenicity endpoints, reports may also include results from exploratory endpoint analyses related to emerging SARS-CoV-2 variant virus, as needed to inform public health decision making. At the time of the writing of this SAP, analysis of the following exploratory endpoints is planned:

- SARS-CoV-2 binding antibody (bAbs) levels to emerging SARS-CoV-2 variant Spike proteins, as obtained by the MSD® 96-well Custom Serology Assay Electrochemiluminescence Immunoassay (10-plex ECLIA).
- SARS-CoV-2 pseudovirus neutralizing titers (ID50 and ID80) specific to the SARS-CoV-2 variants of concern.

Descriptive summaries and graphs used to describe results for variants of concern will be like those described above for primary endpoints. Details on the specific antigens or Pseudovirus tested will be provided in each report.

Other exploratory endpoints of interest, as described in the current Central Assay Plan (Version 1.4, dated 2021), are as follows:

- SARS-CoV-2 CD4+ and CD8+ T cells, by 7-Color ICS/Flow cytometry
- SARS-CoV-2 Memory B cells and Innate Immunity

Given the highly specialized nature of these assays, the specific methods for the analysis of these exploratory endpoints will be described elsewhere.

12 REFERENCES

[1] USG COVID-19 Response Team / Coronavirus Prevention Network (CoVPN) Biostatistics; Gilbert, Peter B.; Fong, Youyi; Benkeser, David; Andriesen, Jessica; Borate, Bhavesh; et al. (2020): USG COVID-19 Response Team / CoVPN Vaccine Efficacy Trial Immune Correlates Statistical Analysis Plan. figshare. Online resource. https://doi.org/10.6084/m9.figshare.13198595.v12.

13 CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
1.0	31/08/20201		First Version.

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APPENDIX I. Mock shell tables and figures for SMC Safety Reports

Table 1: Disposition of Participants, by Group

	Group 1	Group 2	Group 3	Total
Screened	x	x	x	x
Enrolled	x (%)	x (%)	x (%)	x (%)
Received the SARS-CoV-2 Vaccine Dosing (Boost)	x (%)	x (%)	x (%)	x (%)
If cohort involves multiple doses/boosts, include each	x (%)	x (%)	x (%)	x (%)
Early Termination from Study	x (%)	x (%)	x (%)	x (%)
Reasons for Early Termination from Study				
Death	x (%)	x (%)	x (%)	x (%)
Voluntary withdrawal by subject	x (%)	x (%)	x (%)	x (%)
Investigator decision	x (%)	x (%)	x (%)	x (%)
Lost to follow up	x (%)	x (%)	x (%)	x (%)
Termination of site by sponsor	x (%)	x (%)	x (%)	x (%)
Protocol deviation	x (%)	x (%)	x (%)	x (%)
Adverse event (not including death)	x (%)	x (%)	x (%)	x (%)
Pregnancy	x (%)	x (%)	x (%)	x (%)
Study terminated by sponsor	x (%)	x (%)	x (%)	x (%)
Participant unable to adhere to visit schedule	x (%)	x (%)	x (%)	x (%)
Participant relocated, no follow-up planned	x (%)	x (%)	x (%)	x (%)
Reactogenicity symptom	x (%)	x (%)	x (%)	x (%)
Became ineligible after enrollment	x (%)	x (%)	x (%)	x (%)
Other	x (%)	x (%)	x (%)	x (%)
On Study Participants	x (%)	x (%)	x (%)	x (%)
Completed the Study	x (%)	x (%)	x (%)	x (%)

Note: The percentage of participants enrolled will use number screened as the denominator. All other percentages will use number of participants enrolled as the denominator.

Note: This disposition summary is based on Cohort 1. Cohort 2 disposition will separate “received the vaccine/boost” into individual rows for each dose/boost.

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Table 2: Number of Participants Completing Visits, by Group

	Group 1 (N=xx)	Group 2 (N=xx)	Group 3 (N=xx)	Total (N=xx)
Visit 2 – Study Day 8				
Expected[1]	x	x	x	x
Completed[2]	x (%)	x (%)	x (%)	x (%)
Visit 3 – Study Day 15				
Expected[1]	x	x	x	x
Completed[2]	x (%)	x (%)	x (%)	x (%)
Visit 4 – Study Day 29				
Expected[1]	x	x	x	x
Completed[2]	x (%)	x (%)	x (%)	x (%)
Visit 5 – Study Day 91				
Expected[1]	x	x	x	x
Completed[2]	x (%)	x (%)	x (%)	x (%)
Visit 6 – Study Day 169				
Expected[1]	x	x	x	x
Completed[2]	x (%)	x (%)	x (%)	x (%)
Visit 7 – Study Day 366				
Expected[1]	x	x	x	x
Completed[2]	x (%)	x (%)	x (%)	x (%)

Note: these visits are based on the Cohort 1 visit schedule; the Cohort 2 version will use the appropriate visit schedule.

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[1] A visit is considered expected only once the participant's visit window has closed.
[2] A visit is considered completed once the Follow-up Visit Summary CRF has been completed and received by SCHARP.

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Table 3: Demographic Baseline Characteristics of Enrolled Participants, by Group

	Group 1 (N=xx)	Group 2 (N=xx)	Group 3 (N=xx)	Total (N=xx)
Age (years)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Age Group (years)				
18-25	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
26-35	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
36-45	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
46-55	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
56-65	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
>=66	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Sex at Birth				
Male	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Female	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Intersex	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Declined to answer	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Ethnicity				
Hispanic or Latino	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Not Hispanic or Latino	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Not Reported	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Unknown	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Race				
American Indian or Alaska Native	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Asian	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Black or African American	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Multiracial	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Native Hawaiian or Other Pacific Islander	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Unknown	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
White	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Height (cm)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

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Weight (kg)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

BMI (kg/m2)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

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Listing 1: Listing of Serious Adverse Events, by Group

Group	Site	Masked ID	MedDRA Pref Term *and AE verbatim*	Severity	Relationship to Study Product	Criteria for Halting Rule?	Study Visit Where AE Reported	Onset Date	Outcome Date	Duration in days	Treatment	Outcome

This listing will be sorted by:
1. Group (Group 1 -> 2 -> 3), then by
2. Relationship to study product (related, then not related)
3. Site
4. Masked ID (smallest to largest)
5. Onset Date (earliest to latest)

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Listing 2: Listing of Adverse Events of Special Interest, by Group

Group	Site	Masked ID	MedDRA Pref Term *and AE verbatim*	Severity	Relationship to Study Product	Criteria for Halting Rule?	SAE?	Study Visit Where AE Reported	Onset Date	Outcome Date	Duration in days	Treatment	Outcome

This listing will be sorted by:
1. Group (Group 1 -> 2 -> 3), then by
2. Relationship to study product (related, then not related)
3. Site
4. Masked ID (smallest to largest)
5. Onset Date (earliest to latest)

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Table 4a: Total Number of Unsolicited AEs by Severity and Relationship to Study Vaccination, Group 1

Number of Participants Enrolled to Group 1 = x
Number of Group 1 Participants with AE = x

	Relationship to Study Product					
	Not Related		Related		Total	
Severity Grade	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Grade 1 - Mild	x	(%)	x	(%)	x	(%)
Grade 2 - Moderate	x	(%)	x	(%)	x	(%)
Grade 3 - Severe	x	(%)	x	(%)	x	(%)
Grade 4 - Potentially Life-Threatening	x	(%)	x	(%)	x	(%)
Grade 5 - Death	x	(%)	x	(%)	x	(%)
Total	x	(%)	x	(%)	x	(%)

1 This table includes only those AEs which have been MedDRA coded by SCHARP clinical staff. The denominator for calculation of percentages is the number of AEs at a given severity level, except for the Total column where the denominator is the total number of AEs.

Table 4b: Total Number of Unsolicited AEs by Severity and Relationship to Study Vaccination, Group 2

This table will repeat Table 4a for Group 2

Table 4c: Total Number of Unsolicited AEs by Severity and Relationship to Study Vaccination, Group 3

This table will repeat Table 4a for Group 3

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Figure 1a: All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 1

[EXAMPLE FIGURE OMMITED FOR CONFIDENTIALITY REASONS]

Note: The figure will include all unsolicited AEs. Data will be presented by group (one page per group in cohort).

Figure 1b: All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 2
This table will repeat Figure 1a for Group 2

Figure 1c: All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 3
This table will repeat Figure 1a for Group 3

Figure 2a: All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 1

[EXAMPLE FIGURE OMMITED FOR CONFIDENTIALITY REASONS]

Note: The figure will include all unsolicited AEs. Data will be presented by group (one page per group in cohort).

Figure 2b: All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 2
This table will repeat Figure 2a for Group 2

Figure 2c: All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 3
This table will repeat Figure 2a for Group 3

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Table 5: Participants Experiencing Unsolicited Adverse Events Related to Study Vaccination, by MedDRA System Organ Class, Preferred Term, Severity, and Group[1]

	Group 1 (N=xx)		Group 2 (N=xx)		Group 3 (N=xx)		Total (N=xx)	
MedDRA System Organ Class and Preferred Term/Maximum Relationship to Study Product	n	(%)	n	(%)	n	(%)	n	(%)
Participants with one or more composite AEs								
Grade 1 - Mild	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 2 - Moderate	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 3 - Severe	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 4 - Potentially Life-Threatening	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 5 - Death	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Total	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
[System Organ Class 1]								
[Adverse event preferred term 1.1]								
Grade 1 - Mild	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 2 - Moderate	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 3 - Severe	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 4 - Potentially Life-Threatening	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 5 - Death	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Total	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
[Adverse event preferred term 1.2]								
Grade 1 - Mild	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 2 - Moderate	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 3 - Severe	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 4 - Potentially Life-Threatening	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 5 - Death	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Total	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
[System Organ Class 2]								
[Adverse event preferred term 2.1]								
Grade 1 - Mild	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 2 - Moderate	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 3 - Severe	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 4 - Potentially Life-Threatening	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 5 - Death	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Total	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
[Body System 2]								
[Adverse event preferred term 2.2]								
Grade 1 - Mild	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 2 - Moderate	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 3 - Severe	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 4 - Potentially Life-Threatening	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Grade 5 - Death	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
Total	n	(x.x%)	n	(x.x%)	n	(x.x%)	n	(x.x%)
[Etc]								

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[1] For participants reporting multiple events with the same MedDRA preferred term the maximum relationship is counted. Percentages are calculated as the number of participants (n) reporting an event of a specific severity divided by the number enrolled.

Table will include all observed System Organ Classes and all Unsolicited Adverse Events

Table 6: Participants Experiencing Unsolicited Adverse Events Not Related to Study Vaccination by MedDRA System Organ Class, Preferred Term, Severity, and Group

This table will repeat Table 5 for Not Related AEs

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Table 7: Participants Experiencing Local Solicited Events by Symptom, Maximum Severity, and Group

	Group 1 (N=xx)	Group 2 (N=xx)	Group 3 (N=xx)	Total (N=xx)
Erythema/redness[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Gradable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Erythema/redness largest diameter[2] (cm)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Induration/swelling[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Gradable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Induration/swelling largest diameter[2] (cm)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Pain and/or tenderness[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

For a given sign or symptom, each participant's solicited AE will be counted once under the maximum severity for all post-administration assessments (e.g., day 0 early assessment through day 7 assessment, inclusive).

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[1] For a given sign or symptom, each participant's solicited AE will be counted once under the maximum severity for all post-administration assessments.

[2] For erythema/redness and induration/swelling, at each assessment time the maximum diameter at the injection site is recorded. For a given largest diameter, each participant will be counted once under the maximum largest diameter for all post-administration assessments.

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Figure 3: All Local Solicited Events by Symptom, Severity, and Group

Note: The figure will include the local solicited AEs for this protocol. Each local solicited AE panel will include one bar per treatment group for the relevant cohort.

[EXAMPLE FIGURE OMMITED FOR CONFIDENTIALITY REASONS]

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Table 9a: All Local Solicited Events by Symptom, Severity, and Day Post Vaccination, Group 1

	Day 0 Early Assessment (N=xx)	Day 0 (N=xx)	Day 1 (N=xx)	… (N=xx)	Day 7 (N=xx)	Total (N=xx)
Erythema/redness						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Gradable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Erythema/redness largest diameter[1] (cm)						
N	xx	xx	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Induration/swelling						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Gradable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Induration/swelling largest diameter[1] (cm)						
N	xx	xx	xx	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
25th,75th %tile	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Pain and/or tenderness						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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[1] For erythema/redness and induration/swelling, at each assessment time the maximum diameter at the injection site is recorded.

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Table 9b: All Local Solicited Events by Symptom, Severity, and Day Post Vaccination, Group 2

This table will repeat Table 9a for Group 2

Table 9c: All Local Solicited Events by Symptom, Severity, and Day Post Vaccination, Group 3

This table will repeat Table 9a for Group 3

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Table 10: Participants Experiencing Systemic Solicited Events by Symptom, Maximum Severity, and Group

	Group 1 (N=xx)	Group 2 (N=xx)	Group 3 (N=xx)	Total (N=xx)
Malaise and/or fatigue[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Myalgia[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Headache[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nausea[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Chills[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Arthralgia[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vomiting[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Fever[1]				
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

For a given sign or symptom, each participant's solicited AE will be counted once under the maximum severity for all post-administration assessments (e.g., day 0 early assessment through day 7 assessment, inclusive).

Figure 4: All Systemic Solicited Events by Symptom, Severity, and Group

Note: The figure will include the systemic solicited AEs for this protocol. Each systemic solicited AE panel will include one bar per treatment group for the relevant cohort.

[EXAMPLE FIGURE OMMITED FOR CONFIDENTIALITY REASONS]

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Table 11a: All Systemic Solicited Events by Symptom, Severity and Day Post Vaccination, Group 1

	Day 0 Early Assessment (N=xx)	Day 0 (N=xx)	Day 1 (N=xx)	… (N=xx)	Day 7 (N=xx)	Total (N=xx)
Malaise and/or fatigue						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Myalgia						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Headache						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nausea						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Chills						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Arthralgia						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vomiting						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Fever						
None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Potentially Life-Threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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Table 11b: All Systemic Solicited Events by Symptom, Severity and Day Post Vaccination, Group 2
This table will repeat Table 11a for Group 2

Table 11c: All Systemic Solicited Events by Symptom, Severity and Day Post Vaccination, Group 3
This table will repeat Table 11a for Group 3

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Listing 3: Listing of Pregnancies, by Group

Group	Site	Subject ID	Visit	Date Pregnancy Reported	Estimated Date of Delivery	Participant's First Pregnancy Since Enrollment?

This listing will be sorted by:
1. Group (Group 1 -> 2 -> 3), then by
2. Site
3. Subject ID (smallest to largest)
4. Visit

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Table 12: Protocol Deviations by Type and Group

	Group 1 (N = xx)	Group 2 (N = xx)	Group 3 (N = xx)	Total (N = xx)
Number of Protocol Deviations	x	x	x	x
Type of Protocol Deviations				
Inappropriate enrollment	x	x	x	x
Failure to follow randomization or blinding procedures	x	x	x	x
Study product management deviation	x	x	x	x
Study product dispensing error	x	x	x	x
Study product use/non-use deviation	x	x	x	x
Conduct of non-protocol procedure	x	x	x	x
Improper AE/EAE	x	x	x	x
Unreported AE	x	x	x	x
Unreported EAE	x	x	x	x
Breach of confidentiality	x	x	x	x
Physical assessment deviation	x	x	x	x
Lab assessment deviation	x	x	x	x
Mishandled lab specimen	x	x	x	x
Staff performing duties that they are not qualified to perform	x	x	x	x
Use of non-IRB/EC-approved materials	x	x	x	x
Use of excluded concomitant meds, devices, or non-study products	x	x	x	x
Informed assent/consent process deviation	x	x	x	x
Visit completed outside of window	x	x	x	x
Other	x	x	x	x

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Listing 4: Listing of Protocol Deviations, by Group

Group	Site	Masked ID	Type of Deviation	Site Awareness Date	Deviation Date	Reported to Local IRB/EC	Description of Deviation	Steps Taken to Address	Steps Taken to Prevent

This listing will be sorted by:
1. Group (Group 1 -> 2 -> 3), then by
2. Site
3. Masked ID (smallest to largest)
4. Deviation date

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APPENDIX II. Mock shell tables and figures for Immunogenicity Reports

Table X. [Endpoint description], by Group and Timepoint – Groups 1E – 3E

	Group 1E *[Dosed Janssen, Boost Moderna]* N=xx	**Group 2E** *[Dosed Moderna, Boost Moderna]* N=xx	**Group 3E** *[Dosed Pfizer, Boost Moderna]* N=xx
Day 1 Visit (Pre-boost)			
N (non-missing)	XX	XX	XX
Median (P_{25}, P_{75})	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)
Minimum - Maximum	X.XX – X.XX	X.XX – X.XX	X.XX – X.XX
Geometric Mean (AU/mL), 95% CI	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)
Day 15 Visit (14 days post-boost)			
N (non-missing)	XX	XX	XX
Median (P_{25}, P_{75})	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)
Minimum - Maximum	X.XX – X.XX	X.XX – X.XX	X.XX – X.XX
Geometric Mean (AU/mL), 95% CI	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)
N* (non-missing pre- and post-boost)	XX	XX	XX
Participants with 2-fold rise[2], 95% CI	XX.X% (XX.X%-XX.X%)	XX.X% (XX.X%-XX.X%)	XX.X% (XX.X%-XX.X%)
Participants with 4-fold rise[2], 95% CI	XX.X% (XX.X%-XX.X%)	XX.X% (XX.X%-XX.X%)	XX.X% (XX.X%-XX.X%)
Geometric Mean Fold Rise[2], 95% CI	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)
Day 29 Visit (28 days post-boost)			
…			
Day 91 Visit (3 months post-boost)			
…			
Day 169 Visit (6 months post-boost)			
…			
Day 366 Visit (1 year post-boost)			
…			

[1] Values below the lower limit of quantification (LLOQ) were assigned a value equal to LLOQ/2. Values greater than the upper limit of quantification (ULOQ) are taken as reported, or a ceiling value equivalent to the ULOQ is assigned if values are not provided.
[2] Relative to pre-vaccination (Day 1 Visit) levels, among participants with no-missing observations at both pre- and post-boost timepoints.

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Table X. [Endpoint description], by Group, Age Group and Timepoint – Groups 1E – 3E

	Group 1E *[Dosed Janssen, Boost Moderna]* Age 18-55 yo	**Group 1E** *[Dosed Janssen, Boost Moderna]* Age ≥56 yo	…	**Group 3E** *[Dosed Pfizer, Boost Moderna]* Age ≥56 yo
Day 1 Visit (Pre-boost)				
N (non-missing)	XX	XX		XX
Median (P_{25}, P_{75})	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)		X.XX (X.XX-X.XX)
Minimum - Maximum	X.XX – X.XX	X.XX – X.XX	…	X.XX – X.XX
Geometric Mean (AU/mL), 95% CI	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)		X.XX (X.XX-X.XX)
Day 15 Visit (14 days post-boost)				
N (non-missing)	XX	XX		XX
Median (P_{25}, P_{75})	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)		X.XX (X.XX-X.XX)
Minimum - Maximum	X.XX – X.XX	X.XX – X.XX	…	X.XX – X.XX
Geometric Mean (AU/mL), 95% CI	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)		X.XX (X.XX-X.XX)
N* (non-missing pre- and post-boost)	XX	XX		XX
Participants with 2-fold rise[2], 95% CI	XX.X% (XX.X%-XX.X%)	XX.X% (XX.X%-XX.X%)	…	XX.X% (XX.X%-XX.X%)
Participants with 4-fold rise[2], 95% CI	XX.X% (XX.X%-XX.X%)	XX.X% (XX.X%-XX.X%)		XX.X% (XX.X%-XX.X%)
Geometric Mean Fold Rise[2], 95% CI	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)		X.XX (X.XX-X.XX)
Day 29 Visit (28 days post-boost)				
…				
Day 91 Visit (3 months post-boost)				
…				
Day 169 Visit (6 months post-boost)				
…				
Day 366 Visit (1 year post-boost)				
…				

[1] Values below the lower limit of quantification (LLOQ) were assigned a value equal to LLOQ/2. Values greater than the upper limit of quantification (ULOQ) are taken as reported, or a ceiling value equivalent to the ULOQ is assigned if values are not provided

[2] Relative to pre-vaccination (Day 1 Visit) levels, among participants with no-missing observations at both pre- and post-boost timepoints.

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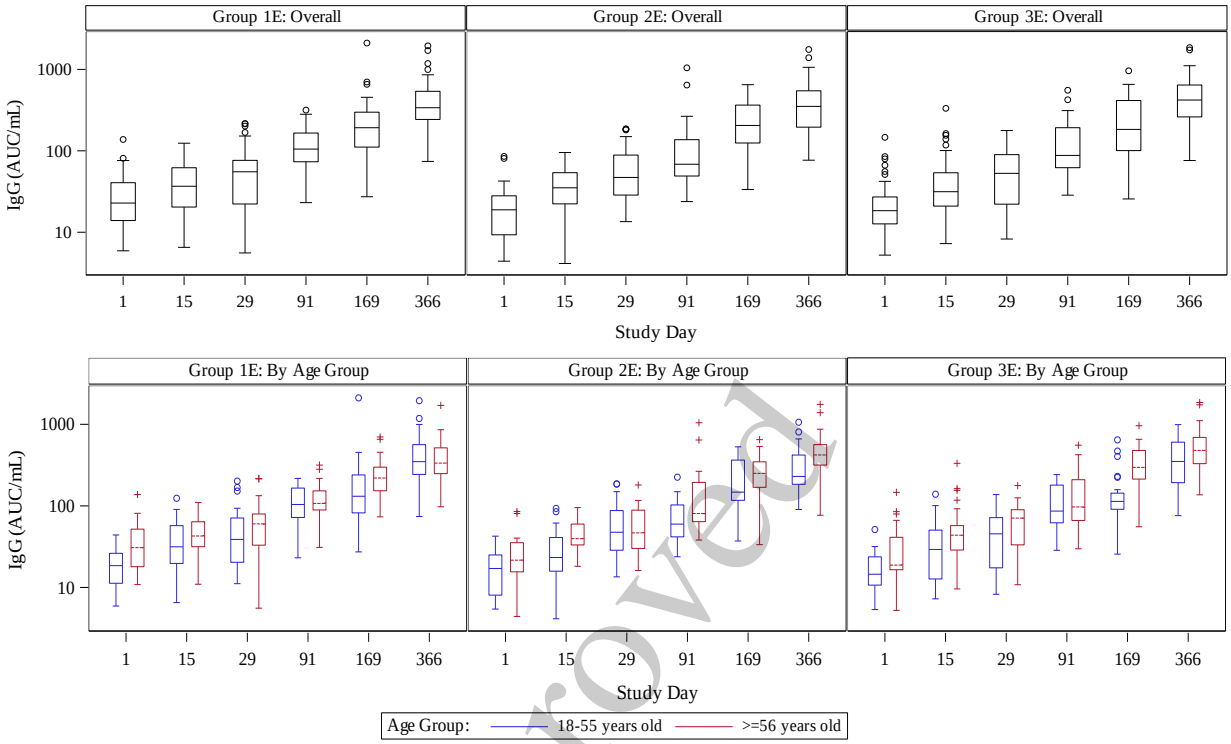
Figure X. [Endpoint description], by Group, Age Group and Timepoint – Groups 1E – 3E



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