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: 10.0

06 April 2023

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

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 1130 healthy individuals aged ≥ 18 years

Sites: Approximately 10 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 to end of planned study participation .

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.
4. To assess, in at least a subset of samples, mucosal (salivary and nasal) SARS-CoV-2 spike protein-specific IgG and IgA responses and assess correlation with serologic responses.

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 (

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

Group	Sample Size*	EUA Dosing Scheme	Interval(weeks)	Delayed Booster Vaccination	Strategy Tested
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
15E	**60**	Previously dosed +/- boosted Janssen – Ad26.COV2-S	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	Same Strain Heterologous platform
16E	**60**	Previously dosed Moderna – mRNA-1273	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	Same Strain Heterologous platform
17E	**60**	Previously dosed	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS	Same Strain Heterologous platform

Group	Sample Size*	EUA Dosing Scheme	Interval(weeks)	Delayed Booster Vaccination	Strategy Tested
		Pfizer/BioNTech –BNT162b2		50 mcg Matrix-M	

2.); and
3. 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 (

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

Group	Sample Size*	EUA Dosing Scheme	Interval(weeks)	Delayed Booster Vaccination	Strategy Tested
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
15E	**60**	Previously dosed +/- boosted Janssen – Ad26.COV2-S	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	Same Strain Heterologous platform
16E	**60**	Previously dosed Moderna – mRNA-1273	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	Same Strain Heterologous platform
17E	**60**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	Same Strain Heterologous platform

). A total of approximately 50* per group will be recruited for each group (combination of EUA primary vaccination plus booster) in Cohort 1. *Note: Due to the surge in Omicron variant cases, vaccinated individuals may be prone to asymptomatic breakthrough infections. Stage 6 (Groups 15E-17E) sample size will be expanded to N = 60/group (approximately 1:1 age strata). This study is designed to be adaptive, and as more vaccines become available either under EUA (or anticipated to have an EUA in the next few months), or new variants of available EUA vaccines 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

Group	Sample Size*	EUA Dosing Scheme	Interval(weeks)	Delayed Booster Vaccination	Strategy Tested
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
15E	60	Previously dosed +/- boosted Janssen – Ad26.COV2-S	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	Same Strain Heterologous platform
16E	60	Previously dosed Moderna – mRNA-1273	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS	Same Strain Heterologous platform

Group	Sample Size*	EUA Dosing Scheme	Interval(weeks)	Delayed Booster Vaccination	Strategy Tested
				50 mcg Matrix-M	
17E	**60**	Previously dosed Pfizer/BioNTech – BNT162b2	≥12	NVX-CoV2373 5 mcg SARS-CoV-2 rS 50 mcg Matrix-M	 Same Strain Heterologous platform

***Sample cohort size, N = approximately 50, two age strata: 18-55 years (n ≈ 25), ≥ 56 years (n ≈ 25), and N= approximately 60, two age strata (N~ 30) for Groups 15E-17E.**

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 booster vaccines have been approved for individuals at an interval of 6 months from the primary series, under EUA, all Cohort 2 volunteers will be offered a booster of mRNA-1273 at the approved 50 mcg dose. Due to the surge of the Omicron variant and breakthrough infections, volunteers who contract symptomatic or asymptomatic COVID-19 between completion of their EUA primary series and the scheduled booster dose will be allowed to continue in the study. The interval between the COVID-19 infection and booster dosing should be a minimum of 28 days. This pool of participants will then be followed to assess the immunogenicity of a 4th dose of bivalent vaccine. The Moderna mRNA-1273.222 vaccine that contains 25-mcg of the prototype strain and 25-mcg of the Omicron BA.4/BA.5 variant (total 50-mcg) will be administered as a second booster 4 to 12 months after administration of the first booster vaccine.

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	Delayed Booster Vaccination 1	Interval	Booster Vaccination 2
1	**250**	Moderna-100 mcg mRNA-1273	28 days	Moderna-100 mcg mRNA-1273	~6 months	Moderna - 50 mcg mRNA-1273	4-12 months	Moderna - 50 mcg mRNA-1273.222

*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 ~6 months after second booster 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 primary mRNA COVID-19 vaccine under EUA dosing guidelines and one or two doses of Ad26.COV2.S 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: Healthy 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 (for Cohort 1 and the primary series of Cohort 2).
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	181	273	366	Illness/ Unscheduled Visit	Early Termination Visit
Visit Number	00[a]	1	2	3	4	5	6	7	8		
Window (+/-)		0	1	2	2	7	14	28	28		
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	X
Physical Exam - Targeted	X	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	X
Nasal or NP swab for PCR & Sequencing										X[g]	
Immunoassays											
Serum- Humoral Assays		32		32	32	32	32	32	32		32
PBMC Cellular Assays & plasma		64		64			64		64		64
Daily Volume (mL)		96		96	32	32	96	32	96		96
Cumulative Volume (mL)		96		192	224	256	352	384	480		

[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 (prior to 2nd booster dose):

Study Day	D-28 to D-1	1	8[b]	29	36[b]	43	Delayed Boost to occur ≥ 181 days (window +/- 30 days) from Dose 2	1B	8B[b]	15B	29B	91B	181B	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[d]	1	2	2	7	14	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 will be the 50 mcg dose of Moderna mRNA-1273. It will be administered on study day 1B which is 181 days with a window of +28 days after the second vaccine dose . If no booster administered; safety visits will continue as per Table 6. If Covid-19 infection is detected in the interval between the primary series and the estimated time of booster administration, volunteers may remain in the study (with a minimum 28 day interval between infection and boost)

[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

Table 5: SOA for Prospective Cohort 2 (2nd booster dose)

Study Day		1C	8C[b]	15C	29C	91C	181C	Illness/Unsch Visit	Early Term Visit
Visit Number		13	14	15	16	17	18		
Window (+/-)		0	1	2	2	7	14		
Informed Consent		X							
Eligibility Criteria		X							
Vaccination		X[a]							
Concomitant Meds		X	X	X	X				
Interim History		X	X	X	X	X	X	X	X
Physical Exam - Targeted		X		X	X	X	X	X	X
Vital Signs[c]		X		X	X			X	
Saliva Mucosal Sample		X		X	X	X	X		X
Nasal Mucosal Sample		X		X	X	X	X		X
Urine β-HCG[d]	Boost to occur ≥ 120 days and ≤ 366 days from Dose 3	X							
Memory Aid, Solicited AEs		X	X	X[e]					
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[f]	
Immunoassays									
Serum- Humoral Assays		32		32	32	32	32		32
PBMC Cellular Assays & plasma		64		64			64		64
Daily Volume (mL)		96		96	32	32	96		96
Cumulative Volume (mL)		800		896	928	960	1056		

[a] Second Booster dose will be the 50 mcg dose of Moderna mRNA-1273.222. It will be administered on study day 1C which is ≥ 120 and ≤ 270 days after the third vaccine dose. If no booster administered; safety visits will continue as per Table 6.
[b] Telephone visit
[c] Vital signs before and after vaccination. Otherwise, only as clinically indicated.
[d] For women of childbearing potential, a negative urine pregnancy test on Day 1C (Second boost) will be performed with negative results confirmed prior to each dosing
[e] Review 7-day Memory Aid data for second booster dose.
[f] Collect nasal or NP swabs (x 2) for PCR. Sequencing will be performed on all Illness visit-confirmed SARS-CoV-2 specimens.

Table 6: SOA for Cohort 2 Volunteers who do not proceed to first Study Booster

Study Day	181[a]	366[a]	Early Term Visit
Visit Number	6	12	
Window (+/-)	28	28	
Informed Consent			
Eligibility Criteria			
Medical History			
Vaccination			
Concomitant Meds			
Interim History	X	X	X
Physical Exam - Targeted	X	X	X
Vital Signs			
Height/Weight (BMI)			
Urine β-HCG			
Memory Aid, Solicited AEs			
Unsolicited AEs			
SAEs, Protocol specified AESIs, MAAEs, and NOCMCs	X	X	X

[a] From the date of the last study vaccine

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 20 January 2022, it has infected over 339 million people worldwide and resulted in over 5.6 million deaths, including > 858,000 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. The Pfizer mRNA vaccine received approval on April 23, 2021, and will be marketed as Comirnaty, for the prevention of COVID-19 disease in individuals 16 years of age and older. The Moderna mRNA vaccine received approval on January 31, 2022, and will be marketed as Spikevax for the prevention of COVID-19 in individuals 18 years of age and older. 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. Novavax (NVX-CoV2373), a recombinant nanoparticle vaccine containing the full-length spike glycoprotein plus Matrix-M adjuvant, showed 86.3% and 90.4% vaccine efficacy in phase 2b-3 trials in the UK and North America (but prior to the delta and omicron surges, respectively).[5,6] . In October 2022, the U.S. has COVID-19 products from 4 different manufacturers approved or available under EUA.

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.[7] 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.[8,9] 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.[10,11] 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. Similarly, mRNA-1273.222 encodes the prefusion stabilize S protein (S-2P) of SARS-CoV-2 along with the key mutations of the Omicron BA.4/BA.5 subvariants (S-2P) in a 1:1 ratio with the wildtype (prototype) Wuhan-Hu-1 strain.

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).[12] 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.[13] 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, mucosal, 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, mRNA-1273.222, BNT162b2, Ad26.COV.2, and NVX-CoV2373, 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, mRNA-1273.222, BNT162b2, Ad26.COV2.S, and NVX-CoV2373. 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, mRNA-1273.222, BNT162b2, Ad26.COV2.S and NVX-CoV2373, 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. Collection of nasal and salivary fluids may be associated with transient discomfort due to placement of the absorptive material in the nares and mouth, respectively.

Risks of mRNA vaccines (mRNA-1273, mRNA-1273.211, mRNA-1273.222 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.[14]

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.[15] 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.[15-17] 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, mRNA-1273.222 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. Similarly, mRNA-1273.222 has not been tested extensively, but it has received EUA for use as a booster in adults.

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 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 of NVX-CoV2373

Across age strata, there were higher frequencies of solicited local and systemic treatment associated AEs among NVX-CoV2373 recipients than among placebo recipients following each vaccination. In the NVX-CoV2373 group, the frequency and intensity of solicited local and systemic AEs increased after second vaccination relative to the first vaccination, but the study vaccine remained well tolerated. Participants in the older age cohort (≥ 65 years of age) reported a lower frequency and intensity of solicited local and systemic AEs than participants in the younger age cohort (18 to ≤ 64 years of age). Across both age strata, frequencies of unsolicited AEs, severe AEs, and treatment-related AEs within 28 days after second vaccination (e.g., Day 49) were higher in the NVX-CoV2373 group than in the placebo group, but most were mild to moderate in severity. The majority of the reactogenic responses (i.e., injection site pain,

fatigue, headache, pyrexia, and myalgia) were mild in severity. The most frequent solicited systemic TEAEs following each vaccination were headache, fatigue, and muscle pain, which had a median duration of ≤ 1.5 days following first vaccination and a median duration of ≤ 2.0 days following second vaccination. Across the two age strata, participants in the older age cohort (65 to 84 years of age) reported a lower frequency and intensity of solicited local and systemic AEs than participants in the younger age cohort (18 to 64 years of age). Of the three deaths detected in the U.K. Phase 3 study, none were deemed related to study product. One SAE in the NVX-CoV2373 U.K. group had an SAE (myocarditis) that was assessed by the investigator as related to study vaccine but assessed by the Sponsor as not related to study vaccine. This event occurred in a 19-year-old male 3 days after the second dose and was also reported as a Potential Immune-Mediated Medical Conditions (PIMMC). The case was also reviewed by an independent Safety Monitoring Committee that considered the event most likely viral myocarditis. Two SAEs in the North American Phase 3 trial were assessed as related to study treatment (angioedema and central nervous system inflammation). No difference in fatal events was noted between the study and placebo groups.

The fully-analyzed human experience to date with Matrix-M adjuvants is confined to adults who have received 1- to 3-dose series of IM doses of 25 to 75 mcg. Local injection site reactogenicity comprising pain, redness, bruising, and swelling have occurred up to approximately twice as commonly following Matrix-M adjuvant-containing vaccine doses than following unadjuvanted vaccine antigen doses when a comparable antigen preparation is used. Persistent nodules, skin breakdown, or ulceration at injection sites have never been reported. Systemic reactogenicity complaints comprising headache, myalgia, arthralgia, fatigue, and chills are similarly 1.5- to 2-fold more frequent following adjuvanted doses, while nausea, diarrhea, and vomiting are only slightly increased. Notably, more than 95% of subjects reporting any solicited reactogenicity events indicate that they are mild to moderate in intensity (i.e., they do not cause major interference with daily activities) and that they are transient (i.e., resolve during the 7-days post-injection follow-up period). When multiple doses of Matrix-M-adjuvanted vaccines are given at a relatively short interval (3 to 4 weeks), the incidence rate of local and systemic reactogenicity events may increase after the second dose, although these remain predominantly mild to moderate in severity, and transient. In older adults, the difference in reactogenicity for Matrix-M-adjuvanted influenza vaccines in contrast to licensed high-dose inactivated or recombinant influenza vaccines has been minimal.

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.[17] 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. It is anticipated that the mRNA-1273.222 strain will provide protection against the currently circulating BA.4 and BA.5 strains.

3 OBJECTIVES AND ENDPOINTS

Table 7: 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 to end of planned study participation.
• 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
• To assess, in at least a subset of samples, mucosal (salivary and nasal) SARS-CoV-2 spike protein-specific IgG and IgA responses	• Magnitude and percentage of SARS-CoV-2 spike protein specific IgA and IgG and correlation with serologic antibody response

*Assays for exploratory endpoints may be performed and the data provided as described in Section 9.4, if available from the research laboratory.

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 (one or two doses for Group 15E) – Ad26.COV2.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
   Group 15E – A dose of NVX-CoV2373 (5 mcg Prototype SARS-CoV-2 rS vaccine with 50 mcg Matrix-M)*

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
   Group 16E – A dose of NVX-CoV2373 (5 mcg Prototype SARS-CoV2 rS vaccine with 50 mcg Matrix-M)*

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
   Group 17E – A dose of NVX-CoV2373 (5 mcg Prototype SARS-CoV2 rS vaccine with 50 mcg Matrix-M)*

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.

*Note – Groups 15E-17E will enroll 60 subjects, split (approximately evenly) between age strata as able. As the use of 2 doses of Ad26COV2.S without additional vaccines is relatively infrequent in the population (and 1 dose without additional vaccines is even less frequent), participants who were enrolled and remain active in Group 4E (homologous prime-boost with Ad26COV2.S) will be offered the opportunity to roll into Group 15E, if eligible.

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, 9, and 12 months after the vaccination.

Table 8: 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
15E	~60	NVX-CoV2373 (5 mcg Prototype SARS-CoV-2 rS with 50 mcg Matrix-M)
16E	~60	NVX-CoV2373 (5 mcg Prototype SARS-CoV-2 rS with 50 mcg Matrix-M)
17E	~60	NVX-CoV2373 (5 mcg Prototype SARS-CoV-2 rS with 50 mcg Matrix-M)

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 homologous and 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
- 15E - Evaluates Ad26.COV2.S EUA vaccination series (one or two doses)* followed by a heterologous platform delayed dose of NVX-CoV2373 (5 mcg SARS-COV-2)
- 16E - Evaluates mRNA-1273 EUA vaccination series followed by a heterologous platform delayed dose of NVX-CoV2373 (5 mcg SARS-COV-2)
- 17E - Evaluates BNT162b2 EUA vaccination series followed by a heterologous platform delayed dose of NVX-CoV2373 (5 mcg SARS-COV-2)

*Since the regimen of one or two doses of Ad26.COV2.S is less prevalent than other EUA dosing regimens, it will make this group harder to recruit. Therefore, Group 4E participants who have received two doses of Ad26.COV2.S will be offered the opportunity to roll into Group 15E. Newly recruited volunteers who have received a single dose of Ad26.COV2.S will also be recruited. Subset analysis will be performed on the one and the two dose arms. Data is needed as to the best means of boosting this under-evaluated regimen.

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 9. Additional pools of subjects can be included if needed as additional COVID-19 vaccines are awarded EUA. These pools of participants were to 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. As booster vaccines have been approved for individuals at an interval of 6 months from the primary series, under EUA, all Cohort 2 volunteers will be offered a booster of mRNA-1273 at the approved 50 mcg dose at Day 181 (+/- 30 days following dose 2 of their primary series. 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. A fourth dose of COVID-19 vaccine will be administered to participants using the Moderna mRNA-1273.222 bivalent vaccine at an interval of 4 to 12 months after the third dose (1st booster). In addition to the other immunologic assays planned for earlier parts of the study (including innate, cellular and humoral responses), samples also will be collected to measure mucosal immune responses before the booster dose and on days 14 and 28, and at 3 months and 6 months after the fourth dose (2nd booster). Due to the surge of the Omicron variant and breakthrough infections, volunteers who contract symptomatic or asymptomatic COVID-19 between completion of their EUA primary series and the scheduled booster dose will be allowed to continue in the study. The interval between the COVID-19 infection and booster dosing should be a minimum of 28 days.

Table 9: Cohort 2 Treatment Arms

Group	Sample Size	First Vaccination	Second Vaccination		Booster Vaccination 1		Booster Vaccination 2	
		Product and Dose	Inter-val	Product and Dose	Inter-val	Product and Dose	Inter-val	Product and Dose
1	250	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273	~6 months	50 mcg mRNA-1273	4-12 months	50 mcg mRNA-1273.222

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).[18,19] 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.[20] 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 mRNA-1273.222 vaccine has received EUA to be used as a booster vaccine in adults in the US beginning in September 2022.

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.[16] 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.[17] 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.

Although current vaccines provide high levels of protection against severe illness and death, the increased transmission of the Delta variant resulted in increasing numbers of contagious breakthrough infections in fully vaccinated individuals.[21-23] This coincided with evidence of waning of immunity in some vaccinated populations.[22-24] Based upon a full review of risks, benefits, and immunogenicity of booster vaccines, the VRBPAC advisory group to the FDA (14 October 2021), affirmed by the ACIP (21 October 2021), recommended booster vaccines for BNT162b2 and mRNA-1273 (the latter at a reduced dose of 50 mcg),[25-27] 6 months after completion of the primary series in those aged ≥65 years or in those vulnerable populations considered at risk for Covid-19 acquisition. Furthermore, heterologous booster vaccines were deemed permissible.

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.[28] Both formulations administered as a single dose had favorable safety and immunogenicity profiles,[29] 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.[28] As with the mRNA vaccines, upon review of risks, benefits, and immunogenicity of a second dose of Ad26.COV2.S,[30] the VRBPAC advisory group to the FDA (15 October 2021), affirmed by the ACIP (21 October 2021), recommended a homologous booster vaccine or a heterologous booster vaccine for Ad26.COV2.S, 2 months after completion of the primary vaccine in those aged 18 years or greater.

Novavax received EUA from the FDA for use as a two-dose priming vaccine in persons 18 and older in July 2022 and for 12-17 year olds the following month (August 2022). On October 19, 2022 the FDA authorized EUA use of Novavax first booster dose in persons 18 years and older 6 months after completion of primary vaccination. Phase 1 (Part 1) of the SARS-CoV-2 rS product with or without Matrix-M adjuvant was conducted in Australia (2019nCoV-101) in adults aged 19-59 inclusive and determined the safety and immunogenicity of the 5 μg vs. 25 μg dose of the SARS-CoV-2 rS recombinant protein with or without 50 μg of Matrix-M. The adjuvant clearly enhanced anti-Spike IgG, anti-ACE2 inhibition and neutralizing antibody and the 5 μg dose of protein was non-inferior to the 25 μg dose of SARS-CoV-2 rS in all assays. Additionally, the study established that a two-dose arm was superior to a one dose design (at an interval of 21 days).[31] The 2019nCoV-101 (Part 2) examined the vaccine constructs in persons up to age 84 years as a one-dose, two-dose or two-dose with a 6-month booster dose (three dose). Data analysis for the booster dosing has not been performed. It was found to be safe, well-tolerated and immunogenic in younger and older individuals with similar trends as to Part 1 of the study. Based upon these data, the Phase 3 trials of NVX-CoV2373 examined the safety, immunogenicity and efficacy of the vaccine with 5 μg of SARS-CoV-2 rS adjuvanted with 50 μg of Matrix-M.[5,6]

5 STUDY POPULATION

Two cohorts will be enrolled. For Cohort 1, approximately 880 individuals (50 subjects/group; Groups 1E-14E, and 60 subjects/group; Groups 15E-17E) 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.

5.5.1 Strategies for Recruitment and Retention

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.

5.5.2 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.

5.5.3 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.

5.5.4 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, mRNA-1273.211, and mRNA-1273.222

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.

mRNA-1273.222 (0.1 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 Omicron BA.4/BA.5 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.

Product: NVX-CoV2373

SARS-CoV-2 rS Drug Substance containing the prototype Wuhan is formulated with saponin-based Matrix-M adjuvant in a buffer of 25 mM sodium phosphate (pH 7.2), 300 mM sodium chloride, and 0.01% (weight per volume [w/v]) polysorbate 80. Quantities of the Drug Substance strain(s) and the Matrix-M adjuvant are added to buffer, and then additional buffer is added to obtain the desired protein concentration. The DP (drug product) solution is filtered and aseptically filled into the United States Pharmacopeia (USP) type-I glass vials, stoppered, and sealed to produce SARS-CoV-2 rS Drug Product.

The product will be available in a co-formulated single or multi-dose vial for this study. The IP consists of 10 mcg/mL SARS-CoV-2 rS vaccine adjuvanted with 100 mcg/mL Matrix-M.

6.1.2 Dosing and Administration

Product: mRNA-1273, mRNA-1273.211, and mRNA-1273.222

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).

mRNA-1273.222 (0.1 mg/mL) will be administered in 0.5 mL doses (50 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).

Product: NVX-CoV2373

NVX-Co-V2373 will be administered in 0.5 mL dose (5 mcg Prototype SARS-CoV-2 rS with 50 mcg Matrix-M adjuvant).

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 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). As of 21 October 2021, this dose was also recommended and approved under EUA as the booster mRNA-1273 dose offered.

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, mRNA-1273.211, and mRNA-1273.222

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.

mRNA-1273.222 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.

Product: NVX-CoV2373

Prototype SARS-CoV-2 rS is a liquid solution formulated in 25 mM phosphate buffer (pH 7.2), 300 mM sodium chloride, and 0.01% (w/v) polysorbate 80, and diluted with the same to specified concentrations co-formulated with Matrix-M adjuvant that also contains phosphate-buffered saline. The SARS-CoV-2 rS vaccine with Matrix-M adjuvant will be supplied in single-dose or multi-dose glass vials with latex-free stoppers; volume of fill to be specified in the study MOP

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.

mRNA-1273.222 vials are stored frozen between -90°C to -60°C (-130°F to -76°F). Once a vial is fully thawed at room temperature for 20-30 min, it must be used within 24 hours. After drawing a dose into a dosing syringe, the syringe may be stored at room temperature for up to 8 hours, as long as the thawed vial expiry (24 hours from thaw) is not exceeded.

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.

Product: NVX-CoV2373

Prototype SARS-CoV-2 rS with Matrix-M adjuvant should be stored at 2 C to 8 C.

DO NOT FREEZE.

Once a product vial has been punctured, all preformulated vaccine with Matrix-M adjuvant from the punctured vial should be administered within 6 hours.

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 through 28 days after each study vaccination and COVID-19 vaccines received outside of the study at any time during study participation. 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:

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

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

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

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.

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, 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 study vaccination. See **Table 5** for a schedule of evaluations in the 12 months after the last study 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 (prior to Dose 2).
- Receipt of SARS-CoV-2 vaccine outside of study
- 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 10, Table 11, and Table 12.

Mucosal Antibody Assays:

Salivary and nasal mucosal samples collected from cohort 2 study participants will be evaluated for total and virus-specific IgG and IgA immune responses using MSD assay. Mucosal antibody

presence and magnitude will be correlated with serologic results. Preparation of the salivary and nasal samples and shipping instructions for immunogenicity assays are outlined in the protocol-specific MOP.

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. If a volunteer is asymptomatic but tests positive for COVID-19, the site may follow-up with a study visit on an optional basis, as staff availability and resources allow. 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 Cohort 2.

Table 10: Venipuncture Volumes for Cohort 1 (One Vaccination – EUA Dosed Cohort)

Study Day	-28 to -1	1	8	15	29	91	181	273	366	Early Termination Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	2	7	14	28	28		
Study Visit	Screening (optional) 00	01	02	03	04	05	06	07	08		
Vaccination		X									
Serum for Serological Immunogenicity Assays[1]		16		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	16[2]	96
Per Visit Blood Volume Total (mL)		96		96	32	32	96	32	96	96[2]	448
Cumulative Blood Volume (mL) (prior 56 days)		96	96	192	224	32	96	32	96		
Running Blood Volume Total (mL)		96	96	192	224	256	352	384	480		

[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 11: Venipuncture Volumes for Cohort 2: (Up to Three Vaccinations)

Study Day	-28 to -1	1	8	29	36	43	Delayed Boost to occur ≥ Day 181 (window +/- 30 days) from Dose 1	1B	8B	15B	29B	91B	181B	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	14	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				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.

Table 12: Venipuncture Volumes for Cohort 2: (Fourth Vaccination)

Study Day	Boost to occur ≥ 120 days ≤ 366 days from Dose 3	1C	8C	15C	29C	91C	181C	Illness/ Unscheduled Visit	Early Termination Visit
Visit Number		13	14	15	16	17	18		
Window (+/-)		0[1]	1[2]	2[2]	2[2]	7[2]	14[2]		
Immunoassays									
Serum- Humoral Assays		32		32	32	32	32		32[3]
PBMC Cellular Assays & plasma		64		64			64		64[3]
Daily Volume (mL)		96		96	32	32	96		96[3]
Cumulative Volume (mL)		96		192	224	256	352		
Running Blood Volume Total (mL) [4]		800		896	928	960	1056		

[1] Visits 13 windows should be based off the actual Visit 06 date.

[2] Visits 14-18 windows should be based off the actual Visit 13 date.

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

[4]Running blood volume continues after visit 11 for those receiving a 2nd booster in cohort 2 (will occur prior to originally planned visit 12). For subjects who are boosted after visit 10, the running blood volume will be 96 mL less.

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 8.3.4). 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 planned study participation, 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 planned study participation, only SAEs, AESIs, MAAEs, and NOCMCs (as detailed in Section 8.3.9) 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 Dose 1 to end of planned study participation.

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.

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
- 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 and must be submitted immediately (within 24 hours of site awareness) 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 planned study participation.
- 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 13. 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 13.

Due to the surge in Omicron variant cases at the time of the writing of Version 6.0, it is anticipated that a non-negligible proportion of vaccinated individuals may be prone to asymptomatic breakthrough infections. To allow for potential larger numbers of participants enrolled in Stage 6 (Groups 15E-17E) that would subsequently be found to have serological evidence of prior infection, the sample size will be expanded to N = 60/group (approximately 1:1 age strata) for these groups.

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 13: 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 14 displays two-sided 95% confidence intervals for the GMT for several values of the observed antibody titer. Table 14 also shows results assuming up to 10% attrition.

Table 14: 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. The final CSR will be completed when all primary and secondary safety, clinical, and immunological endpoint data are available. Available data from the exploratory endpoints at the time of compilation of the final CSR may also be included. Other remaining exploratory 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 to end of planned study participation. 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. At the time of the writing of Version 8.0 of the protocol there are no scheduled mandatory reviews by the SMC after participants in Cohort 2 receive the prime, first boost or second boost vaccinations. This is due to the safety database known for EUA vaccines and vaccinations being administered in accordance to CDC guidelines. SMC reviews for Cohort 2 will occur if halting rules are triggered, or as requested by the sponsor or PI.

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. For group 15E, which will enroll participants with one or two prior doses of Janssen, a subgroup analysis by this baseline characteristic may also 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.

Summaries of mucosal immune responses, from nasal and salivary samples of participants in Cohort 2 who receive a second boost, will be summarized at each timepoint post-boost. Also, the correlation between the mucosal and the serological immune responses will be evaluated at each timepoint post-boost. The possibility of conducting these analysis by status of prior infection (as given by N-protein ELISA assay) will be assessed.

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, and mucosal samples 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. At the time of writing of Version 8.0 of the protocol, there is no additional scheduled mandatory review by the SMC for Cohort 2, unless halting rules are triggered. 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 15: 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)
MSD	MesoScale Discovery
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
PIMMC	Potential Immune-Mediated Medical Conditions
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
VRBPAC	Vaccine and Related Biological Product Advisory Committee
WBC	White Blood Cell
WHO	World Health Organization
WIV1	Chinese Horseshoe Bat Coronavirus WIV1

10.4 Protocol Amendment History

Table 16: 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

Version 5.0 of the protocol was amended 10 November 2021

Version 6.0 of the protocol was amended 09 February 2022

Version 7.0 of the protocol was amended 04 April 2022

Version 8.0 of the protocol was amended 29 September 2022

Version 9.0 of the protocol was amended 26 October 2022

Version 10.0 of the protocol was amended 06 April 2023

11 REFERENCES

1. WHO. World Health Organization, Weekly Operational Update on COVID-19. 2020a. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed on 20 January 2022.

2. JHU. COVID-19 Dashboard, Center for Systems Science and Engineering (CCSE) at Johns Hopkins University (JHU). https://coronavirus.jhu.edu/map.html. Accessed January 20, 2022. 2021.

3. Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature 2020;586:567-71.

4. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. npj Vaccines 2020;5:91.

5. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med 2021;385:1172-83.

6. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med 2021.

7. Tegally H, Wilkinson E, Giovanetti M, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. medRxiv 2020:2020.12.21.20248640.

8. Callaway E, Mallapaty S. Novavax offers first evidence that COVID vaccines protect people against variants. Nature 2021;590:17.

9. Cohen J. One-dose COVID-19 vaccine offers solid protection against severe disease. Science 2021.

10. Wang P, Nair MS, Liu L, et al. Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization. bioRxiv 2021.

11. Wu K, Werner AP, Moliva JI, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv 2021.

12. Spencer AJ, McKay PF, Belij-Rammerstorfer S, et al. Heterologous vaccination regimens with self-amplifying RNA and Adenoviral COVID vaccines induce robust immune responses in mice. bioRxiv 2021:2021.01.28.428665.

13. Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet 2020;396:887-97.

14. Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations--a post-marketing surveillance review. Eur J Pediatr 2002;161:21-5.

15. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-16.

16. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 2020;383:2439-50.

17. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383:2603-15.

18. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020;383:1920-31.

19. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med 2020;383:2427-38.

20. Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine 2021.

21. Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep 2021;70:1059-62.

22. Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep 2021;70.

23. Nanduri S, Pilishvili T, Derado G, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morb Mortal Wkly Rep 2021;70.

24. Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1167-9.

25. Falsey AR, Frenck RW, Jr., Walsh EE, et al. SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3. N Engl J Med 2021.

26. Chu L, Montefiori D, Huang W, et al. Immune Memory Response After a Booster Injection of mRNA-1273 for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). medRxiv 2021.

27. Choi A, Koch M, Wu K, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med 2021.

28. Janssen Biotech I. FDA Briefing Document - Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19 Vaccines and Related Biological Products Advisory Committee MeetingFebruary 26, 2021

29. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021.

30. Sadoff J, Le Gars M, Cardenas V, et al. Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late boosting. MedRxiv 2021.

31. Keech C, Albert G, Cho I, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. N Engl J Med 2020;383:2320-32.

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: Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days 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 > 3-fold elevation above the upper normal limit for ALT or AST OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
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: Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Peripheral facial nerve palsy (Bell's palsy) Transverse myelitis Encephalitis/Encephalomyelitis Aseptic meningitis Febrile seizures Generalized seizures/convulsions Stroke (Hemorrhagic and non-hemorrhagic) 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