A Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a Quadrivalent Hemagglutinin Nanoparticle Influenza and SARS-CoV-2 rS Nanoparticle Combination Vaccine with Matrix-M1™ Adjuvant in Healthy Participants ≥ 50 to ≤ 70 Years of Age

Phase 1/2 Study of the Safety and Immunogenicity of Influenza and COVID-19 Combination Vaccine

Investigational Products	• Quadrivalent Hemagglutinin Nanoparticle Influenza Vaccine (qNIV) (containing the World Health Organization recommended strains for the 2019 - 2020 northern hemisphere influenza season, ie, A/Brisbane/02/2018 [H1N1] pdm09; A/Kansas/14/2017 [H3N2]; B/Maryland/15/2016; B/Phuket/3073/2013) with Matrix-M1™ adjuvant • SARS-CoV-2 rS Nanoparticle Vaccine with Matrix-M1 Adjuvant • qNIV and SARS-CoV-2 rS Nanoparticle Vaccine with Matrix-M1 Adjuvant
Protocol Number	2019nCoV-ICC-E-101
Clinical Trial Registry Identifiers	NCT04961541
Version Number	4.0
Version Date	06 May 2022
Amendment	2
IND Number	TBD
Sponsor	Novavax, Inc 21 Firstfield Road Gaithersburg, MD 20878 United States [redacted]

Confidentiality Statement

The information in this document is considered privileged and confidential by Novavax, Inc. and may not be disclosed to others except to the extent necessary to obtain Independent Ethics Committee (HREC) approval and informed consent, or as required by national and local laws. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonisation (ICH) E6, and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2019nCoV-ICC-E-101 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and GCP as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each participant's participation and all data required by the protocol

Name	**Title**	**Institution**

Signature	**Date**

SPONSOR'S APPROVAL

Title	A Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a Quadrivalent Hemagglutinin Nanoparticle Influenza and SARS-CoV-2 rS Nanoparticle Combination Vaccine with Matrix-M1™ Adjuvant in Healthy Participants ≥ 50 to ≤ 70 years of Age
Protocol Number	2019nCoV-ICC-E-101
Version Number	4.0
Version Date	06 May 2022
Amendment	3

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Medical Representative		
Name:	**Title:**	**Signature/Date**
[redacted]	VP, Clinical Development	[redacted]
Clinical Operations Representative		
Name:	**Title:**	**Signature/Date**
[redacted]	Associate Director, Clinical Operations	[redacted]

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 4.0/Amendment 3, dated 06 May 2022) relative to the prior approved version (Version 3.0/Amendment 2, dated 07 October 2021) are summarized in the table below. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
Sponsor's Approval	Updated signatory from [redacted] to [redacted]	Update to study personnel.
6 (Study Conduct)	Removed blood sampling for anti-NP antibodies on Day 84	Updated for consistency.
8 (Safety Monitoring)	Updated text to indicate unsolicited AEs of any severity are collected through Day 70 (ie, until 14 days after the second vaccination)	Updated for consistency.
7.2.1 (Treatment Allocation)	Updated text to indicate that approximately 50% of all participants, not 5%, will be allocated to the CMI subset population for the analysis of CMI endpoints.	Updated error.
7.2.2 (Randomization Strategy and Procedure)	Updated text to indicate that randomization was stratified by age group.	Updated for consistency.

Abbreviations: AE = adverse event; NP = Nucleocapsid protein.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
24/7	24 hours 7 days a week
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CI	Confidence interval
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease 2019
DAIDS	Division of AIDS, NIAID, NIH
DoE	Design of Experiments
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic participant-reported outcome diary application
ELISA	Enzyme-linked immunosorbent assay
EoS	End of study
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMEU	Geometric mean ELISA Unit
GMEUR	Geometric mean ELISA unit ratio (between groups)
GMFR	Geometric mean fold rise (within group)
GMT	Geometric mean titer
GMTR	Geometric mean titer ratio (between groups)
GP	Glycoprotein(s)
HA	Hemagglutinin
hACE2	Human angiotensin-converting enzyme 2
HAI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
HREC	Independent Ethics Committee
IB	Investigator's brochure
ICC	Influenza COVID-19 combination
ICCS	Intracellular cytokine staining
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IM	Intramuscular
IRB	Institutional Review Board

Abbreviation	Definition
IWRS	Interactive Web Response System
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHC	Major histocompatibility complex
MN	Microneutralization (assay)
MN_{50}	Microneutralization assay with an inhibitory concentration of 50%
mRNA	Messenger ribonucleic acid
NP	Nucleocapsid protein
NI	Non-inferiority
NIAID	National Institutes of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIV	Nanoparticle influenza vaccine
NVX-CoV2373	SARS-CoV-2 rS with Matrix-M1 adjuvant
NZW	New Zealand White
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
PVSS	Pharmacovigilance and Safety Services
qNIV	Quadrivalent hemagglutinin nanoparticle influenza vaccine
r	Recombinant
RBD	Receptor binding domain
RSV F	Respiratory syncytial virus fusion
rS	recombinant spike (protein)
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	Severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine
SCR	Seroconversion rate
SOC	System organ class
SOE	Schedule of Events
SOP	Standard operating procedure
SPR	Seroprotection rate
TEAE	Treatment-emergent adverse event
Th1	Type 1 T helper

Abbreviation	Definition
Th2	Type 2 T helper
US	United States
VE	Vaccine efficacy
VLP	Virus-like particle
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 SYNOPSIS

Title	A Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a Quadrivalent Hemagglutinin Nanoparticle Influenza and SARS-CoV-2 rS Nanoparticle Combination Vaccine with Matrix-M1™ Adjuvant in Healthy Participants ≥ 50 to ≤ 70 years of Age
Short Title	Phase 1/2 Study of the Safety and Immunogenicity of Influenza and COVID-19 Combination Vaccine
Phase	1/2
Study Design	This is a randomized, observer-blinded, Phase 1/2 study evaluating the safety and immunogenicity of a quadrivalent hemagglutinin (HA) nanoparticle influenza vaccine (qNIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant spike (rS) nanoparticle combination vaccine with Matrix-M1™ adjuvant; this combination vaccine is referred to as Influenza COVID-19 Combination (ICC) vaccine. The study will enroll approximately 640 healthy (based on history and physical examination) adult male and female participants 50 to 70 years of age, inclusive, targeting participants who are baseline seropositive (either previously infected with SARS-CoV-2 ≥ 8 weeks prior to enrollment, or have been previously immunized against SARS-CoV-2 with a completed regimen of an authorized vaccine at ≥ 8 weeks prior to enrollment).Randomization will be stratified on age ≥ 50 to <60 or ≥ 60 to ≤ 70 years to distribute the proportions of each age stratum evenly across vaccine groups. Participants will be simultaneously enrolled and randomly assigned equally into 1 of 16 vaccine groups as per the Study Deign Table below. The doses of the influenza and SARS-CoV-2 rS components included in the various vaccine groups have been selected based on the known performance of the antigens separately and the ability to obtain response data over a broad range of mixtures. These data will in turn be used in statistical modeling to predict one, or a few, optimal formulations for further clinical testing. All participants in Vaccine groups A through P will receive 2 intramuscular (IM) doses of the investigational combination vaccine, the first on Day 0 and the second on Day 56 (+ 5 days) and remain on study for immunogenicity and safety data collection through Day 182 (End of Study [EoS]); participants in Vaccine Group O will receive an additional IM dose of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant on Day 70 to ensure this group receives 2 doses of COVID-19 vaccine. The key informative immunogenicity time points for antibody responses will be Days 0 and 70 (14 days post-second dose), and for cell-mediated immunity (CMI) will be Days 0 and 63 (7 days post-second dose). Reference formulations of 60 µg HA/strain qNIV with 75 µg Matrix-M1 adjuvant and 5µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant will be included as vaccine groups to benchmark optimal immune responses to each antigen administered as a standalone vaccine. The study will enable selection of one or more optimized ICC vaccine formulations (through Design of Experiments [DoE] response surface modeling) to advance into further development for dose/formulation confirmation in a future Phase 2 study.
Rationale	Novavax is developing a novel recombinant qNIV with Matrix-M1 adjuvant for the prevention of disease due to influenza virus in adults ≥ 65 years of age, using a recombinant baculovirus and insect cell vaccine platform technology. With a flexible nanoparticle structure in which multiple antigen surfaces are exposed, recombinant wild-type sequenced HAs, and use of a saponin-based adjuvant, Matrix-M1, qNIV can be expected to offer several important advantages over existing licensed egg-derived seasonal influenza vaccines. These include avoidance

	of antigenic mismatch due to egg-adaptive mutations; induction of both broadly cross-reactive antibody responses against emerging drift variants of seasonal influenza viruses and potent cross-reactive polyfunctional CD4+ T cells. In a recent Phase 3 study (qNIV-E-301; NCT04120194), qNIV with Matrix-M1 adjuvant demonstrated an acceptable safety profile, immunologic non-inferiority (NI) to quadrivalent inactivated influenza vaccine (IIV4) based on egg-based hemagglutination inhibition (HAI) antibody responses against 4 vaccine-homologous strains, and 34% to 46% higher wild-type HAI antibody responses against 6 heterologous A(H3N2) strains. Additionally, qNIV with Matrix-M1 adjuvant showed a 126% to 189% improvement in various post-vaccination antigen-specific CD4+ T-cell markers compared to that for IIV4. In response to the coronavirus disease 2019 (COVID-19) pandemic caused by the emergence of SARS-CoV-2, Novavax is also developing SARS-CoV-2 rS with MAtrix-M1 adjuvant for the prevention of COVID-19 in adults ≥ 18 years of age, using the same recombinant baculovirus and insect cell vaccine platform technology employed to produce qNIV. Both nonclinical and clinical data to date support continued clinical development of SARS-CoV-2 rS with Matrix-M1 adjuvant. In an ongoing Phase 1/2 study involving healthy adults in the United States (US) and Australia (2019nCoV-101; NCT04368988), 5 µg and 25 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant demonstrated an acceptable safety profile and was associated with strong neutralizing-antibody and Type 1 T helper (Th1)-based antigen-specific polyfunctional CD4+ T-cell responses in participants 18 to 84 years of age. In an ongoing 15,000-person Phase 3 efficacy study in healthy and medically stable adult participants 18 to 84 years of age in the United Kingdom (UK) (2019nCoV-302; NCT04583995), the overall efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was 89.7% (95% confidence interval [CI]: 80.2, 94.6) and, in post hoc analyses, efficacy estimates for the B.1.1.7 (Alpha) variant and for the original strain were 86.3% and 96.4%, respectively. In an ongoing 4,400-person Phase 2b efficacy study in healthy human immunodeficiency virus (HIV)-negative adult participants 18 to 84 years of age and medically stable HIV-positive adult participants 18 to 64 years of age in South Africa (2019nCoV-501; NCT04533399) conducted during a period of > 94% B.1.351 (Beta) variant virus circulation, the efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant in all study participants was 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) in participants who were HIV-negative. In an ongoing 30,000-person Phase 3 efficacy study in healthy and medically stable adult participants ≥ 18 years of age in the US, Mexico, and Puerto Rico (2019nCoV-301; NCT04611802), the overall efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was 90.4% (95% CI: 82.9, 94.6) against symptomatic COVID-19 and 100% (95% CI: 87.0, 100) against moderate or severe COVID-19. Across all clinical studies conducted to date, SARS-CoV-2 rS with Matrix-M1 adjuvant has continued to demonstrate good tolerability and an acceptable safety profile. Given the ongoing emergence of antigenic variants of SARS-CoV-2, some of which appear to partially or completely escape naturally acquired or vaccine-derived immunity to ancestral virus, it appears increasingly likely that SARS-CoV-2 will continue to circulate for the foreseeable future, potentially in a seasonally recurrent pattern consistent with other seasonal human coronaviruses. In the setting of potential future seasonal circulation of SARS-CoV-2, the continued emergence of antigenic drift variants, and the possible waning of neutralizing antibody responses in 6 to 12 months following SARS-CoV-2 vaccination or infection, an annual booster dose of a SARS-CoV-2 vaccine, potentially with periodic strain updates, may be needed to confer ongoing protection against COVID-19 due to infection with circulating SARS-CoV-2 viruses.

	The first full year of the COVID-19 global pandemic has witnessed little to no global circulation of other seasonally important viral respiratory pathogens such as influenza – likely due to unprecedented nature of non-pharmaceutical interventions and public health measures implemented globally to control the spread of SARS-CoV-2. Notwithstanding, we are likely to observe a rebound and return of seasonal circulation of influenza viruses in the upcoming Northern and Southern Hemisphere winters with continued easing of pandemic restrictions and a gradual return pre-pandemic life. In anticipation of a future need to immunize against both SARS-CoV-2 and influenza virus in advance of the winter transmission season, Novavax is undertaking development of an ICC (ie, qNIV and SARS-CoV-2 rS with Matrix-M1 adjuvant). ICC vaccines, adjuvanted with Matrix-M1, have been studied in ferrets and hamsters. In ferrets, HAI antibody responses to all 4 HAs a showed minimal dose response and no negative effect of co-administration with SARS-CoV-2 rS and Matrix-M1 adjuvant and human angiotensin-converting enzyme 2 (hACE2) binding inhibition antibody responses to rS were slightly lower, but not significantly different, in the combined vaccine group relative to the monovalent SARS-CoV-2 rS with Matrix-M1 adjuvant recipients. In hamsters, for each influenza strain examined, HAI titers and virus neutralization titers showed no clear dose-response and were comparable with or without SARS-CoV-2 rS with Matrix-M1 adjuvant co-administration, anti-rS immunoglobulin G (IgG) levels induced by SARS-CoV-2 rS with Matrix-M1 adjuvant showed no significant impact of influenza vaccine co-administration, and hACE2 binding inhibiting antibodies were slightly, albeit not significantly, lower in animals receiving the combined vaccines. Thus, co-administration with qNIV had no detectable effect on the potent protective efficacy of the SARS-CoV-2 rS with Matrix-M1 adjuvant. An ICC vaccine would address 2 major vaccine-preventable diseases with a single vaccination approach. The initial target population for ICC vaccine development is older adults because this population bears a disproportionate burden of morbidity and mortality due to both influenza and COVID-19. The purpose of this Phase 1/2 study is to evaluate the safety and immunogenicity of multiple formulations of ICC vaccines in older adults. The main objective of the study is to identify one or more optimal dose levels of HA and rS antigens administered as a combination vaccine, which minimize both antigen doses and manage any immunologic interference, using a DoE modeling approach.
Target Population	Adult participants ≥ 50 to ≤ 70 years of age who are baseline seropositive to SARS-CoV-2 defined as either: • Having completed a primary vaccination series against SARS-CoV-2 with an authorized COVID-19 vaccine with receipt of second/final dose of authorized vaccine ≥ 8 weeks prior to enrollment (first study vaccination). OR • Previously infected with SARS-CoV-2 ≥ 8 weeks prior to enrollment (first study vaccination). Baseline SARS-CoV-2 seropositivity determination at screening will be based on vaccination documentation (eg, vaccination cards or vaccination registry) or participant report of a previous SARS-CoV-2 infection.

Number of Participants and Dosing Regimens

Total: Approximately 640 participants
Per treatment:

Study Design Table[1]

Vaccine Group	N[2]	Day 0			Day 56 (+ 5 days)		
		HA Dose per Strain, µg	rS, µg	Matrix-M1, µg	HA Dose per Strain, µg	rS, µg	Matrix-M1, µg
ICC vaccine formulations							
A	40	60	22.5	50	60	22.5	50
B	40	10	2.5	50	10	2.5	50
C	40	60	22.5	50	60	22.5	50
D	40	10	7.5	50	10	7.5	50
E	40	10	22.5	50	10	22.5	50
F	40	35	7.5	50	35	7.5	50
G	40	5	22.5	50	5	22.5	50
H	40	60	2.5	50	60	2.5	50
I	40	5	7.5	50	5	7.5	50
J	40	5	2.5	50	5	2.5	50
K	40	35	22.5	50	35	22.5	50
L	40	35	2.5	50	35	2.5	50
M	40	60	7.5	50	60	7.5	50
N	40	60	2.5	50	60	2.5	50
qNIV with Matrix-M1 adjuvant reference formulation							
O[3]	40	60	0	75	0	5	50
SARS-CoV-2 rS with Matrix-M1 adjuvant reference							
P	40	0	5	50	0	5	50
Total	640						

Abbreviations: COVID-19 = coronavirus disease 2019; HA = hemagglutinin; rS = recombinant spike protein; qNIV = quadrivalent hemagglutinin nanoparticle influenza vaccine; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Antigen and adjuvant dose values are nominal and reflect target doses. Details of the final product in-clinic mixing scheme, the actual content of doses achieved by the in-clinic mixing of drug product lots, and injected volumes used are provided in the Study Pharmacy Manual.
2. Due to uncertainties in the pace of national SARS-CoV-2 vaccine deployment and evolving COVID-19 epidemic conditions, it is acknowledged that the targeted sample size for the study may be revised in response to the impact these evolving conditions may have on enrollment.
3. Participants from treatment Vaccine Group O will receive an additional dose of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 at Day 70.

Length of Participation

On study (including screening and follow-up): 182 Days with vaccine administrations on Days 0 and 56 (and Day 70 for participants in Vaccine Group O).

Interventions	Each participant will receive 2 injections, the first dose on Day 0 and the second dose on Day 56 in the same deltoid (except for participants in Vaccine Group O who will receive a third injection at Day 70). Treatments will comprise 1 of 16 regimens of investigational vaccines delivering either: • One of 14 formulations of an ICC vaccine (comprising 12 unique formulations and 2 pairs of duplicate formulations) containing 1 of 4 dose levels of influenza HA protein (5, 10, 35, or 60 µg) and 1 of 3 dose levels of SARS-CoV-2 rS protein (2.5, 7.5, or 22.5 µg) with Matrix-M1 adjuvant (50 µg); in a two-dose regimen (Vaccine Groups A-N); OR • A reference formulation of SARS-CoV-2 rS (5 µg) nanoparticle vaccine with Matrix-M1 adjuvant (50 µg), in a two-dose regimen (Vaccine Group P); OR • A reference formulation of qNIV (60 µg HA per strain) vaccine with Matrix-M1 adjuvant (75 µg), followed by a reference formulation of SARS-CoV-2 rS (5 µg) nanoparticle vaccine with Matrix-M1 adjuvant, in a two-dose regimen, (Vaccine Group O). The antigens and adjuvant dose values in the Study Design Table are nominal and reflect target doses. The qNIV antigen, SARS-CoV-2 rS antigen, and Matrix-M1 adjuvant will each be available in separate drug product vials and will be mixed in the clinic prior to administration to achieve the target doses of ICC, qNIV with Matrix-M1 adjuvant, or SARS-CoV-2 rS with Matrix-M1 adjuvant (actual doses will be within ± 10% to 20% of intended target doses). Details of the final product mixing schemes to be implemented by the site pharmacist or designee, the actual content of doses achieved by the in-clinic mixing of drug product lots, and injected volumes used are provided in the Pharmacy Manual. For all doses of test article, the assigned vaccine will be administered by IM injection in an approximate total volume of 0.3 to 1.0 mL.
Primary Objective and Primary Endpoints	Hypothesis: ICC investigational vaccines will have comparable safety and tolerability profiles to those of the reference formulations. Objective: • To describe the tolerability and safety profiles associated with the receipt of the multiple vaccine formulations/regimens included in the study. Safety profiles will include: – Solicited adverse events (AEs) over 7 days after each of the first and second doses (including immediate AEs in the 30 minutes after dosing), to encompass both local injection site symptoms/signs and systemic symptoms/signs. – Unsolicited AEs over 70 days after the first dose. – Medically attended adverse events (MAAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) (including potential immune-mediated medical conditions [PIMMCs]) over 6 months (approximately 182 days) after first dose. Endpoints: • Numbers and percentages (with 95% CIs) of participants with solicited local and systemic AEs over the 7 days post-injection after first and second doses. • Proportions of participants reporting all AEs, solicited and unsolicited, over 70 days after the first dose. • Proportions of participants with MAAEs, AESIs (including PIMMCs), SAEs, will be collected for 6 months (approximately 180 days) after the first dose.

Secondary Objectives and Corresponding Endpoints	Objective: • To describe the immune response to immunization with various vaccine formulations/regimens at approximately Day 28 (post-first dose), Day 56, and Day 70 (post-second dose), and other follow-up time points, in terms of the: – Influenza HAI antibody responses (assayed with wild-type virus-like particle [VLP] reagents) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain – Influenza microneutralization (MN) antibody responses (assayed with wild-type virus) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain – SARS-CoV-2 anti-spike (S) IgG antibody responses to vaccine homologous virus antigen. Cross-reactive responses to virus variants may be assessed if available. – SARS-CoV-2 neutralizing antibody responses to vaccine homologous virus. Cross-reactive responses to virus variants may be assessed if available. Endpoints: • HAI antibody titers specific for the HA receptor binding domains of vaccine-homologous A and B strain(s), and antigenically drifted influenza strains. Derived/calculated endpoints based on these data will include: – Geometric mean titer (GMT), defined as the antilog of the mean of the log-transformed HAI titers on Days 56, 70, and other follow-up time points. – Geometric mean fold rise ($GMFR_{Post/Pre}$) – defined as the within group ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs within the same vaccine group on Days 56, 70, and other follow-up time points. – Seroconversion rate (SCR) – defined as proportion of participants in a given treatment group with either a baseline reciprocal (Day 0) titer of < 10 and a post-vaccination reciprocal titer ≥ 40, or a baseline reciprocal (Day 0) titer of ≥ 10 and a post-vaccination titer $\geq$ 4-fold higher than the baseline titer as measured on Days 56, 70, and other follow-up time points. – Seroprotection rate (SPR) – defined as the proportion of participants with a reciprocal HAI titer ≥ 40 on Days 56, 70, and other follow-up time points. – GMT ratio (GMTR) between select treatment arms at Days 56, 70, and other follow-up time points post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). • Microneutralization (MN_{50}) antibody responses: neutralizing antibody titers specific to vaccine homologous wild-type A and B strain(s) and/or antigenically drifted influenza strains, as measured by a MN assay. Derived/calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to HAI antibodies described above. • IgG geometric mean enzyme-linked immunosorbent assay (ELISA) unit (GMEU) concentrations (EU/mL) to the SARS-CoV-2 S protein from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/calculated endpoints for GMEU, GMFR, and SCR, and geometric mean ELISA unit ratio (GMEUR) will be defined in manner similar to that for HAI antibodies described above. • MN_{50} GMTs to the SARS-CoV-2 from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to that for HAI antibodies described above.

	Objective: • To determine one or more optimal dose levels of HA and rS antigens delivered in combination that maximize HAI antibody and anti-S antibody responses using a DoE modeling approach. Endpoint: • Post-vaccination time point HAI and anti-S antibody responses (eg, ratio of post-vaccination to pre-vaccination antibody levels) used to construct separate models of HAI and anti-S responses, respectively, to assess primary effects of each antigen's dose level and interactive effects between dose levels of the 2 antigens. Modeled responses in turn used to optimize dose levels of each antigen in relation to the other to maximize HAI and anti-S antibody responses.
Exploratory Objectives and Corresponding Endpoints	Objective: • To describe the cell-medicated immunity (CMI) responses to the various formulations/regimens in terms of peripheral blood CD4+ T cells which elaborate one or more cytokines or activation markers (interleukin [IL]-2, tumor necrosis factor alpha [TNFα], interferon gamma [IFNγ], or CD40 ligand [CD40L]) in response to in-vitro stimulation with either strain-specific HAs and/or rS. Other markers of CMI may be measured. Due to the laborious nature of the CMI assays, they will be performed on all participants drawn from a limited number of preselected sites and results may be reported as an addendum to the main clinical study report. (Note: multiple informative strains may be tested in informative random subsets of participants.) Endpoint: • Counts and/or proportions of Days 0, 7, 63, and 182 peripheral blood effector memory T-cell populations that secrete/express one or more of IL-2, CD40L, IFN-γ, and TNF-α cytokines following in-vitro restimulation with strain specific HAs and/or rS in participants selected for CMI response monitoring. Counts and/or proportions of additional markers of CMI as appropriate. Objective: • To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs. Endpoint: • Additional endpoints to evaluate immune responses may be developed based on the assays used.
Number of Sites	Approximately 4-12 sites located in Australia.
Study Duration	Estimated start date: September 2021; projected stop date: March 2022 Estimated duration: 6 Months

1.1 Schedule of Events

The Schedule of Events (SOE) is presented in Table 1.

Table 1 Schedule of Events for Study 2019nCoV-ICC-E-101

Study Day:	0	7	28	56	63	70	84	182[8]
Window (days):	0	+ 3	+ 3	+ 5	+ 3	+ 5	± 7	± 14
Study Visit:	1	2	3	4	5	6	7	8
Informed consent	X							
Medical history	X							
Inclusion/exclusion criteria, including determination of baseline seropositivity to SARS-CoV-2 based on SARS-CoV-2 vaccination documentation or history of prior SARS-CoV-2 infection	X							
Randomization	X							
Demographics	X							
Prior/concomitant medications	X	X	X	X	X	X	X[11]	X[11]
Vital signs measurements	X[1]	X	X	X[1]	X	X	X	X
Urine pregnancy test	X			X		X[12]		
Physical examination (at baseline and as required thereafter)[9]	X	X	X	X	X	X	X	X
Vaccination	X[2]			X[5]		X[10]		
Reactogenicity / Participant Diary Completion	X[3]	X		X[4,5]	X			
Blood sampling for SARS-CoV-2 (anti-NP) antibodies	X[6]					X		X
Blood sampling for SARS-CoV-2 immunogenicity (ELISA), HAI serology, and influenza virus MN_{50} assay (testing performed at Novavax)	X[6]		X	X[6]		X	X	X
Blood sampling for SARS-CoV-2 MN_{50} assay	X		X	X		X	X	X
Whole blood sampling and PBMC harvest for SARS-CoV-2 spike-specific T cell counts at a pre-specified subset of sites[7]	X	X			X			X
Unsolicited AEs	X	X	X	X	X	X		
MAAEs	X	X	X	X	X	X	X	X
SAE	X	X	X	X	X	X	X	X
AESIs (including PIMMCs)	X	X	X	X	X	X	X	X

ELISA = enzyme-linked immunosorbent assay; EoS = End of Study; HAI = hemagglutination inhibition; IFNγ = interferon gamma; IL-2 = interleukin-2; MAAE = medically attended adverse events; MN = microneutralization; NP = nucleoprotein; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Th1 = Type 1 T helper; Th2 = Type 2 T helper; TNFα = tumor necrosis factor alpha.

1. Vital signs to be captured pre-vaccination and between 30 to 60 minutes post-vaccination.
2. Participants should be free of acute illness (defined as the presence of a moderate or severe illness in the clinical judgment of the investigator) with or without fever, or an oral temperature ≥ 38°C in order to receive the test article injection. Participants presenting with an acute illness on screening/Day 0 may return to the trial site within the next 7 days to receive their injection provided symptoms have resolved.
3. Starting on the first vaccination day (Day 0) and for 6 days thereafter (Day 0 through Day 6, inclusive), participants will maintain diaries for daily recording of their body temperature and any AE spontaneously offered (reactogenicity).
4. Starting on the second vaccination day (Day 56) and for 6 days thereafter (Day 56 through Day 62, inclusive), participants will maintain diaries for daily recording of their body temperature and any AE spontaneously offered (reactogenicity).
5. Participants presenting with an acute illness on Day 56 may return to the trial site within the next 7 days to receive their second vaccination. If a participant has experienced any AEs/AESI/SAEs between trial Days 0 and 56, the Day 56 vaccination may be administered or delayed for up to 7 days based on the investigator's discretion.
6. Day 0 prior to vaccination.
7. Including IL-2, TNFα, CD40L, and IFNγ.
8. EoS.
9. After physical examination at baseline determines eligibility, subsequent physical examination assessments are symptom directed as triggered by AE or symptom reports.
10. In order to receive a complete 2-dose series of COVID-19 vaccine, participants from treatment group O will receive a third dose of vaccine consisting of 5 µg SARS-CoV-2 rS nanoparticle vaccine and 50 µg Matrix-M1 at Day 70. Note that because Vaccine Group O is the only treatment group receiving a vaccine at Day 70, Vaccine Group O participants and site staff will

be unblinded to participant's treatment status from Day 70 onwards. The Sponsor recognizes this partial unblinding and assesses it as having minor impact to the data.

11. After Day 70, only those concomitant medications taken for any of the following events will be recorded: any MAAEs, SAEs, or AESIs (including PIMMCs).
12. Participants in Vaccine Group O who are women of childbearing potential will have a urine pregnancy test performed at the Day 70 visit prior to dosing.

2 INTRODUCTION

2.1 Background

2.1.1 Influenza

Influenza is an airborne, respiratory pathogen that is generally transmitted by inhalation of infectious droplets of respiratory secretions, although transmission via fomites can also occur. Infections in humans often lead to annual outbreaks and worldwide epidemics, mainly in the winter seasons. The virus infects the upper respiratory epithelium of the nose, throat, bronchi, and occasionally the lungs. Clinical characteristics of influenza infection include sudden onset of fever, myalgia, headache, severe malaise, dry cough, sore throat, and rhinitis. Although the majority of people recover within 1 to 2 weeks without any major medical interventions, influenza can be associated with pneumonia and even death, especially in the very young, the elderly, and persons with underlying medical conditions such as pulmonary, cardiovascular, renal, and liver diseases [Paules 2017].

Influenza viruses are enveloped viruses belonging to the family of Orthomyxoviridae and are divided into 3 types, designated A, B, and C. Type A and B influenza viruses are responsible for yearly epidemic outbreaks of respiratory illness. Type A influenza viruses are further subdivided into subtypes based on the antigen structure of the 2 major surface glycoproteins (GP), HA, and neuraminidase. Among influenza A viruses, 18 HA subtypes and 11 NA subtypes are known to exist in viruses circulating among wild waterfowl. However, at this time, viruses characterized by only 2 combinations of HA and NA subtypes, H1N1 and H3N2, are stably established and circulate widely among humans, although H2N2 and H3N8 viruses have been established in humans in the past [Paules 2017]. Unlike Type A, Type B viruses are restricted to humans. Currently, 2 influenza B virus genetic lineages are in co-circulation. These lineages, termed Yamagata and Victoria based on their prototype strains, have limited antigenic cross-reactivity and often circulate together during the yearly epidemic [Paules 2017].

2.1.1.1 Influenza Disease Burden

Older adults are at the greatest risk of hospitalization and death due to influenza infection [CDC 2019b]. A retrospective study of 3 managed-care organizations during 1996 to 1997 through 1999 to 2000 estimated that the incidence rate of hospitalization during influenza season among people ≥ 65 years of age with underlying high-risk conditions was 55.6 pneumonia and influenza-associated hospitalizations per 10,000 persons, compared with 18.7 per 10,000 among lower-risk people of the same age group. Older adults between the ages of 50 to 64 with underlying conditions were also at increased risk for hospitalization during influenza seasons (12.3 per 10,000), compared with healthy older adults (1.8 per 10,000) [Mullooly 2007]. Between the years 1976 to 2007, approximately 21,098 older adults (≥ 65 years) were estimated to have died annually due to an influenza-related cause, corresponding to 90% of estimated annual average influenza-related mortality across all age groups [CDC 2010]. Data from modeling analyses of population-based surveillance covering 2010 to 2011 through 2012 to 2013 influenza seasons suggests that 71 to 85% of all influenza-related deaths occurred in adults ≥ 65 years of age [Reed 2015, Grohskopf 2016].

2.1.1.2 Licensed Influenza Vaccines

Vaccination is the cornerstone of influenza control, particularly for high-risk individuals older than 65 years, immunocompromised patients, and young children; and offers the most cost-effective approach to reduce the morbidity, mortality, and economic burden associated with influenza infection [Paules 2017]. To date, 7 quadrivalent inactivated or recombinant influenza vaccines, consisting of 2 A virus strains (A/H3N2 and A/H1N1) and strains of both B lineages, are licensed for sale in the US and marketed for the 2018 – 19 influenza season, indicated for various populations [FDA 2019, CDC 2019a]. These include the egg-derived inactivated virus vaccines Afluria® (Seqirus), Fluarix® (GlaxoSmithKline), FluLaval® (ID Biomedical Corp. of Quebec), Fluzone® (Sanofi Pasteur), and Fluzone intradermal (Sanofi Pasteur); the cell culture-derived vaccine Flucelvax® (Seqirus), and the recombinant DNA technology-derived Flublok® (Sanofi Pasteur, previously Protein Sciences). Three trivalent inactivated or recombinant influenza vaccines are also approved and marketed for the 2018 - 19 influenza season in the US [CDC 2019a]. Only 1 influenza vaccine is approved with an adjuvant (FLUAD™ with adjuvant MF59) [CDC 2019a].

Of all currently licensed vaccines, 2 are specifically approved for use in older adults, and include a high-dose (ie, Fluzone® High-Dose [Fluzone HD] initially approved in the US in 2009) and an adjuvanted standard dose inactivated vaccine (ie, FLUAD initially approved in the US in 2015); both are trivalent [CDC 2019a]. There are currently no data available that compares the immunogenicity of FLUAD to Fluzone HD in a randomized clinical trial. Although Fluzone HD has reported an increased relative vaccine efficacy (VE) of approximately 24% in the older adult population compared with standard-dose Fluzone [DiazGranados 2014, Monto 2017], effectiveness rates reported in older adults have remained quite variable, though uniformly suboptimal, from season-to-season since the approval of Fluzone HD in 2009, ranging anywhere from -5.8% to 45% from 2009 to 2018 [Griffin 2011, Treanor 2012, Ohmit 2014, Reed 2014, McLean 2015, Flannery 2018, Zimmerman 2016, CDC 2019a]. This variability is multifactorial, but likely, in part due to antigenic drift or mismatch between circulating and vaccine influenza strains, leading to reduced effectiveness of seasonal influenza vaccines. The most recent example of unanticipated drift occurred in the Northern hemisphere 2014 - 15 influenza season, when A(H3N2) clade 3C.3a viruses replaced A/Texas/50/12-like clade 3C viruses represented in the vaccines. This mismatch between vaccine and circulating viruses resulted in vaccine effectiveness not different from zero [Skonwronski 2016]. Emerging data also demonstrate that other mechanisms may account for reduction in VE, specifically the increasingly recognized problem of antigenic changes arising from egg-based influenza vaccine production. It has been shown that HA proteins produced by viruses replicating in eggs can undergo adaptive mutations which can critically alter the antigenic structure of key HA head epitopes and consequently, the immune response in the vaccinee and thereby result in an apparent antigenic mismatch between egg-produced vaccine strains and circulating strains [Zost 2017]. This mechanism, compounded by a degree of antigenic evolution, may explain the poor effectiveness of 2017 vaccines against A(H3N2) viruses in Australia [Sullivan 2017]. Thus, there remains a significant need for new influenza vaccines with improved efficacy, and, in particular, the capacity to mitigate the consequences of both naturally occurring antigenic drift between strain selection and circulation of the virus, as well as, potential egg-adaptive mutations giving rise to deleterious antigenic changes. The need for improved vaccine performance is greatest in the older adult population,

which remains vulnerable to serious complications, including death, resulting from influenza infection. Accordingly, a vaccine with both strong homologous HAI and broadly neutralizing antibody responses, which might address drifted strains, and is produced without eggs to avoid adaptive mutations in vaccine strains, could be of added value and could help meet the unmet medical need of influenza prevention in older adults [Shinde 2018].

2.1.2 COVID-19

Coronaviruses are medium sized, enveloped, positive-stranded ribonucleic acid viruses, with a characteristic crown-like appearance in electron micrographs due to circumferential studding of the viral envelope with projections comprising the S protein. There are 4 different strains (229E, OC43, NL63, and HKU1), which are ubiquitous in humans and generally result in mild upper respiratory illnesses and other common cold symptoms including malaise, headache, nasal discharge, sore throat, fever, and cough (Su 2016). In addition, other coronavirus strains are widespread in animals, where they typically cause enteric disease. These zoonotic coronaviruses have been known to evolve into strains that can infect humans with serious consequences including severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, Middle East Respiratory Syndrome (MERS)-CoV since 2012, and most recently, the novel SARS-CoV-2 since 2019 (Habibzadeh 2020).

In late December of 2019, an outbreak of respiratory disease caused by novel coronavirus (2019-nCoV) was detected in Wuhan, Hubei province, China. The virus' rapidly discerned genetic relationship with the 2002-2003 SARS-CoV has resulted in adoption of the name "SARS-CoV-2," with the disease being referred to as COVID-19. Despite containment efforts since the start of the outbreak, the SARS-CoV-2 has spread rapidly with over 214 countries/territories/areas outside of China reporting laboratory confirmed COVID-19 cases as of 15 May 2020. On 30 January 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) designated the outbreak as a public health emergency of international concern and subsequently declared a pandemic on 11 March 2020 (WHO 2020). As of 30 April 2021, there have been over 151 million confirmed cases and over 3.2 million deaths due to COVID-19 around the world [WHO 2020c]; this includes over 30.3 million confirmed cases and over 678,000 deaths in Europe, 18.8 million confirmed cases and over 208,000 deaths in India, and over 32.3 million confirmed cases and over 575,000 deaths in the US.

More recent reports from the UK, Brazil, India, and South Africa revealed the emergence of the B.1.1.7 (Alpha), P1 (Gamma), B.1.617.2 (Delta), and B.1.351 (Beta) variants of SARS-CoV-2, respectively, with confirmed acquisition of mutations in key antigenic sites in the receptor binding domain (RBD) and N-terminal domain of the S protein [MHRA 2021, EMA 2021]. Intense transmission during the first wave in South Africa, high levels of resulting population immunity to prototype viruses, and conditions sustaining a high force of infection in advance of the second wave, may have created a milieu favorable to the emergence of the B.1.351 (Beta) variant (Cele 2021, Greaney 2021, Sabino 2021, Tegally 2020, Volz 2021, Wang P 2021).

The B.1.351 (Beta) variant is reported to have emerged in the Eastern Cape Province, South Africa, in October 2020, and rapidly spread to become the dominant circulating strain throughout the country during November and December 2020 coincident with the surge of the second wave

of transmission nationally (Tegally 2020). The B.1.351 (Beta) variant is characterized by 3 deleterious mutations at key antigenic sites in the RBD, including N501Y, K417N, and E484K, with the latter two having particular antibody functional significance (Greaney 2021,Tegally 2020,Wang P 2021,Wang Z 2021). The N501Y mutation is known to increase binding affinity of the S protein to the hACE2 receptor (Starr 2020), and has been reported to increase transmissibility of the B.1.1.7 (Alpha) variant circulating in the UK (Volz 2021). The E484K mutation has been reported to abolish or substantially reduce neutralization by multiple potent monoclonal antibodies and polyclonal convalescent sera in both wild-type virus and pseudovirus neutralization assays (Cele 2021,Greaney 2021,Wang P 2021,Wang Z 2021,Wibmer 2021). Additionally, post-vaccination sera derived from volunteers receiving either of the messenger ribonucleic acid (mRNA) vaccines has also been reported to show 6.5- to 8.6-fold reductions in neutralizing capacity to the B.1.351 (Beta) variants relative to prototype virus in pseudovirus neutralization (Wang P 2021), however, the impact on clinical efficacy for mRNA vaccines remains unclear.

Reduced clinical efficacy against the B.1.351 (Beta) variant for more traditional viral vector COVID-19 vaccines, however, has been observed (Johnson 2021, Madhi 2021). For the SARS-CoV-2 rS vaccine, clinical efficacy results are available from studies run in the UK and South Africa where these variants have circulated. In the UK study, the overall efficacy of the vaccine was 89.7% (95% CI]: 80.2, 94.6) and, in post hoc analyses, efficacy estimates for the B.1.1.7 (Alpha) variant and for the original strain were 86.3% and 96.4%, respectively. The efficacy estimates in South Africa were generated in a period of > 90% B.1.351 (Beta) variant virus circulation. The efficacy of the vaccine in all study participants was 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) in participants who were HIV-negative [Shinde 2021].

2.1.3 Description of qNIV, SARS-CoV-2 rS, and Matrix-M1

2.1.3.1 qNIV

Novavax's qNIV is based on purified, recombinant, full-length HA that self-assemble into distinct nanoparticle structures of approximately 20 to 40 nm [Smith 2017, Shinde 2018]. A baculovirus/*Spodoptera frugiperda* (Sf9) insect cell system is used to clone and express recombinant influenza HAs from the 4 influenza strains recommended for the 2019 - 20 Northern Hemisphere influenza season: A/Brisbane/02/2018 pdm09 (H1N1); A/Kansas/14/2017 (H3N2); B/Maryland/15/2016 (Victoria/2/87 lineage); and B/Phuket/3073/2013 (Yamagata 16/88 lineage) [WHO 2019].

Novavax was also developing Tri-NIV, a trivalent precursor to qNIV, which was based on purified, recombinant, full-length HA that self-assemble into distinct nanoparticle structures of approximately 20 to 40 nm [Smith 2017, Shinde 2018], and manufactured using the same Sf9 technology used to manufacture qNIV. Tri-NIV comprised recombinant influenza HAs from influenza strains recommended for the 2017 - 18 Northern Hemisphere influenza season: A/Michigan/45/2015 (H1N1); A/HongKong/4801/2014 (H3N2); and B/Brisbane/60/2008 (Victoria lineage) [WHO 2017].

Product information including supportive clinical and nonclinical study summaries can be found in the qNIV Investigator's Brochure (IB) (Novavax 2021).

2.1.3.2 SARS-CoV-2 rS

SARS-CoV-2 rS is the prototype SARS-CoV-2 rS protein nanoparticle vaccine adjuvanted with Matrix-M1 adjuvant that is intended to be used for the active immunization for the prevention of mild, moderate, and severe COVID-19 caused by SARS-CoV-2 in adults 18 years of age and older. SARS-CoV-2 rS is constructed from the full-length, wild-type SARS-CoV-2 S GP based on the GenBank gene sequence MN908947, nucleotides 21563-25384 from the 2019 SARS-CoV-2 genome. In the wake of emerging SARS-CoV-2 variants, Novavax has initiated the production and investigation of an rS nanoparticle vaccine using the sequenced genome from the B.1.351 (Beta) variant virus adjuvanted with Matrix-M1 adjuvant (product name: NVX-CoV2438). The S protein from each virus is a type 1 trimeric GP of that is produced as an inactive S0 precursor. The S-gene was codon-optimized for expression in Sf9 insect cells.

Additional product information including supportive clinical and nonclinical study summaries can be found in the SARS-CoV-2 rS IB (Novavax 2021).

2.1.3.3 Matrix-M1 Adjuvant

Adjuvants are compounds which, when combined with a specific vaccine antigen, serve to increase the immune response to the vaccine. In general, adjuvants work by engaging one or more component of the innate immune system. Matrix-M1 is a saponin-based adjuvant, derived from the bark of the *Quillaja saponaria* Molina tree, which can be co-administered with an antigen to induce a targeted and enhanced immune response. The proposed mode of action of Matrix-M1 adjuvant does not include a depot effect, but rather is through a combination of activities including recruitment and activation of innate immune cells to the site of vaccine injection, rapid antigen delivery to antigen-presenting cells, and enhanced antigen presentation via both major histocompatibility complex (MHC) I and MHC II molecules in the draining lymph nodes.

2.1.4 Nonclinical Studies

2.1.4.1 qNIV

A range of non-clinical studies support the nanoparticle influenza HA and SARS-CoV-2 rS vaccines adjuvanted with Matrix-M1. Nanoparticle influenza vaccine has been studied primarily in ferrets, chosen for susceptibility to human influenza viruses and immune responses to influenza vaccines resembling the human response. A key nonclinical pharmacology immunogenicity and protective efficacy study was conducted in the ferret model with a Tri-NIV combined with Matrix-M1 adjuvant, a precursor to qNIV. Compared to licensed influenza vaccines, multivalent NIV with Matrix-M1 induced higher titers of HAI and neutralizing antibodies to virus strains in the vaccine, and also a range of historical strains, suggesting a broadened response (Smith 2017). When challenged with either vaccine-homologous or historical A(H3N2) viruses, animals immunized with NIV with Matrix-M1 adjuvant cleared influenza virus from their respiratory tract more rapidly than controls or animals immunized with licensed egg-derived vaccine (Smith 2017, Portnoff 2020). In addition, a toxicology study was conducted in New Zealand White (NZW) rabbits with a precursor NIV (containing HA nanoparticles from 2 influenza strains, as well as NA nanoparticles from 1 influenza strain) alone or in combination with respiratory syncytial virus F protein (also produced on the baculovirus-

insect cell platform) and with or without Matrix-M1 adjuvant. All of the vaccine formulations were well tolerated, with only transient inflammation at the injection sites and some hyperplasia of the draining lymph nodes – both of which were deemed expected and non-adverse responses to a vaccine. The results of these supportive nonclinical study summaries can be found in the qNIV IB (Novavax 2021).

2.1.4.2 SARS-CoV-2 rS

SARS-CoV-2 rS with Matrix-M1 adjuvant has been studied in mice, golden Syrian hamsters, cynomolgus and rhesus macaques, and baboons. In all species evaluated, the SARS-CoV-2 rS with Matrix-M1 adjuvant induced anti-S IgG antibodies, including antibodies that inhibit binding of the spike protein to its host cell receptor, hACE2, and high titers of neutralizing antibodies to wild-type virus. Where examined, vaccine-induced T-cell responses to adjuvanted vaccine showed a Th1-biased antigen-specific CD4+ T-cell response. Immunized mice, hamsters, and macaques all showed more rapid clearance of SARS-CoV-2 after respiratory challenge (Tian 2021, Guebre-Xabier 2020, Gorman 2021), and hamsters – the only model with significant clinical disease – showed reduced weight loss and maintenance of activity relative to controls. No animal model showed histologic evidence of vaccine-enhanced disease.

A Good Laboratory Practice (GLP)-compliant toxicity study in NZW rabbits was performed to evaluate 50 µg of SARS-CoV-2 rS with and without 50 µg Matrix-M adjuvant. Immunization of rabbits up to 4 times with full human doses of SARS-CoV-2 rS, with or without 50 µg Matrix-M1 adjuvant, was well tolerated, had no effects on mortality, cage side observations, body weight, food consumption, or physical examination findings. There were no test article-related gross or histopathologic findings aside from subacute inflammation at the injection sites, which was deemed a typical response to immunization.

A GLP-compliant developmental and reproductive toxicity study was completed in Sprague-Dawley rats. Dams immunized with antigen plus adjuvant, but not adjuvant alone, had strong anti-S IgG responses, and vaccine-induced antibody was transferred transplacentally to the fetuses. Mating and fertility, as well as the number and viability of fetuses, were unaffected by adjuvant or complete vaccine. There was no treatment effect on fetal malformations or skeletal abnormalities. In dams allowed to deliver, receipt of adjuvant or complete vaccine did not affect the gestational duration at delivery or the number of live pups; and there was also no impact of the attainment of developmental milestones by pups through 21 days of life.

Additional supportive nonclinical study summaries can be found in the SARS-CoV-2 rS IB (Novavax 2021).

2.1.4.3 Influenza COVID-19 Combination Vaccine

ICC vaccines, adjuvanted with Matrix-M1, have been studied in ferrets and hamsters. Groups of ferrets received two IM doses, separated by 21 days, of 15 or 60 µg of each of 4 HAs with Matrix-M1 adjuvant, and with or without 5 µg of SARS-CoV-2 rS. HAI antibody responses to all 4 HAs showed minimal dose response and no negative effect of co-administration with SARS-CoV-2 rS. hACE2 binding inhibition antibody responses to the SARS-CoV-2 S were slightly lower, but not significantly different, in the combined vaccine group relative to the monovalent of SARS-CoV-2 rS recipients. In a second experiment, hamsters were immunized

with two-dose regimens of 1 or 5 µg of SARS-CoV-2 rS alone, or with qNIV comprising 2.5 or 10 µg of each HA, or qNIV alone. All groups received a constant dose of 15 µg of Matrix-M1 adjuvant with each injection. For each influenza strain examined, HAI titers and virus neutralization titers at two weeks after the first and second doses showed no clear dose-response and were comparable with or without of SARS-CoV-2 rS co-administration (Massare 2021). Similarly, anti-rS IgG levels induced by of SARS-CoV-2 rS showed no significant impact of influenza vaccine co-administration. hACE2 binding inhibiting antibodies were slightly, albeit not significantly, lower in animals receiving the combined vaccines (Massare 2021). At 21 days after the second dose, all hamsters were challenged intranasally with SARS-CoV-2. All animals immunized with either dose of SARS-CoV-2 rS, with or without qNIV, demonstrated accelerated clearance of SARS-CoV-2 subgenomic RNA from the upper airway, and essentially complete protection against weight loss, viral replication in the lower respiratory tract, and lung histopathology. Thus, co-administration with qNIV had no detectable effect on the potent protective efficacy of the of SARS-CoV-2 rS vaccine.

Additional supportive nonclinical study summaries can be found in the ICC IB (Novavax 2021).

2.1.5 Supportive Clinical Data

Supportive clinical data are available from 2 completed studies in the qNIV clinical development program (qNIV-E-201 and qNIV-E-301) and from 4 ongoing studies in the SARS-CoV-2 rS clinical development program (2019nCoV-101, 2019nCoV-501, 2019nCoV-302, and 2019nCoV-301).

2.1.5.1 qNIV

2.1.5.1.1 Study qNIV-E-201

Study qNIV-E-201 was a Phase 2, randomized, observer-blinded, active-controlled, dose-finding, formulation-optimizing trial in healthy adults ≥ 65 years of age to 1) describe the safety and tolerability of qNIV at different doses and formulations (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain), without adjuvant or with 1 of 2 different doses of Matrix-M1 adjuvant (mixed in-clinic or co-formulated in advance of the trial), and of 2 US-licensed comparators, Fluzone HD (Sanofi Pasteur) and Flublok Quadrivalent (Sanofi Pasteur, previously Protein Sciences Corp), in 1375 healthy adults ≥ 65 years of age; and 2) to demonstrate a Matrix-M1 adjuvant effect by confirming the immunogenic superiority of qNIV (60 µg HA per A and B strain) co-formulated with 50 µg Matrix-M1 as compared to qNIV (60 µg HA per A and B strain) without adjuvant. qNIV with Matrix-M1 adjuvant was well tolerated and had a similar safety profile to the 2 US-licensed comparators, Fluzone HD and Flublok Quadrivalent [Shinde 2020].

Overall, the proportion of participants with AEs was comparable across all adjuvanted qNIV groups (41% to 52%) and the active comparators, Fluzone HD (47%) and Flublok (44%). The safety profile of qNIV remained comparable across groups regardless of increasing the total antigen dose or adjuvant dose (ie, 50 or 75 µg Matrix-M1 in the present trial).

Solicited AEs occurred with similar frequency in the selected qNIV group (38%) compared with the Fluzone HD and Flublok groups (37-38%). Local solicited AEs were generally transient

among all participants. Injection site pain was the most common local AE among all groups. There were no severe local AEs in the qNIV group.

Systemic solicited AEs were also transient and incidences were slightly higher in the qNIV group (29%) than in the Fluzone HD (24%) or the Flublok group (26%). The most common systemic AEs (> 10%) were headache (15%) and muscle pain (10%) in the qNIV group. Severe events were rare.

Unsolicited AEs were reported by similar proportions of participants in the qNIV (18%) and Fluzone HD (20%) groups. Reports of severe unsolicited AEs were uncommon. None of these events were reported by the investigator as related to study treatment.

Medically attended adverse events (MAAEs) were reported in a similar proportion of participants across all groups (7% qNIV and Fluzone HD; 6% Flublok).

At Day 28, SAEs were reported in 0.6% of participants in both the qNIV (malignant melanoma) and Fluzone HD (dehydration) groups. By Day 182 of the trial, SAEs were reported among 5% of qNIV recipients; none were considered related to trial treatment; 19%, participants reported a MAAE.

The key conclusions based on the Day 28 immunogenicity data from the dose-optimizing qNIV-E-201trial are:

1. The primary endpoint of the clinical trial, demonstration of adjuvant effect, was met, as determined by VLP-based HAI responses.
2. These trends seen that support a positive adjuvant are confirmed using egg-based HAI responses, with increased sensitivity to benefits in the A(H3N2) response.
3. Co-formulated qNIV/Matrix-M1 adjuvant had similar immunogenicity (based on egg-based HAIs) as compared to the bedside mixed formulation. These data allow bridging to the Phase 1/2 clinical data of Tri-NIV.
4. Co-formulated, quadrivalent formulations of qNIV induce robust HAI responses against homologous A/B, and drifted H3N2 strains.
5. Day 28 and 56 immunogenicity data support inclusion of co-formulated qNIV (60 µg per HA strain and 75 µg of Matrix-M1 adjuvant) for the future Phase 3 clinical trial.
6. Increasing the Matrix-M1 adjuvant dose from 50 to 75 µg induced comparable HAI responses to any of the A or B strains.
7. Immune responses to the B strains were not further enhanced by increasing B antigen dose from 60 to 90 µg; therefore, 60 µg of each B strain will be adequate for the Phase 3 qNIV formulation.
8. CMI responses for 60 µg HA/strain with 75 µg Matrix-M1 adjuvant responses far exceeded that of any other qNIV dose/formulation, as well as that of active comparators.

2.1.5.1.2 Study qNIV-E-301

Study qNIV-E-301 was a Phase 3, randomized, observer-blinded, active-controlled study to evaluate the noninferior immunogenicity and safety of 240 µg qNIV (60 µg HA antigen per influenza strain) co-formulated with 75 µg Matrix-M1 adjuvant (investigational product) against a US licensed active comparator, Fluzone Quadrivalent, in 2,652 clinically stable adults ≥ 65 years of age in the US. Each study vaccine contained the WHO/Vaccines and Related Biological

Products Advisory Committee (VRBPAC) recommendations for the 2019-2020 Northern Hemisphere influenza season (A/Brisbane/02/2018 [H1N1] pdm09, A/Kansas/14/2017 ([H3N2], B/Maryland/15/2016 [Victoria lineage], and B/Phuket/3073/2013 [Yamagata lineage]) [WHO, VRBPAC 2019]. Both groups were stratified by site, age (65 to < 75 and ≥ 75 years), and history of prior year receipt of the 2018-19 influenza vaccine [Shinde 2020b]. On Day 0, all participants received a single dose of study vaccine (qNIV with Matrix-M1 adjuvant or Fluzone Quadrivalent) by IM injection in the nondominant arm, if available for injection. qNIV with Matrix-M1 adjuvant was well tolerated and had a similar safety profile to the 2 US-licensed comparators, Fluzone HD and Flublok Quadrivalent.

In a total safety population of 2,652 participants, the proportion of participants with AEs was higher in the qNIV with Matrix-M1 adjuvant group (49.4%) as compared to the active comparator group, Fluzone Quadrivalent (41.8%). This difference was primarily attributable to differences in solicited AEs during the 7 days following vaccination and, in particular, mild to moderate and transient injection site pain.

A higher proportion of solicited AEs occurred among participants who received qNIV with Matrix-M1 adjuvant (41.3%) relative to Fluzone Quadrivalent (31.8%). This difference in turn was attributable to differences in expected local solicited AEs (27.9% versus 18.4% for qNIV with Matrix-M1 adjuvant and Fluzone Quadrivalent, respectively), the majority of which were injection site pain (25.6% vs 16.1%) and swelling (6.3% vs 3.1%) with severe local solicited events reported infrequently in both groups (0.6% vs 0.2% for qNIV with Matrix-M1 adjuvant and Fluzone Quadrivalent, respectively).

Severe unsolicited and severe/related unsolicited AEs were infrequent in both groups.

SAEs were uncommon and reported in < 1% of participants across the entire study (0.8% vs 0.4% for qNIV with Matrix-M1 adjuvant versus Fluzone Quadrivalent, respectively). No AESIs were reported.

All 4 vaccine-homologous influenza strains met the success criteria for GMTR (lower bound of the 95% CI of GMTRs ≥ 0.67) and SCR difference (lower bound of the 95% CI seroconversion difference ≥ -10%) using the PP Population. For egg HAI antibody responses, the post-vaccination GMTRs at Day 28 for Quad-NIV with Matrix-M1 adjuvant were statistically significantly greater, based on both GMTR and SCR difference, than those in Fluzone Quadrivalent recipients for 3 of the 4 vaccine-homologous influenza strains.

When HAI antibody responses to the vaccines were assessed in the wild-type HAI assay format, which features known wild-type HA sequences and human, rather than avian, glycans as HA receptors in the agglutination reaction, the relative improvements in HAI antibody responses were further accentuated in favor of qNIV with Matrix-M1 adjuvant.

In terms of CMI responses, the vaccines were compared for an influenza A and an influenza B strain, qNIV with Matrix-M1 adjuvant induced substantially higher antigen-specific (total and) effector $CD4^+$ T cells against A/Kansas/14/2017 (H3N2) and B/Maryland/15/2016 (Victoria lineage) strains at Day 7 post-vaccination as compared to Fluzone Quadrivalent, representing a 126% to 189% improvement in various polyfunctional phenotypes of effector $CD4^+$ T cells for qNIV with Matrix-M1 adjuvant. Notably, and in contrast to Fluzone Quadrivalent, qNIV with Matrix-M1 adjuvant was able to activate influenza-specific polyfunctional cellular immune

responses even among participants with the lowest levels of baseline T-cell reactivity—a crucial feature for developing protective immune responses in those with a greater degree of immunosenescence due to advanced age, physiological frailty, or multi-morbidity. qNIV demonstrated marked induction of cell-mediated immune responses in a manner not previously reported for currently available enhanced influenza vaccines targeting older adults [Cowling 2019].

2.1.5.2 SARS-CoV-2 rS

2.1.5.2.1 Study 2019nCoV-101

Study 2019nCoV-101 (NCT04368988) is the first clinical study initiated with SARS-CoV-2 rS nanoparticle vaccine [Keech 2020]. This ongoing 2-part, randomized, observer-blinded, placebo-controlled, Phase 1/2 trial has results through Day 189 for study Part 1 and through Day 35 for study Part 2. Study 2019nCoV-101 - Part 1 (Phase 1) is designed to evaluate the immunogenicity and safety of 5 and 25 µg SARS-CoV-2 rS nanoparticle vaccine with or without 50 µg Matrix-M1 adjuvant in 131 healthy participants ≥ 18 to ≤ 59 years of age. Results of an interim analysis for the Phase 1 portion of the trial at Day 189 showed that SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated and elicited robust immune responses. There were no SAEs or AESIs reported. Reactogenicity was mainly mild in severity and of short duration (mean ≤ 2 days), with second vaccinations inducing greater local and systemic reactogenicity. The adjuvant significantly enhanced immune responses (anti-S IgG, hACE2 receptor binding inhibition antibody, and neutralizing antibody) and was antigen dose-sparing. The vaccine also induced antigen-specific T-cells with a largely Th1 phenotype. An interim analysis performed at Day 35 using COVID-19 convalescent sera found the 2-dose 5 µg SARS-CoV-2 rS/Matrix-M adjuvant induced mean anti-S IgG and neutralizing antibody responses that exceeded the mean responses in convalescent sera from COVID-19 patients with clinically significant illnesses.

Study 2019nCoV-101 - Part 2 (Phase 2) is designed to evaluate the immunogenicity, safety, and preliminary efficacy of 5 and 25 µg SARS-CoV-2 rS nanoparticle vaccine with 50 µg Matrix-M1 adjuvant in up to 1,500 healthy adults ≥ 18 to ≤ 84 years of age with more comorbidities than the participant population in Part 1 of the study. An interim 35-day safety and immunogenicity analysis was conducted on 1,283 participants. This analysis comprised 700 participants aged 18 to 59 years (the same age range of Part 1 of the study) and 583 participants aged 60 to 84 years. Overall, local and systemic reactogenicity data from this analysis were consistent with the reactogenicity data in Part 1 of the study, with no safety concerns between the younger and older age cohorts. Both the 5 and 25 µg doses of SARS-CoV-2 rS with Matrix-M1 adjuvant were well tolerated with few participants (9; 0.7%) having SAEs. Regarding immunogenicity, robust responses were observed in both younger and older adults in the 2-dose 5 µg SARS-CoV-2 rS/Matrix-M adjuvant arm. While an attenuation of immune responses (approximately 2-fold lower SARS-CoV-2 wild-type neutralizing antibody activity in older participants) was observed when stratified by age group (18 to 59 years and 60 to 84 years), geometric mean fold increases in neutralizing antibody were still increased > 95-fold compared to baseline.

2.1.5.2.2 Study 2019nCoV-501

Study 2019nCoV-501 is a Phase 2a/b, randomized (1:1), observer-blinded, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant, administered 21 days apart on Days 0 and 21 as a coformulation, in 4,164 healthy HIV-negative participants ≥ 18 to ≤ 84 years of age and 244 medically stable HIV-positive participants ≥ 18 to ≤ 64 years of age conducted in South Africa [Shinde 2021]. An analysis of the primary efficacy endpoint, which included both immunogenicity and safety data, was recently performed. A total of 147 polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 cases were accrued for the complete analysis of the primary efficacy endpoint, with 51 (3.62%) cases for SARS-CoV-2 rS with Matrix-M1 adjuvant versus 96 (7.05%) cases for placebo. The resultant VE of SARS-CoV-2 rS with Matrix-M1 adjuvant in prevention of symptomatic mild, moderate, or severe COVID-19 in adult participants, seronegative (to SARS-CoV-2) at baseline, was 48.6% (95% CI: 28.4, 63.1), meeting the success criterion of a lower bound CI > 0. In HIV-negative and HIV-positive participants, respectively, the resultant VEs were 55.4% (95% CI: 35.9, 68.9) and -35.4% (95% CI: -236.9, 45.6). Forty-one (93.2%) of 44 participants with a primary endpoint had whole genome sequence data available (samples from 3 cases in the placebo group could not be sequenced), and 38 (92.7%) of 41 were identified as the B.1.351 (Beta) variant, resulting in a post-hoc VE of SARS-CoV-2 rS with Matrix-M1 adjuvant in prevention of symptomatic mild, moderate, or severe COVID-19 in all and HIV-negative adult participants, seronegative (to SARS-CoV-2) at baseline, of 43.0% (95% CI: -9.8, 70.4) and 51.0% (95% CI: -0.6, 76.1), respectively, for the B.1.351 (Beta) variant. SARS-CoV-2 rS with Matrix-M1 adjuvant induced robust immune responses (anti-S IgG and neutralizing antibody) in both HIV-negative and HIV-positive participants versus placebo. In baseline seronegative participants, immune responses were approximately 2-fold lower in HIV-positive participants versus HIV-negative participants. SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated in both HIV-negative and HIV-positive participants, with similar frequencies of severe AEs, SAEs, MAAEs, and AESIs compared to placebo. Solicited local and systemic reactogenicity in all participants were higher for SARS-CoV-2 rS with Matrix-M1 adjuvant than placebo, but the majority of participants reported grade 1 events after each vaccination. Pain and tenderness were the most frequently reported local AEs after each vaccination, with relatively short median durations (2.0 days for SARS-CoV-2 rS with Matrix-M1 adjuvant and 1.0 day for placebo). Headache, fatigue, and muscle pain were the most frequently reported systemic AEs after each vaccination, with relatively short median durations (2.0 days for SARS-CoV-2 rS with Matrix-M1 adjuvant and placebo).

2.1.5.2.3 Study 2019nCoV-302

Study 2019nCoV-302 is a Phase 3, randomized (1:1), observer-blinded, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant, administered 21 days apart on Days 0 and 21 as a coformulation, in 15,139 healthy and medically stable (with comorbidities) participants ≥ 18 to ≤ 84 years of age conducted in the UK [Heath 2021]. An analysis of the primary efficacy endpoint, which included both immunogenicity and safety data, was recently performed. A total of 106 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 were accrued for the final

prespecified analysis of the primary endpoint, with 10 (0.1%) in the SARS-CoV-2 rS with Matrix-M1 adjuvant group and 96 (1.4%) in the placebo group. All but 5 cases were mild or moderate in severity, with all 5 severe cases occurring in the placebo group. The resultant VE of SARS-CoV-2 rS with Matrix-M1 adjuvant to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS-CoV-2) adult participants was 89.7% (95% CI: 80.2, 94.6; $p < 0.001$), with an LBCI > 30% meeting the prespecified study success criterion. PCR results of the final analysis by SARS-CoV-2 strain showed VEs of 86.3% (95% CI: 71.3, 93.5) for the UK (Kent) variant B.1.1.7 (Alpha) and 96.4% (95% CI: 73.8, 99.5) for the ancestral (Wuhan) strain. SARS-CoV-2 rS with Matrix-M1 adjuvant induced robust immune responses (anti-S IgG and neutralizing antibody), which were 1.3-fold (anti-S IgG) and 1.4-fold (neutralizing antibody) higher in the younger age cohort (18 to 64 years) than in the older age cohort (65 to 84 years), but SCRs were at least 98% in both age cohorts. SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated, with similar frequencies of SAEs, MAAEs, and AESIs compared to placebo. Solicited local and systemic reactogenicity in a subset of 2,714 participants were higher for SARS-CoV-2 rS with Matrix-M1 adjuvant than placebo, but the majority of participants reported Grade 1 events following first vaccination and grade 1 or grade 2 events following second vaccination. The most frequent local AEs following each vaccination were tenderness and pain, with relatively short median durations following first (≤ 2.0 days) and second (≤ 3.0 days) vaccination. The most frequent solicited systemic AEs following each vaccination were headache, fatigue, and muscle pain, with relatively short median durations following first (≤ 1.5 days) and second (≤ 2.0 days) vaccination. Across the 2 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 treatment-emergent adverse events (TEAEs) than participants in the younger age cohort (18 to 64 years of age).

2.1.5.2.4 Study 2019nCoV-301

Study 2019nCoV-301 is a Phase 3, randomized (2:1), observer-blinded, placebo-controlled trial with a pediatric expansion to evaluate the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant, administered 21 days apart on Days 0 and 21 as a coformulation, in 29,868 healthy and medically stable (with comorbidities or at high risk for COVID-19) adult participants 18 years of age and older conducted in the US and Mexico and to evaluate the safety and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant in healthy adolescent participants 12 to < 18 years of age conducted in the US. An analysis of the primary efficacy endpoint for the adult participants, which included preliminary safety data, has recently been reported. VEs of SARS-CoV-2 rS with Matrix-M1 adjuvant to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS-CoV-2) participants were 90.4% (95% CI: 82.9, 94.6) overall; 96.7% (95% CI: 74.6, 99.6) against variants not considered variants of interest/concern; and 93.4% (95% CI: 84.3, 97.2) against variants of interest/concern. VE against all moderate or severe disease was 100% (95% CI: 87.0, 100). Preliminary data indicate a favorable safety and reactogenicity profile. Serious and severe AEs were infrequent and balanced among vaccine and placebo recipients. No single unsolicited AE was reported by more than 1% of participants. The most frequent local AEs following each vaccination were tenderness and pain, with relatively short median durations (≤ 3.0 days). The most frequent solicited systemic AEs following each vaccination were headache, fatigue, and muscle pain, with relatively short median durations (≤ 2.0 days).

2.1.5.3 Matrix-M1 Adjuvant

Matrix-M1 adjuvant has been administered to over 33,000 participants (of which, approximately 30,798 received SARS-CoV-2 rS) with acceptable short-term reactogenicity and an unremarkable long-term safety profile.

2.1.5.4 Other Baculovirus-Sf9-Produced Nanoparticle Vaccines

Novavax has, in its internally sponsored clinical trials, tested baculovirus-Sf9-produced nanoparticle vaccines in over 55,000 participants comprising older adults, young adults, and a limited number of children 2 to 5 years of age; and also including 3,075 pregnant women, with acceptable safety.

2.1.6 Benefit: Risk Assessment

2.1.6.1 qNIV

2.1.6.1.1 Risks Associated with qNIV

Overall, qNIV with Matrix-M1 adjuvant showed an acceptable safety profile, with good tolerability. SAEs were uncommon and reported in < 1% of participants across the entire study, and there were no AESIs or vaccine-related deaths reported. The safety and reactogenicity profiles were generally comparable to the active comparator influenza vaccine Fluzone Quadrivalent, except for a higher incidence of mild to moderate transient local and systemic reactogenicity, in particular injection site pain, with no other emergent safety signals. These results support the conclusion that the risk of vaccination with qNIV with Matrix-M1 adjuvant is acceptable.

2.1.6.1.2 Benefits Associated with qNIV

Overall, qNIV with Matrix-M1 adjuvant showed an acceptable safety profile, with good tolerability. SAEs were uncommon and reported in < 1% of participants, and there were no AESIs or vaccine-related deaths reported. The safety and reactogenicity profiles were generally comparable to the active comparator influenza vaccine Fluzone Quadrivalent, except for a higher incidence of mild to moderate transient local and systemic reactogenicity, in particular injection site pain, with no other emergent safety signals.

Overall, qNIV with Matrix-M1 adjuvant induced a broadly cross-reactive antibody response against vaccine-homologous and antigenically drifted A/H3N2 influenza strains, and a potent polyfunctional $CD4^+$ T-cell response in older adults.

2.1.6.2 SARS-CoV-2 rS

2.1.6.2.1 Risks Associated with SARS-CoV-2 rS

The SARS-CoV-2 rS nanoparticle vaccines contain purified protein antigens. They cannot replicate, the protein is not produced using infectious SARS-CoV-2, nor can the vaccines cause COVID-19. However, in common with all vaccines produced in cell culture or other systems, the SARS-CoV-2 rS nanoparticle vaccines contain residual non-vaccine proteins derived from the

production system, and sensitization to these, or the SARS-CoV-2 S protein itself, may theoretically occur. While the occurrence of anaphylaxis is possible with the administration of any vaccine, whether licensed or in development, no such reactions have been observed in any of the Sponsor's clinical trials to date. As clinical data become available with increased exposure, it is possible that this profile may change. The risk of AEs related to hypersensitivity will be mitigated by observation of participants for at least 30 minutes after each study vaccination.

The risk for enhanced COVID-19 in immunized participants is a theoretical risk. Enhanced disease in coronavirus vaccine-immunized animals after infectious virus challenge has been demonstrated in nonclinical studies of several, but not all, coronavirus vaccine candidates. There is currently no evidence for immunoenhancement in nonclinical testing of SARS-CoV-2 rS or other Novavax baculovirus-Sf9-based vaccines taken into nonclinical evaluation or clinical trials.

No risks have been identified in nonclinical or early clinical testing of SARS-CoV-2 or other coronavirus vaccines (SARS-CoV and MERS-CoV) developed using the baculovirus-Sf9 system to date. In supportive toxicology studies with other viral GP nanoparticle vaccines developed using the baculovirus-Sf9 system with different antigens, findings were generally consistent with an immune response to the vaccine formulations. These toxicological investigations indicated that baculovirus-Sf9-produced antigens (up to 240 µg total nanoparticle dose) with Matrix-M1 adjuvant (up to 100 µg) were well tolerated in the animal and antigen system tested with no evidence of toxicity suggestive of any unusual risk or target organ for toxicity. Non-adverse findings, including local injection site inflammation and serum chemical markers of inflammation (such as C-reactive protein), were transient and considered consistent with immune system stimulation consequent to immunization.

Novavax baculovirus-Sf9-produced nanoparticle vaccines comprising viral GPs, with and without Matrix-M1 or aluminum adjuvants, have been shown to induce robust and protective immune responses in relevant animal models to influenza HAs, respiratory syncytial virus fusion (RSV F) protein, SARS-CoV and MERS-CoV S proteins, rabies GP, and Zaire ebolavirus GP. In addition, the Novavax RSV F protein candidate adsorbed to aluminum phosphate has induced antibodies in pregnant women which, when transferred trans-placentally, were associated with reduced rates of respiratory syncytial virus lower respiratory tract infections in their infants during the first 90 to 180 days of life. The goal of this program is to investigate the efficacy, safety, and immunogenicity of Novavax baculovirus-Sf9-produced nanoparticle vaccines with Matrix-M1 adjuvant in prevention of clinically significant diseases.

2.1.6.2.2 Benefits Associated with SARS-CoV-2 rS

A 5-µg dose of SARS-CoV-2 rS co-formulated with 50 µg Matrix-M1 adjuvant (NVX-CoV2373) has proven to be highly efficacious against COVID-19 in randomized clinical trials. When administered 21 days apart, in approximately 29,960 adult participants 18 years of age or older across 119 sites in the US and Mexico, VEs of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS-CoV-2) participants were 90.4% (95% CI: 82.9, 94.6) overall; 96.7% (95% CI: 74.6, 99.6) against variants not considered variants of interest/concern; and 93.4% (95% CI: 84.3, 97.2) against variants of interest/concern. VE against all moderate or severe disease was 100% (95% CI: 87.0, 100).

When administered 21 days apart, in 15,187 adult participants 18 to 84 years of age across 33 sites in the UK, VEs of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS-CoV-2) participants were 86.3% (95% CI: 71.3, 93.5) for the UK (Kent) B.1.1.7 (Alpha) variant and 96.4% (95% CI: 73.8, 99.5) for the ancestral (Wuhan) strain.

In a separate randomized trial conducted in South Africa (comprising 2,770 participants [(1,408 with NVX-CoV2373 and 1,362 with placebo]), the prevention of symptomatic mild, moderate, or severe COVID-19, in a complete analysis reached a VE of 48.6% (95% CI: 28.4, 63.1). The prevalence of the B.1.351 (Beta) SARS-CoV-2 variant among the 41 (93.2%) of 44 cases in the official event-driven primary efficacy analysis (VE = 49.4% [95% CI: 6.1, 72.8]) for which virus sequencing data were available, was 92.7%. The post-hoc VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in HIV-negative and HIV-positive participants, seronegative (to SARS-CoV-2) at baseline, respectively, was 43.0% (95% CI: -9.8, 70.4) and 51.0% (95% CI: -0.6, 76.1) for the B.1.351 (Beta) variant.

Findings to date suggest that SARS-CoV-2 rS when administered with Matrix-M1 adjuvant demonstrated acceptable safety and robust immunogenicity profiles in adult participants aged 18 to 84 years of age. Generally, reactogenicity profiles were similar between younger and older participants, with both local and systemic reactogenicity events occurring less frequently in older adults. Furthermore, severe unsolicited TEAEs occurred in < 1% of participants across treatment groups. Overall, frequencies of unsolicited TEAEs after first vaccination including severe TEAEs, SAEs, MAAEs, and AESIs were similar between the NVX-CoV2373 and placebo groups for all participants regardless of baseline serostatus or stratified by baseline serostatus and separately for HIV-negative and HIV-positive participants. The majority of participants had unsolicited TEAEs that were mild in severity regardless of baseline serostatus or HIV positivity. No deaths related to study vaccination have been reported.

A two-dose regimen of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant markedly increased anti-S IgG and neutralizing antibody levels relative to placebo at 2 weeks after the second vaccination regardless of baseline serostatus, with higher levels in the younger adult cohort (18 to 64 years) than in the older adult cohort (65 to 84 years) but with similarly high SCRs.

2.1.6.3 Marix-M1 Adjuvant

2.1.6.3.1 Risks Associated with Matrix-M1

Finally, risks identified in human clinical trials with the Matrix-M1 adjuvant have been described in detail in the current Matrix-M Adjuvant Safety Data Supplement, which is provided for information with the protocol and the qNIV IB (Novavax).

2.1.6.3.2 Benefits Associated with Matrix-M1 Adjuvant

Matrix-M1 adjuvant is co-administered with an antigen to induce a targeted and enhanced immune response.

2.2 Study Rationale

Novavax is developing a novel recombinant qNIV with Matrix-M1 adjuvant for the prevention of disease due to influenza virus in adults ≥ 65 years of age, using a recombinant baculovirus and insect cell vaccine platform technology. With a flexible nanoparticle structure in which multiple antigen surfaces are exposed, recombinant wild-type sequenced HAs, and use of a saponin-based adjuvant, Matrix-M1, qNIV can be expected to offer several important advantages over existing licensed egg-derived seasonal influenza vaccines. These include avoidance of antigenic mismatch due to egg-adaptive mutations; induction of both broadly cross-reactive antibody responses against emerging drift variants of seasonal influenza viruses and potent cross-reactive polyfunctional CD4+ T cells. In a recent Phase 3 study [Shinde 2021] (qNIV-E-301; NCT04120194), qNIV with Matrix-M1 adjuvant demonstrated an acceptable safety profile, immunologic NI to IIV4 based on egg based HAI antibody responses against 4 vaccine-homologous strains, and 34% to 46% higher wild-type HAI antibody responses against 6 heterologous A(H3N2) strains. Additionally, qNIV with Matrix-M1 adjuvant showed a 126% to 189% improvement in various post-vaccination antigen-specific CD4+ T cell markers compared to that for IIV4.

In response to the COVID-19 pandemic caused by the emergence of SARS-CoV-2, Novavax is also developing SARS-CoV-2 rS with Matrix-M1 adjuvant for the prevention of COVID-19 in adults ≥ 18 years of age, using the same recombinant baculovirus and insect cell vaccine platform technology employed to produce qNIV. Both nonclinical and clinical data to date support continued clinical development of SARS-CoV-2 rS with Matrix-M1 adjuvant. In an ongoing Phase 1/2 study involving healthy adults in the US and Australia (2019nCoV-101; NCT04368988), 5 and 25 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant demonstrated an acceptable safety profile and was associated with strong neutralizing-antibody and Th1-based antigen-specific polyfunctional CD4+ T-cell responses in participants 18 to 84 years of age. In an ongoing 15,000-person Phase 3 efficacy study in healthy and medically stable adult participants 18 to 84 years of age in the UK (2019nCoV-302; NCT04583995), the overall efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was 89.7% (95% CI: 80.2, 94.6) and, in post hoc analyses, efficacy estimates for the B.1.1.7 (Alpha) variant and for the original strain were 86.3% and 96.4%, respectively. In an ongoing 4,400-person Phase 2b efficacy study in healthy HIV-negative adult participants 18 to 84 years of age and medically stable HIV-positive adult participants 18 to 64 years of age in South Africa (2019nCoV-501; NCT04533399) conducted during a period of > 94% B.1.351 (Beta) variant virus circulation, the efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant in all study participants was 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) in participants who were HIV-negative. In an ongoing 30,000-person Phase 3 efficacy study in healthy and medically stable adult participants ≥ 18 years of age in the US, Mexico, and Puerto Rico, the overall efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was 90.4% (95% CI: 82.9, 94.6). Across all clinical studies conducted to date, SARS-CoV-2 rS with Matrix-M1 adjuvant has continued to demonstrate good tolerability and an acceptable safety profile.

Given the ongoing emergence of antigenic variants of SARS-CoV-2, some of which appear to partially or completely escape naturally acquired or vaccine-derived immunity to ancestral virus, it appears increasingly likely that SARS-CoV-2 will continue to circulate for the foreseeable future, potentially in a seasonally recurrent pattern consistent with other seasonal human

coronaviruses. In the setting of potential future seasonal circulation of SARS-CoV-2, the continued emergence of antigenic drift variants, and the possible waning of neutralizing antibody responses in 6 to 12 months following SARS-CoV-2 vaccination or infection, an annual booster dose of a SARS-CoV-2 vaccine, potentially with periodic strain updates, may be needed to confer ongoing protection against COVID-19 due to infection with circulating SARS-CoV-2 viruses.

The first full year of the COVID-19 global pandemic has witnessed little to no global circulation of other seasonally important viral respiratory pathogens such as influenza – likely due to unprecedented nature of non-pharmaceutical interventions and public health measures implemented globally to control the spread of SARS-CoV-2. Notwithstanding, we are likely to observe a rebound and return of seasonal circulation of influenza viruses in the upcoming Northern and Southern Hemisphere winters with continued easing of pandemic restrictions and a gradual return pre-pandemic life.

In anticipation of a future need to immunize against both SARS-CoV-2 and influenza virus in advance of the winter transmission season, Novavax is undertaking development of an ICC (ie, qNIV and SARS-CoV-2 rS with Matrix^{-}M1 adjuvant). ICC vaccines, adjuvanted with Matrix-M1, have been studied in ferrets and hamsters. In ferrets, HAI antibody responses to all 4 HAs a showed minimal dose response and no negative effect of co-administration with SARS-CoV-2 rS and Matrix-M1 adjuvant and human angiotensin-converting enzyme 2 (hACE2) binding inhibition antibody responses to rS were slightly lower, but not significantly different, in the combined vaccine group relative to the monovalent SARS-CoV-2 rS with Matrix^{-}M1 adjuvant recipients. In hamsters, for each influenza strain examined, HAI titers and virus neutralization titers showed no clear dose-response and were comparable with or without SARS-CoV-2 rS with Matrix^{-}M1 adjuvant co-administration, anti-rS immunoglobulin G (IgG) levels induced by SARS-CoV-2 rS with Matrix^{-}M1 adjuvant showed no significant impact of influenza vaccine co-administration, and hACE2 binding inhibiting antibodies were slightly, albeit not significantly, lower in animals receiving the combined vaccines. Thus, co-administration with qNIV had no detectable effect on the potent protective efficacy of the SARS-CoV-2 rS with Matrix^{-}M1 adjuvant. An ICC vaccine would address 2 major vaccine-preventable diseases with a single vaccination approach. The initial target population for ICC vaccine development is older adults because this population bears a disproportionate burden of morbidity and mortality due to both influenza and COVID-19.

The purpose of this Phase 1/2 study is to evaluate the safety and immunogenicity of multiple formulations of ICC vaccines in older adults. The main objective of the study is to identify one or more optimal dose levels of HA and rS antigens administered as a combination vaccine, which minimize both antigen doses and manage any immunologic interference, using a DoE modeling approach.

3 OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the safety and immunogenicity of multiple formulations of ICC vaccines in older adults. As a primary objective, the study is designed to examine the hypothesis that ICC investigational vaccines will have comparable safety and tolerability profiles to those of the reference formulations.

Study participants in Vaccine Groups A through P will receive 2 injections of vaccine, the first dose on Day 0 and the second dose on Day 56; participants in Vaccine Group O will receive an additional IM dose of 5 µg SARS CoV-2 rS with 50 µg Matrix-M1 adjuvant on Day 70 to ensure this group received 2 doses of COVID-19 vaccine. A total of 14 formulations of ICC vaccine (comprising 12 unique formulations and 2 pairs of duplicated formulations) and 2 reference vaccines, will be administered in this study.

The primary goal of this study is to identify one or more optimal dose levels of HA and rS antigens administered as a combination vaccine, which minimize both antigen doses and manage any immunologic interference, using a DoE modeling approach. An overview of all study objectives and endpoints in provided in

Table 2 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
Primary Safety	To describe the tolerability and safety profiles associated with the receipt of the multiple vaccine formulations/regimens included in the study. Safety profiles will include: • Solicited AEs over 7 days after each of the first and second doses (including immediate AEs in the 30 minutes after dosing), to encompass both local injection site symptoms/signs and systemic symptoms/signs. • Unsolicited AEs over 70 days after the first dose. • MAAEs, SAEs, and AESIs over 6 months (approximately 182 days) after first dose.	• Numbers and percentages (with 95% CIs) of participants with solicited local and systemic AEs over the 7 days post-injection after first and second doses. • Proportions of participants reporting all AEs, solicited and unsolicited over 70 days after first dose. • Proportions of participants with MAAEs, SAEs, and AESIs will be collected for 6 months after the first dose.
Secondary Immunogenicity	To describe the immune response to immunization with various vaccine formulations/regimens at approximately Day 28 (post-first dose), Day 56, and Day 70 (post-second dose), and other follow-up time points, in terms of the: • Influenza HAI antibody responses (assayed with wild-type VLP reagents) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain	HAI antibody titers specific for the HA receptor binding domains of vaccine-homologous A and B strain(s), and antigenically drifted influenza strains. Derived/calculated endpoints based on these data will include: • GMT, defined as the antilog of the mean of the log-transformed HAI titers on Days 56, 70, and other follow-up time points. • $GMFR_{Post/Pre}$ – defined as the within group ratio of post-vaccination to

Table 2 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
	• Influenza MN antibody responses (assayed with wild-type virus) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain • SARS-CoV-2 anti-S IgG antibody responses to vaccine homologous virus antigen. Cross-reactive responses to virus variants may be assessed if available. • SARS-CoV-2 neutralizing antibody responses to vaccine homologous virus. Cross-reactive responses to virus variants may be assessed if available.	pre-vaccination (Day 0) HAI GMTs, within the same vaccine group on Days 56, 70, and other follow-up time points. • SCR – defined as proportion of participants in a given treatment group with either a baseline reciprocal (Day 0) titer of < 10 and a post-vaccination reciprocal titer ≥ 40, or a baseline reciprocal (Day 0) titer of ≥ 10 and a post-vaccination titer ≥ 4-fold higher than the baseline titer as measured on Days 56, 70, and other follow-up time points. • SPR – defined as the proportion of participants with a reciprocal HAI titer ≥ 40 on Days 56, 70, and other follow-up time points. • GMTR between select treatment arms at Days 56, 70, and other follow-up time points post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). MN_{50} antibody responses: neutralizing antibody titers specific to vaccine homologous wild-type A and B strain(s) and/or antigenically drifted influenza strains, as measured by a MN assay. Derived/ calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to HAI antibodies described above. IgG geometric mean ELISA unit concentrations (EU/mL) to the SARS-CoV-2 S protein from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/calculated endpoints for GMEU, GMFR, and SCR and GMEUR will be defined in manner similar to that for HAI antibodies described above.
		MN_{50} GMTs to the SARS-CoV-2 from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/ calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to that for HAI antibodies described above.

Table 2 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
	To determine one or more optimal dose levels of HA and rS antigens delivered in combination that maximize HAI antibody and anti-S antibody responses using a DoE modeling approach.	Post-vaccination time point HAI and anti-S antibody responses (eg, ratio of post-vaccination to pre-vaccination antibody levels) used to construct separate models of HAI and anti-S responses, respectively, to assess primary effects of each antigen's dose level and interactive effects between dose levels of the 2 antigens. Modeled responses in turn used to optimize dose levels of each antigen in relation to the other to maximize HAI and anti-S antibody responses.
Exploratory Immunogenicity	To describe the CMI responses to the various formulations/regimens in terms of peripheral blood CD4+ T cells which elaborate one or more cytokines or activation markers (IL-2, TNFα, IFNγ, or CD40L) in response to in-vitro stimulation with either strain-specific HAs and/or rS. Other markers of CMI may be measured. Due to the laborious nature of the CMI assays, they will be performed on all participants drawn from a limited number of preselected sites and results may be reported as an addendum to the main clinical study report. (Note: multiple informative strains may be tested in informative random subsets of participants)	Counts and/or proportions of Days 0, 7, 63, and 182 peripheral blood effector memory T-cell populations that secrete/express one or more of IL-2, CD40L, IFNγ, and TNFα cytokines following in-vitro restimulation with strain specific HAs and/or rS in participants selected for CMI response monitoring. Counts and/or proportions of additional markers of CMI as appropriate.
	To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs	Additional endpoints to evaluate immune responses may be developed based on the assays used.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CD40L = CD40 ligand; CI = confidence interval; CMI = cell-medicated immunity; DoE = Design of Experiments; ELISA = enzyme-linked immunosorbent assay; EU = ELISA unit; GMEU = geometric mean ELISA unit; GMEUR = geometric mean ELISA unit ratio; GMFR = geometric mean fold rise; GMT = geometric mean titer; GMTR = geometric mean titer ratio; HA = hemagglutinin; HAI = hemagglutination inhibition; IgG = immunoglobulin G; IL = interleukin; IFNγ = interferon gamma; MAAE = medically attended adverse event; MN = microneutralization; rS = recombinant spike protein; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SPR = seroprotection rate; TNFα = tumor necrosis factor alpha; VLP = virus-like particle.

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Table 2 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
Primary Safety	To describe the tolerability and safety profiles associated with the receipt of the multiple vaccine formulations/regimens included in the study. Safety profiles will include: • Solicited AEs over 7 days after each of the first and second doses (including immediate AEs in the 30 minutes after dosing), to encompass both local injection site symptoms/signs and systemic symptoms/signs. • Unsolicited AEs over 70 days after the first dose. • MAAEs, SAEs, and AESIs over 6 months (approximately 182 days) after first dose.	• Numbers and percentages (with 95% CIs) of participants with solicited local and systemic AEs over the 7 days post-injection after first and second doses. • Proportions of participants reporting all AEs, solicited and unsolicited over 70 days after first dose. • Proportions of participants with MAAEs, SAEs, and AESIs will be collected for 6 months after the first dose.
Secondary Immunogenicity	To describe the immune response to immunization with various vaccine formulations/regimens at approximately Day 28 (post-first dose), Day 56, and Day 70 (post-second dose), and other follow-up time points, in terms of the: • Influenza HAI antibody responses (assayed with wild-type VLP reagents) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain • Influenza MN antibody responses (assayed with wild-type virus) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain • SARS-CoV-2 anti-S IgG antibody responses to vaccine homologous virus antigen. Cross-reactive responses to virus variants may be assessed if available. • SARS-CoV-2 neutralizing antibody responses to vaccine homologous virus. Cross-reactive responses to virus variants may be assessed if available.	HAI antibody titers specific for the HA receptor binding domains of vaccine-homologous A and B strain(s), and antigenically drifted influenza strains. Derived/calculated endpoints based on these data will include: • GMT, defined as the antilog of the mean of the log-transformed HAI titers on Days 56, 70, and other follow-up time points. • $GMFR_{Post/Pre}$ – defined as the within group ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs, within the same vaccine group on Days 56, 70, and other follow-up time points. • SCR – defined as proportion of participants in a given treatment group with either a baseline reciprocal (Day 0) titer of < 10 and a post-vaccination reciprocal titer ≥ 40, or a baseline reciprocal (Day 0) titer of ≥ 10 and a post-vaccination titer $\geq$ 4-fold higher than the baseline titer as measured on Days 56, 70, and other follow-up time points. • SPR – defined as the proportion of participants with a reciprocal HAI titer ≥ 40 on Days 56, 70, and other follow-up time points. • GMTR between select treatment arms at Days 56, 70, and other follow-up time

Table 2 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
		points post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). MN_{50} antibody responses: neutralizing antibody titers specific to vaccine homologous wild-type A and B strain(s) and/or antigenically drifted influenza strains, as measured by a MN assay. Derived/ calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to HAI antibodies described above. IgG geometric mean ELISA unit concentrations (EU/mL) to the SARS-CoV-2 S protein from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/calculated endpoints for GMEU, GMFR, and SCR and GMEUR will be defined in manner similar to that for HAI antibodies described above.
		MN_{50} GMTs to the SARS-CoV-2 from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/ calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to that for HAI antibodies described above.
	To determine one or more optimal dose levels of HA and rS antigens delivered in combination that maximize HAI antibody and anti-S antibody responses using a DoE modeling approach.	Post-vaccination time point HAI and anti-S antibody responses (eg, ratio of post-vaccination to pre-vaccination antibody levels) used to construct separate models of HAI and anti-S responses, respectively, to assess primary effects of each antigen's dose level and interactive effects between dose levels of the 2 antigens. Modeled responses in turn used to optimize dose levels of each antigen in relation to the other to maximize HAI and anti-S antibody responses.
Exploratory Immunogenicity	To describe the CMI responses to the various formulations/regimens in terms of peripheral blood CD4+ T cells which elaborate one or more cytokines or activation markers (IL-2, TNFα, IFNγ, or CD40L) in response to in-vitro stimulation with either strain-specific HAs and/or rS. Other markers of CMI may be measured. Due to the laborious nature of the CMI	Counts and/or proportions of Days 0, 7, 63, and 182 peripheral blood effector memory T-cell populations that secrete/express one or more of IL-2, CD40L, IFNγ, and TNFα cytokines following in-vitro restimulation with strain specific HAs and/or rS in participants selected for CMI response

Table 2 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

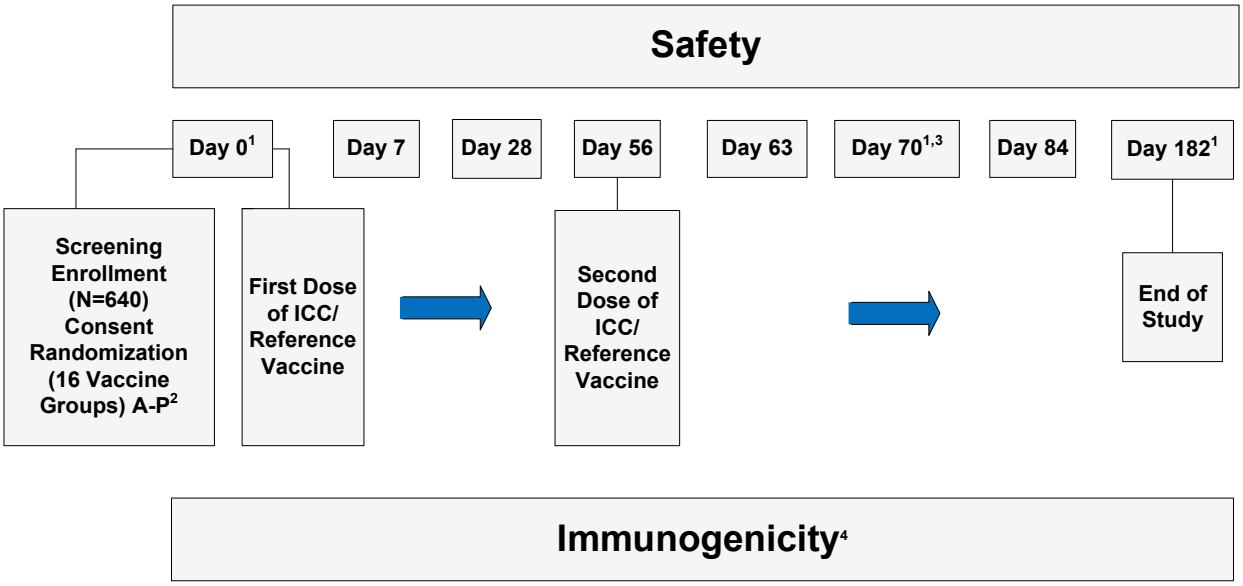
Tier	Objectives	Endpoints
	assays, they will be performed on all participants drawn from a limited number of preselected sites and results may be reported as an addendum to the main clinical study report. (Note: multiple informative strains may be tested in informative random subsets of participants)	monitoring. Counts and/or proportions of additional markers of CMI as appropriate.
	To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs	Additional endpoints to evaluate immune responses may be developed based on the assays used.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CD40L = CD40 ligand; CI = confidence interval; CMI = cell-medicated immunity; DoE = Design of Experiments; ELISA = enzyme-linked immunosorbent assay; EU = ELISA unit; GMEU = geometric mean ELISA unit; GMEUR = geometric mean ELISA unit ratio; GMFR = geometric mean fold rise; GMT = geometric mean titer; GMTR = geometric mean titer ratio; HA = hemagglutinin; HAI = hemagglutination inhibition; IgG = immunoglobulin G; IL = interleukin; IFNγ = interferon gamma; MAAE = medically attended adverse event; MN = microneutralization; rS = recombinant spike protein; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SPR = seroprotection rate; TNFα = tumor necrosis factor alpha; VLP = virus-like particle.

4 STUDY PLAN

4.1 Study Schematic

Figure 1 Flow Diagram for Study 2019nCoV-ICC-E-101



Abbreviations: COVID-19 = coronavirus disease 2019; HAI = hemagglutination inhibition; ICC = influenza COVID-19 combination; NP = nucleoprotein; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SOE = Schedule of Events.

1. SARS-CoV-2 anti-NP antibodies to be assessed.
2. Consisting of 14 formulations of ICC vaccine (comprising 12 unique formulations and 2 pairs of duplicated formulations) and 2 reference vaccines.
3. Participants from Vaccine Group O only will receive a third dose of COVID-19 vaccine consisting of 5 µg SARS-CoV-2 rS nanoparticle vaccine and 50 µg Matrix-M1 adjuvant at Day 70.
4. PBMCs will be harvested for SARS-CoV-2 spike-specific T-cell counts on Days 0, 7, 63, and 182. See the SOE for the timing of HAI serology and the remaining immunogenicity assessments.

4.2 Study Design

This is a randomized, observer-blinded, Phase 1/2 study evaluating the safety and immunogenicity of a quadrivalent HA nanoparticle influenza and SARS-CoV-2 rS nanoparticle combination vaccine with Matrix-M1 adjuvant; this combination is referred to as ICC vaccine.

The study will enroll approximately 640 healthy adult male and female participants 50 to 70 years of age, inclusive, targeting participants who are baseline seropositive (either previously infected with SARS-CoV-2 ≥ 8 weeks prior to enrollment, or have been previously immunized against SARS-CoV-2 with a completed regimen of an authorized vaccine at ≥ 8 weeks prior to enrollment). Randomization will be stratified on age ≥ 50 to <60 or ≥ 60 to ≤ 70 years to distribute the proportions of each age stratum evenly across vaccine groups.

Participants will be simultaneously enrolled and randomly assigned equally into 1 of 16 vaccine groups as per the Study Deign Table (Table 3). The doses of the influenza and SARS-CoV-2 rS components included in the various vaccine groups have been selected based on the known performance of the antigens separately and the ability to obtain response data over a broad range of mixtures. These data will in turn be used in statistical modeling to predict one, or a few, optimal formulations for further clinical testing. All participants in Vaccine Groups A through P will receive 2 IM doses of the investigational vaccine, the first on Day 0 and the second on

Day 56 + 5 days) and remain on study for immunogenicity and safety data collection through Day 182 (EoS); participants in Vaccine Group O will receive an additional IM dose of 5 µg SARS CoV-2 rS with 50 µg Matrix-M1 adjuvant on Day 70 to ensure this group received 2 doses of COVID-19 vaccine. The key informative immunogenicity time points for antibody responses will be Days 0 and 70 (14 days post-second dose), and for CMI will be Days 0 and 63 (or 7 days following the second dose). Reference formulations of 60 µg HA/strain qNIV with 75 µg Matrix-M1 adjuvant and 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 will be included as vaccine groups to benchmark optimal immune responses to each antigen administered as a standalone vaccine. The study will enable selection of one or more optimized ICC vaccine formulations (through DoE response surface modeling) to advance into further development for dose/formulation confirmation in a future Phase 2 study.

The number of participants and dosing regimens are presented in the Study Design Table (Table 3):

Table 3 Number of Participants and Dosing Regimens

Vaccine Group[1]	N[2]	Day 0			Day 56 (+ 5 days)		
		HA Dose per Strain, µg	rS, µg	Matrix-M1, µg	HA Dose per Strain, µg	rS, µg	Matrix-M1, µg
ICC vaccine formulations							
A	40	60	22.5	50	60	22.5	50
B	40	10	2.5	50	10	2.5	50
C	40	60	22.5	50	60	22.5	50
D	40	10	7.5	50	10	7.5	50
E	40	10	22.5	50	10	22.5	50
F	40	35	7.5	50	35	7.5	50
G	40	5	22.5	50	5	22.5	50
H	40	60	2.5	50	60	2.5	50
I	40	5	7.5	50	5	7.5	50
J	40	5	2.5	50	5	2.5	50
K	40	35	22.5	50	35	22.5	50
L	40	35	2.5	50	35	2.5	50
M	40	60	7.5	50	60	7.5	50
N	40	60	2.5	50	60	2.5	50
qNIV with Matrix-M1 adjuvant reference formulation							
O[3]	40	60	0	75	0	5	50
SARS-CoV-2 rS with Matrix-M1 adjuvant reference							
P	40	0	5	50	0	5	50
Total	640						

Abbreviations: COVID-19 = coronavirus disease 2019; HA = hemagglutinin; rS = recombinant spike protein; qNIV = quadrivalent hemagglutinin nanoparticle influenza vaccine; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Antigen and adjuvant dose values are nominal and reflect target doses. Details of the final product in-clinic mixing scheme, the actual content of doses achieved by the in-clinic mixing of drug product lots, and injected volumes used are provided in the Study Pharmacy Manual.
2. Due to uncertainties in the pace of national SARS-CoV-2 vaccine deployment and evolving COVID-19 epidemic conditions, it is acknowledged that the targeted sample size for the study may be revised in response to the impact these evolving conditions may have on enrollment.
3. Participants from Vaccine Group O will receive an additional dose of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 at Day 70.

4.3 Design Rationale

This randomized, observer-blinded, Phase 1/2 study is designed to evaluate the safety and immunogenicity of multiple formulations of ICC vaccines in older adults.

Reference formulations of 60 µg HA/strain qNIV with 75 µg Matrix-M1 adjuvant and 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 will be included as study arms to benchmark optimal immune responses to each antigen administered as a standalone vaccine. The study will enable selection of one or more optimized ICC formulations (through DoE response surface modeling) to advance into further development for dose/formulation confirmation in a future Phase 2 study.

The HA and rS antigen levels to be studied (and input for the DoE modeling) were selected based on benefit-risk assessment, accounting for past safety, immunogenicity, and manufacturing experience, while simultaneously allowing study of the maximum/widest antigen ranges possible. The design was constrained by the need for simplicity (keeping antigen doses 1 and 2 the same), both to minimize human error during administration of the eventual selected formulation/presentation, and to reduce manufacturing complexity. Four dose levels of HA/strain were chosen for this study: 5, 10, 35, and 60 µg HA/strain. The choice of the lowest HA/strain was informed by the lowest dose likely to induce an adequate HAI antibody response, and the choice of the highest dose was informed by the dose shown to induce a robust HAI antibody and antigen-specific CD4+ T-cell response in the prior Phase 3 study of qNIV with Matrix-M1. The two intermediate dose levels of HA/strain were selected by DoE design software which selects ideal intermediate dose levels to allow optimal DoE modeling. Likewise, 3 dose levels of SARS-CoV-2 rS were chosen for this study: 2.5, 7.5, and 22.5 µg. The choice of the lowest rS dose was informed by the lowest dose likely to induce an adequate anti-S antibody response, and the choice of the highest dose was informed by the highest dose assessed in older adults in the Phase 1/2 study of SARS-CoV-2 rS with Matrix-M1 adjuvant. The one intermediate dose level of rS was selected by DoE design software to again allow optimal DoE modeling. The Matrix-M1 dose will be held constant at 50 µg in each of the ICC vaccine groups and this selection is informed by the extensive safety and immunogenicity experience across multiple Matrix-M1 adjuvanted vaccine programs (SARS-CoV-2 rS, RSV, and Ebola virus vaccines), which collectively indicate that 50 µg dose of Matrix-M1 provides an optimal balance of immunogenicity and tolerability when used in a 2-dose regimen.

This study specifies that a full two-dose regimen of SARS-CoV-2 rS with Matrix-M1 adjuvant be administered to all participants despite their seropositive status at baseline. This is based on the observations of the Sponsor and others that a completed immunization regimen may provide superior protection against variant virus disease than prior infection. For Vaccine Group O, the second dose of SARS-CoV-2 rS will be administered on Day 70. Since no other vaccine groups will be dosed on Day 70, study site personnel and participants will be unblinded to their

treatment assignment. The Sponsor acknowledges this partial unblinding and any potential bias that may result.

5 POPULATON

5.1 Recruitment

Approximately 1,000 potential participants will be screened in order to meet the goal of 640 randomized participants. Participants will be screened across approximately 4 to 12 different study sites located in Australia.

5.2 Definitions

Participants officially enter the Screening Period following provision of informed consent.

A screen failure is a consented participant who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may not be rescreened.

An enrolled participant is one who has been deemed eligible and has been assigned to a treatment group.

5.3 Inclusion Criteria

To be included in this study, each individual must satisfy all of the following criteria:

1. Healthy, medically stable adult male or females ≥ 50 to ≤ 70 years of age at screening.
2. Willing and able to give informed consent prior to study enrollment.
3. Able to attend study visits, comply with study requirements, and provide reliable and complete reports of AEs.
4. Participants must have been baseline seropositive to SARS-CoV-2 defined as either:

   - Having completed a primary vaccination series against SARS-CoV-2 with an authorized COVID-19 vaccine with receipt of second/final dose of authorized vaccine ≥ 8 weeks prior to enrollment (first study vaccination).

     OR

   - Previously infected with SARS-CoV-2 ≥ 8 weeks prior to enrollment (first study vaccination).

     Note: Baseline SARS-CoV-2 serostatus determination at screening will be based on vaccination documentation (eg, vaccination card or vaccination registry) or participants' report of a previous SARS-CoV-2 infection.

5. Women of childbearing potential (defined as any female participant who is NOT surgically sterile [ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months]) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through the end of the study OR agree to consistently use a medically acceptable method of contraception listed below from at least 28 days prior to enrollment and through the end of the study.
   a. Condoms (male or female) with spermicide (if acceptable in country)
   b. Diaphragm with spermicide

c. Cervical cap with spermicide
d. Intrauterine device
e. Oral or patch contraceptives
f. Norplant®, Depo-Provera®, or other in-country regulatory approved contraceptive method that is designed to protect against pregnancy
g. Abstinence, as a form of contraception, is acceptable if in line with the participant's lifestyle

Note: Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. These procedures and laboratory test results must be confirmed by physical examination, by subject recall of specific date and hospital/facility of procedure, or by medical documentation of said procedure.

6. Participants must be healthy and medically stable, as determined by the investigator (based on review of health status, vital signs [to include body temperature], medical history, and targeted physical examination [to include body weight]). Participants must have a body mass index (BMI) of 17 to 34 kg/m^2, inclusive, at screening. Vital signs must be within medically acceptable ranges prior to the first vaccination.
7. Participants must agree to not participate in any other SARS-CoV-2 or influenza prevention or treatment studies for the duration of the study. **Note**: For participants who become hospitalized with COVID-19, participation in investigational treatment studies is permitted.

5.4 Exclusion Criteria

If an individual meets any of the following criteria, he or she is ineligible for this study:

1. Any ongoing, symptomatic acute or chronic illness requiring medical or surgical care.
   - Asymptomatic chronic conditions or findings (eg, mild hypertension, dyslipidemia) that are <u>not</u> associated with evidence of end-organ damage are **not** exclusionary provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time-course of this study), in the opinion of the investigator.
   - Acute or chronic illnesses or condition which may be reasonably predicted to become symptomatic if treatment were withdrawn or interrupted are exclusionary, even if stable.
   - Acute or chronic illnesses reasonably expected to be associated with increased risks in the event of influenza or SARS-CoV-2 infection (eg, cardio-pulmonary diseases, diabetes mellitus, renal or hepatic dysfunction, hemoglobinopathies) are exclusionary, even if stable.
     Note: Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (see exclusion criteria 2, 6, 8, 9, 14).
2. Participation in research involving an investigational product (drug / biologic / device) within 90 days before planned date of first injection.
3. Use of COVID-19 prophylactic or treatment monoclonal antibodies or antibody cocktails within 90 days prior to planned date of first injection.

4. History of a serious reaction to a prior influenza vaccination or known allergy to constituents of influenza vaccines - including egg proteins - or polysorbate 80; or any known allergies to products contained in the investigational product.
5. Any history of anaphylaxis to any prior vaccine.
6. History of Guillain-Barré Syndrome within 6 weeks following a previous influenza vaccine.
7. Receipt of any vaccine in the 4 weeks preceding the study vaccination and any influenza vaccine within 2 months preceding the study vaccination. Note: Routine vaccinations will not be allowed until after study Day 70.
8. Any known or suspected autoimmune or immunosuppressive illness, congenital or acquired, based on medical history and/or physical examination.
9. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study vaccines. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
10. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study vaccine or during the study.
11. Active cancer (malignancy) therapy within 3 years prior to first study vaccination (with the exception of adequately treated non-melanomatous skin carcinoma or lentigo maligna and uterine cervical carcinoma in situ without evidence of disease, at the discretion of the investigator).
12. Participants who are breastfeeding, pregnant, or who plan to become pregnant prior by the EoS.
13. Known disturbance of coagulation.
14. Suspected or known history of alcohol abuse or drug addiction within 2 years prior to the first trial vaccine dose that, in the opinion of the investigator, might interfere with protocol compliance.
15. Acute disease at the time of enrollment (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature > 38.0°C, on the planned day of vaccine administration).
16. Any condition that in the opinion of the investigator would pose a health risk to the participant if enrolled or could interfere with evaluation of the vaccine or interpretation of study results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).
17. Study team member or immediate family member of any study team member (inclusive of Sponsor, Contract Research Organization, and study site personnel involved in the conduct or planning of the study).

5.5 Other Considerations for Eligibility Criteria

Participants meeting any of the following criteria may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment.

- Respiratory symptoms in the past 3 days (ie, cough, sore throat, difficulty breathing). Participant may be vaccinated once all symptoms have been resolved for > 3 days. Out-of-window study vaccination is allowed for this reason (see NOTE).

- Temperature of > 38°C within 24 hours of planned study vaccination (site measured or participant measured). Participant may be vaccinated once the fever has resolved and there has not been any temperature measured as being > 38°C for > 3 days. Out-of-window study vaccination is allowed for this reason (see NOTE).

  Note: PCR testing for SARS-CoV-2 is likely to be indicated for either of the above reasons or if COVID-19 is suspected based on other symptoms or for potential exposure to SARS-CoV-2 infection through close contacts or based on local epidemiology.

Any participant who is otherwise eligible with a blood pressure of ≥ 151/96 mmHg may be retested onsite several times over a 3-hour interval to achieve a lower blood pressure. If the blood pressure remains ≥ 151/96 mmHg, study vaccination should be deferred for a later date if the baseline blood pressure is found to be < 151/96 mmHg.

NOTE: Participants should be free of acute illness (defined as the presence of a moderate or severe illness in the clinical judgment of the investigator) with or without fever, or an oral temperature ≥ 38.0°C in order to receive the test article injection. Participants presenting with an acute illness on screening/Day 0 may return to the trial site within the next 7 days to receive their injection provided symptoms have resolved and study enrollment is still open; baseline Day 0 serology should be performed on the day of actual Day 0 dosing. “Day 0” should indicate the actual day that Day 0 dosing occurs.

6 STUDY CONDUCT

Study conduct and procedures will not vary for Vaccine Groups A through N or P; participants in Vaccine Group O will receive an additional IM dose of 5 µg SARS CoV-2 rS with 50 µg Matrix-M1 adjuvant on Day 70 to ensure this group received 2 doses of COVID-19 vaccine. Note that because Vaccine Group O is the only treatment group receiving a vaccine at Day 70, Vaccine Group O participants and site staff will be unblinded to participant's treatment status from Day 70 onwards. The Sponsor recognizes this partial unblinding and assesses it as having minor impact to the data.

Due to the ongoing pandemic, national regulatory and local HREC/Institutional Review Board (IRB) and public health guidance may be applied if study participants are not able to attend a study site for protocol-specified visits. Safety assessments may be conducted at an alternative location (eg, local laboratories or home visits), via telephone, email, or text message contact. Blood samples may be drawn using local phlebotomy services, home health, or other modalities if site visits cannot occur. Vaccination visits must have adequate oversight for issues associated with immediate severe reactions but may need to occur outside of the study site depending on the pandemic situation (eg, home vaccinations).

Scheduled study visits will occur for Days 0, 7, 28, 56, 63, 70, 84, and 182 (EoS):

- Screening Visit (Day 0): Randomization and first vaccine administration.
- Day 7: Safety and immunogenicity follow-up for all participants.
- Day 28: Safety and immunogenicity follow-up for all participants.
- Day 56: Second vaccine administration.
- Day 63: Safety and immunogenicity follow-up for all participants.
- Day 70: Third SARS-CoV-2 rS vaccine administration for Vaccine Group O only and safety and immunogenicity follow-up for all participants.
- Day 84: Safety and immunogenicity follow-up for all participants.
- Day 182: EoS visit for all participants via site visit. These procedures should also be conducted for all participants upon early termination.

On vaccination days (Day 0 and Day 56 for Vaccine Groups A through P and Day 70 for Vaccine Group O), participants will remain in the clinic or under study staff observation for at least 30 minutes post-vaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions. Participants will utilize an electronic participant-reported outcome diary application (eDiary) to record reactogenicity following vaccination (on Day 0 and Day 56). All participants will record reactogenicity on the day of vaccination and for an additional 6 days after vaccination (ie, Day 0 through Day 6, inclusive; and Day 56 through Day 62, inclusive). Should any reactogenicity event extend beyond 6 days after vaccination (toxicity grade ≥ 1), then it will be recorded as an AE with start dates of either Day 7 or Day 63 (the first day after completion of the participant solicited symptom eDiary) and followed to resolution per ICH guidelines for dataset capture. The toxicology grading scale implemented in the eDiary for the study is included in Appendix 2 (Table 7).

The toxicology grading scale implemented in the electronic participant-reported outcome diary application (eDiary) for the study is included in in Appendix 2.

A complete description of study procedures is provided in Section 6.1, and a summary SOE is provided in Table 1.

Due to the ongoing pandemic, national regulatory and local HREC/Institutional Review Board (IRB) and public health guidance may be applied if study participants are not able to attend a study site for protocol-specified visits. Safety assessments may be conducted at an alternative location (eg, local laboratories or home visits), via telephone, email, or text message contact. Blood samples may be collected using local phlebotomy services, home health, or other modalities if site visits cannot occur. Vaccination visits must have adequate oversight for issues associated with immediate severe reactions but may need to occur outside of the study site depending on the pandemic situation (eg, home vaccinations).

6.1 Study Procedures

6.1.1 Screening and Day 0 Visit

The Screening visit and Day 0 visit will be combined. The following procedures will be performed on Day 0.

- Written informed consent will be obtained in conformance with Section 10.3 of this protocol.
- Review of medical history, including prior and concomitant medical conditions, recent vaccinations (≥ 90 days) and COVID-19 vaccination or therapy, and significant surgical procedures.
- Inclusion and exclusion criteria review via participant discussion and medical history review consistent with Section 5. Specific exclusions to study vaccination will be assessed before any vaccination. Waivers to enrolling participants with exclusions will not be given.
- Demographics, including date of birth (day, month, and year), sex, race, ethnicity, weight, height, and BMI (derived).
- Prior and concomitant medications, including recent and current medications at the time of screening to be reviewed to ensure eligibility criteria are fulfilled (see definitions in Section 0).
- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Urine pregnancy test for women of childbearing potential only. A positive urine pregnancy test at Screening will result in screen failure.
  - A serum follicle-stimulating hormone test may be performed at screening to confirm postmenopausal status if directed by investigator request.
- Physical examination to include height and weight; HEENT, neck, lungs, heart, cardiovascular, abdomen, and musculoskeletal system/extremities to allow for study vaccination.
- Randomization.
- Blood sampling for SARS-CoV-2 (anti-NP) antibodies.

- Blood sampling for SARS-CoV-2 immunogenicity (ELISA for anti-rS-protein serology), HAI serology, and influenza virus MN_{50} assay.
- Blood sampling for SARS-CoV-2 MN_{50} assay.
- Assessment of unsolicited AEs, MAAEs, SAEs, and AESIs (including PIMMC).
- CMI Subset Participants ONLY: Blood sampling for CMI (as measured by ELISpot and/or intracellular cytokine staining (ICCS) and assay for cytokines IL-2, TNFα, and IFNγ.

At the time of first study vaccination, the following procedures will be conducted for all randomly assigned participants:

- Alcohol swab cleansing of the injection sites for study vaccine administration.
- Vaccination with study vaccine as an IM injection.
- Monitoring for reactogenicity. Participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.

Following vaccination, participants will be trained to utilize an eDiary to record reactogenicity. All participants will record reactogenicity on the day of vaccination and for an additional 6 days after vaccination (ie, Day 0 through Day 6, inclusive). Study site personnel will regularly review the eDiary for completeness. Should any reactogenicity event extend beyond 6 days after vaccination (toxicity grade ≥ 1), then it will be recorded as an AE with start dates of Day 7 (the first day after completion of the participant solicited symptom eDiary) and followed to resolution per ICH guidelines for dataset capture. The toxicology grading scale implemented in the eDiary for the study is included in Appendix 2 (Table 7).

6.1.1.1 Day 7 (+3 Days)

- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Review prior/concomitant medications.
- Monitoring for reactogenicity; review of eDiary.
- Symptom-directed (targeted) physical examination.
- Assessment of unsolicited AEs, MAAEs, SAEs, and AESIs (including PIMMCs).
- CMI Subset Participants ONLY: Blood sampling for CMI (as measured by ICCS and/or ELISpot) assay for cytokines IL-2, TNFα, CD40L, and IFNγ.

6.1.1.2 Day 28 (+ 3 Days)

- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Review prior/concomitant medications.
- Symptom-directed (targeted) physical examination.
- Blood sampling for SARS-CoV-2 immunogenicity (ELISA for anti-rS-protein serology), HAI serology, and influenza virus MN_{50} assay.
- Blood sampling for SARS-CoV-2 MN_{50} assay.
- Assessment of unsolicited AEs, MAAEs, SAEs, and AESIs (including PIMMCs).

6.1.1.3 Day 56 - Second Study Vaccination (+ 5 Days)

All participants with confirmed eligibility will have the following procedures performed prior to the second study vaccination:

- Prior and concomitant medications, including recent and current medications to be reviewed to ensure eligibility criteria are fulfilled (see definitions in Section 0).
- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Urine pregnancy test for women of childbearing potential only. A urine pregnancy test will be performed prior to each study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- Symptom-directed (targeted) physical examination.
- Blood sampling for SARS-CoV-2 immunogenicity (ELISA for anti-rS-protein serology), HAI serology, and influenza virus MN_{50} assay.
- Blood sampling for SARS-CoV-2 MN_{50} assay.
- Assessment of unsolicited AEs, MAAEs, SAEs, and AESIs (including PIMMC).

At the time of second study vaccination, the following procedures will be conducted for all randomly assigned participants:

- Alcohol swab cleansing of the injection sites for study vaccine administration
- Vaccination with study vaccine as an IM injection.
- Monitoring for reactogenicity; participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.

Following vaccination, participants will utilize an eDiary to record reactogenicity. All participants will record reactogenicity on the day of vaccination and for an additional 6 days after vaccination (ie, Day 56 through Day 62, inclusive). Study site personnel will regularly review the eDiary for completeness. Should any reactogenicity event extend beyond 6 days after vaccination (toxicity grade ≥ 1), then it will be recorded as an AE with start dates of Day 63 (the first day after completion of the participant solicited symptom eDiary) and followed to resolution per ICH guidelines for dataset capture. The toxicology grading scale implemented in the electronic diary for the study is included in Appendix 2 (Table 7).

6.1.2 Safety Follow-up Period

6.1.2.1 Day 63 – (+ 3 Days)

- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Prior and concomitant medications (see definitions in Section 0).
- Monitoring for reactogenicity; review of eDiary.
- Symptom-directed (targeted) physical examination.
- Assessment of unsolicited AEs, MAAEs, SAEs, and AESIs (including PIMMC).
- CMI Subset Participants ONLY: Blood sampling for CMI (as measured by ICCS and/or ELISpot) assay for cytokines IL-2, TNFα, CD40L, and IFNγ.

6.1.2.2 Day 70 – Third Study Vaccination Dose for Participants in Vaccine Group O and Follow-up Visit (+ 5 Days)

All participants will have the following procedures performed:

- Prior and concomitant medications (see definitions in Section 0).
- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Urine pregnancy test for women of childbearing potential only. A urine pregnancy test will be performed prior to each study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- Symptom-directed (targeted) physical examination
- Blood sampling for SARS-CoV-2 (anti-NP) antibodies
- Blood sampling for SARS-CoV-2 immunogenicity (ELISA for anti-rS-protein serology), HAI serology, and influenza virus MN_{50} assay.
- Blood sampling for SARS-CoV-2 MN_{50} assay.
- Assessment of unsolicited AEs, MAAEs, SAEs, and AESIs (including PIMMC).

At the time of third study vaccination for participants in Vaccine Group O, the following procedures will be conducted for all randomly assigned participants:

- Alcohol swab cleansing of the injection sites for study vaccine administration
- Vaccination with study vaccine as an IM injection.
- Participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.

6.1.2.3 Day 84 – Follow-up Visit (± 7 Days)

During this visit, the following procedures will be performed:

- Prior and concomitant medications (only concomitant medications taken for any MAAEs, SAEs, or AESIs (including PIMMCs) will be recorded) (see definitions in Section 0).
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Symptom-directed (targeted) physical examination.
- Blood sampling for SARS-CoV-2 immunogenicity (ELISA for anti-rS-protein serology), HAI serology, and influenza virus MN_{50} assay (testing performed at Novavax).
- Blood sampling for SARS-CoV-2 MN_{50} assay.
- Assessment of MAAEs, SAEs, and AESIs (including PIMMC).

6.1.3 End of Study

6.1.3.1 Day 182 – EoS Visit (± 14 Days)

During this EoS visit, the following procedures will be performed:

- Prior and concomitant medications (only concomitant medications taken for any MAAEs, SAEs, or AESIs (including PIMMCs) will be recorded) (see definitions in Section 0).
- Vital signs measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Symptom-directed (targeted) physical examination.
- Blood sampling for SARS-CoV-2 (anti-NP) antibodies.
- Blood sampling for SARS-CoV-2 (ELISA for anti-rS-protein serology), HAI serology, and influenza virus MN_{50} assay (testing performed by Novavax).
- Blood sampling for SARS-CoV-2 MN_{50} assay.
- Assessment of MAAEs, SAEs, and AESIs (including PIMMC).
- CMI Subset Participants ONLY: Blood sampling for CMI (as measured by ICCS and/or ELISpot) assay for cytokines IL-2, TNFα, CD40L, and IFNγ.
- Completion of the EoS form.

Also, at the EoS visit, it should be confirmed that no pregnancy has occurred in women of childbearing potential since the last contact.

6.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected before vaccination (Day 0) and at selected time points following vaccination (Table 1). As a secondary objective, serum HAI antibody response (assayed with wild-type VLP reagents) at Day 28 (post-first dose of trial vaccine), Day 56, and Day 70 (post-second dose of trial vaccine) and at other follow-up time points, against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain will be assessed. In addition, neutralizing antibody responses (assayed with wild-type virus) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain will be conducted. Serum (IgG) antibody responses (ELISA) for vaccine homologous SARS-CoV-2 rS antigen and cross-reactive virus variants, if available, will be conducted. CMI responses to the various formulations/regimens in terms of peripheral blood CD4+ T cells which elaborate one or more cytokines or activation markers (eg, IL-2, TNFα, IFNγ, or CD40L) produced after in vitro stimulation of peripheral blood mononuclear cells (PBMCs) will be assessed at selected time points in all participants at a selected subset of sites. Aliquots of all collected samples from this study may be retained for additional testing of antigens specific to influenza HA or SARS-CoV-2 (or related variants), or for assay development or qualification for other pathogens (excluding HIV) for a maximum of 25 years (starting from the date at which the last participant had the last study visit), unless local rules, regulations, or guidelines require different timeframes or different procedures, in accord with participant consent. Retained sera may also be used for clinical laboratory testing for safety if needed to evaluate an AE.

6.3 Discontinuation or Withdrawal

6.3.1 Individual Subjects

6.3.1.1 Treatment Discontinuation

The investigator will withhold further study vaccination from a participant in the study if the participant:

1. Is noncompliant with the protocol to an extent that, in the opinion of the investigator, jeopardizes the integrity of the study.
2. Experiences an SAE or intolerable AE(s) for which study vaccination is not advised by the investigator.
3. Becomes pregnant (discontinuation of further study vaccination required).
4. Receives an approved or deployed SARS-CoV-2 vaccine.

6.3.1.2 Withdrawal from Study

Participants are free to withdraw from the study at any time upon written request. Participant participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Participants may refuse further procedures (including study vaccination) but are encouraged to remain in the study for safety follow-up. In such cases where only safety is being conducted, participant contact could be managed via telemedicine contact (eg, telephone, web chat, video, FaceTime).

Vaccination with an approved or deployed SARS-CoV-2 vaccine alone will not require withdrawal from the study; and such subjects will be encouraged to continue their participation.

6.3.1.3 Replacement of Participants

Participants who withdraw, are withdrawn or terminated from this study, or are lost to follow up after signing the informed consent form (ICF) but prior to first study vaccination may be replaced. Participants who receive study vaccine and subsequently withdraw, are discontinued from further study vaccination, are terminated from the study, or are lost to follow-up will not be replaced.

6.3.1.4 Participants Lost to Follow-up

Whenever possible, any participant who withdraws from the study prematurely will undergo all EOS assessments. Any participant who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

All reasonable efforts, including contact of emergency contact, must be made to locate participants to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, text messages, faxes or emails (not performed on the same day), as well as a lack of response by the participant to one registered mail letter. All attempts should be documented in the participant's source documents and/or medical records. If it is determined that the participant has died, the study site

will use permissible local methods to obtain the date and cause of death and as much other information as can be obtained, including post-mortem reports.

The status of participants who fail to complete final assessments will be documented in the electronic case report form (eCRF). Data that would have been collected at subsequent visits will be considered missing.

6.4 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last study visit (including the EoS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

7 STUDY INTERVENTIONS

Each participant will receive 2 injections, one on each of study Days 0 and 56 in the same arm (except for participants in Group O who will receive a third injection at Day 70 – see Table 3). Treatments will comprise 1 of 16 regimens of investigational vaccines delivering either:

- One of 12 formulations of an ICC containing 1 of 4 dose levels of influenza HA protein (5, 10, 35, or 60 µg and 1 of 3 dose levels of SARS-CoV-2 rS protein (2.5, 7.5, or 22.5 µg) with Matrix-M1 adjuvant (50 µg); in a two-dose regimen (Vaccine Groups A-N); OR
- A reference formulation of SARS-CoV-2 rS (5 µg) nanoparticle vaccine with Matrix-M1 adjuvant (50 µg), in a two-dose regimen (Vaccine Group P); OR
- A reference formulation of qNIV (60 µg HA per strain) vaccine with Matrix-M1 adjuvant (75 µg), followed by a reference formulation of SARS-CoV-2 rS (5 µg) nanoparticle vaccine with Matrix-M1 adjuvant, in a two-dose regimen, (Vaccine Group O).

The antigens and adjuvant dose values in the Study Design Table (Table 3) and Table 4 are nominal and reflect target doses. The qNIV antigen, SARS-CoV-2 rS antigen, and Matrix-M1 adjuvant will each be available in separate drug product vials and will be mixed in the clinic prior to administration to the achieve target doses of ICC, qNIV with Matrix-M1adjuvant, or SARS-CoV-2 rS with Matrix-M1 adjuvant (actual doses will be within ± 10% to 20% of intended target doses). Details of the final product mixing schemes to be implemented by the site pharmacist or designee, the actual content of doses achieved by the in-clinic mixing of drug product lots, and injected volumes used are provided in the Pharmacy Manual.

For all doses of test article, the assigned vaccine will be administered by IM injection in an approximate total volume of 0.3 to 1.0 mL.

Table 4 Investigational Treatments Used in This Study

Product	Section	Antigen Dose[1] (µg)	Route	Regimen	Manufacturer
qNIV Nanoparticle Vaccine[2] in-clinic mixed with 75 µg Matrix-M1 Adjuvant (reference formulation)	7.1.1	60	IM	2 doses: 1 on Day 0 1 on Day 56	Novavax, Inc
SARS-CoV-2 rS Nanoparticle Vaccine in-clinic mixed with 50 µg Matrix-M1 Adjuvant (reference formulation)	**Error! Reference source not found.**	5	IM	2 doses: 1 on Day 0 1 on Day 56	Novavax, Inc
ICC Vaccine (in-clinic mix of various doses of qNIV[2], SARS-CoV-2 rS, and 50 µg Matrix-M1 Adjuvant)	7.1.3	qNIV: 5, 10, 35, or 60 **AND** SARS-CoV-2 rS: 2.5, 5, 7.5, 22.5 Refer to Table 3	IM	2 doses: 1 on Day 0 1 on Day 56	Novavax, Inc

Abbreviations: HA = hemagglutinin; ICC = influenza COVID-19 combination; IM = intramuscular; qNIV = Quadrivalent HA Nanoparticle Influenza Vaccine; WHO = World Health Organization.

1. Each dose is nominal and reflects target doses. Details of the final product in-clinic mixing scheme, the actual content of doses achieved by the in-clinic mixing of drug product lots, and injected volumes used are provided in Pharmacy Manual.

Table 4 Investigational Treatments Used in This Study

Product	Section	Antigen Dose[1] (µg)	Route	Regimen	Manufacturer

2. The influenza strains contained in the qNIV HA dose are WHO recommended strains for the 2019 - 2020 northern hemisphere influenza season, ie, A/Brisbane/02/2018 [H1N1] pdm09; A/Kansas/14/2017 [H3N2]; B/Maryland/15/2016; B/Phuket/3073/2013) in-clinic mixed with 50 µg Matrix-M1 adjuvant.

7.1 Description of Products

7.1.1 qNIV

7.1.1.1 Formulation, Storage, Preparation, and Handling

Each HA bulk drug substance is stored at ≤ -60°C until the 4 strains are mixed and diluted to the target concentration 100 µg/mL per strain with buffer and filled as drug product. The dilution buffer composition is the same as that of the bulk antigen, ie, 25 mM sodium phosphate, 150 mM sodium chloride, 100 mM arginine hydrochloride, 5% weight per volume (w/v) trehalose, and 0.03% PS80, pH 7.5. The drug product is filled into 2R single-use glass vials.

qNIV contains the WHO recommended strains for the 2019 - 2020 northern hemisphere influenza season, ie, A/Brisbane/02/2018 [H1N1] pdm09; A/Kansas/14/2017 [H3N2]; B/Maryland/15/2016; B/Phuket/3073/2013).

qNIV drug product vials should be stored at 2°C to 8°C in a secured location. DO NOT FREEZE. The study site will maintain a temperature log to establish a record of compliance with storage conditions.

7.1.1.2 Dosing and Administration

The qNIV antigen will be mixed with Matrix-M1 adjuvant in the clinic pharmacy, or an area designated for this function, according to the Pharmacy Manual on the day of administration by a qualified member of the study site personnel. The vaccine should be administered according to standard aseptic practice by qualified study site personnel in a way so as to maintain the blind, as directed in the Pharmacy Manual.

Following in-clinic mixing according to the Pharmacy Manual, the qNIV with Matrix-M1 vaccine can be stored at room temperature, in a secured location, for up to 3 hours in the mixing vial or 1 hour in the final administration syringe. DO NOT FREEZE or REFRIGERATE once mixed.

The qNIV with Matrix-M1 adjuvant vaccine regimen will comprise one IM injection (Day 0 for Vaccine Group O) (Table 3; Table 4).

7.1.2 SARS-CoV-2 rS

7.1.2.1 Formulation, Storage, Preparation, and Handling

SARS-CoV-2 rS is to be supplied as a solution for preparation for injection, at one of two concentrations of 25 or 225 µg/mL. 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 (2.5, 7.5, and 22.5 µg). The drug product is filled into 2R single-use glass vials.

SARS-CoV-2 rS drug product vials should be stored at 2°C to 8°C in a secured location. DO NOT FREEZE. The study site will maintain a temperature log to establish a record of compliance with storage conditions.

Further details on the trial vaccine can be found in the SARS-CoV-2 rS IB and description of the presentation are defined in the Pharmacy Manual.

7.1.2.2 Dosing and Administration

The SARS-CoV-2 rS antigen will be mixed with Matrix-M1 adjuvant in the clinic pharmacy, or an area designated for this function, according to the Pharmacy Manual on the day of administration by a qualified member of study site personnel. The vaccine should be administered according to standard aseptic practice by qualified study site personnel in a way so as to maintain the blind, as directed in the Pharmacy Manual.

Following in-clinic mixing according to the Pharmacy Manual, the SARS-CoV-2 rS with Matrix-M1 vaccine can be stored at room temperature, in a secured location, for up to 3 hours in the mixing vial or 1 hour in the final administration syringe. DO NOT FREEZE or REFRIGERATE once mixed.

The SARS-CoV-2 rS with Matrix-M1 adjuvant vaccine regimen will comprise 2 identical IM injections (Day 0 and Day 56 for Group P; and Day 56 and Day 70 for Group O) (Table 3; (Table 4).

7.1.3 ICC Vaccine (qNIV + SARS-CoV-2 rS with Matrix-M1 Adjuvant)

7.1.3.1 Formulation, Storage, Preparation, and Handling

ICC vaccine will be mixed at the clinical site prior to administration using separate drug product vials of qNIV antigen, SARS-CoV-2 rS antigen, and Matrix-M1 adjuvant. All individual ICC vaccine components (qNIV antigen, SARS-CoV-2 rS antigen, and Matrix-M1 adjuvant) must be stored at 2°C to 8°C (until mixing according to the Pharmacy Manual) in a secure cabinet or room with access restricted to necessary clinic personnel as further described in the Pharmacy Manual. The study site will maintain a temperature log to establish a record of compliance with storage conditions.

7.1.3.2 Dosing and Administration

The ICC vaccine will be mixed according to the Pharmacy Manual in the clinic pharmacy, or an area designated for this function, on the day of administration by a qualified member of study site personnel. The vaccine should be administered according to standard aseptic practice by qualified study site personnel in a way so as to maintain the blind, as directed in the Pharmacy Manual.

Following in-clinic mixing according to the Pharmacy Manual, the ICC vaccine can be stored at room temperature, in a secured location, for up to 3 hours in the mixing vial or 1 hour in the final administration syringe. DO NOT FREEZE or REFRIGERATE once mixed.

The ICC vaccine regimen will comprise 2 identical IM injections (Day 0 and Day 56).

7.1.4 Matrix-M1 Adjuvant

7.1.4.1 Formulation, Storage, Preparation, and Handling

Matrix-M1 adjuvant is to be supplied as a solution for preparation for injection, at a concentration of 375 µg/mL. Matrix-M1 adjuvant contains phosphate buffered saline.

Matrix-M1 drug product vials should be stored at 2°C to 8°C in a secured location. DO NOT FREEZE. The study site will maintain a temperature log to establish a record of compliance with storage conditions.

7.1.4.2 Dosing and Administration

Matrix-M1 adjuvant will be in-clinic mixed with qNIV and/or SARS-CoV-2 rS and administered in a total volume of 0.3 to 1.0 mL. Details are provided in the Pharmacy Manual.

7.2 Treatment Assignment and Bias Minimization

7.2.1 Treatment Allocation

An Interactive Web Response System (IWRS) will be responsible for the allocation of randomization numbers to individual participants. A copy of the randomization code with true treatment allocations will be held by PPD during the study. Another randomization list (containing treatment) will be provided to clinical supplies.

Approximately 50% of all participants will be allocated to the CMI Subset population for the analysis of CMI endpoints. The participants will be chosen based on site location and feasibility of testing.

7.2.2 Randomization Strategy and Procedure

Randomization will take place at Day 0 after confirmation that the participant meets the inclusion/exclusion criteria. Participants will be randomly assigned to receive monovalent SARS-CoV-2 rS with Matrix-M1 adjuvant, qNIV with Matrix-M1 adjuvant, or qNIV + SARS-CoV-2 rS with Matrix-M1 adjuvant (Table 3).

Participants will be randomly assigned to study vaccine according to a list produced by PPD. Randomization will be stratified by age group. Prior to production, the randomization specification will be reviewed and agreed by the study team (Sponsor and PPD). As block size is considered potentially unblinding information, it will be known to the Study Biostatistician only.

7.2.3 Extent and Maintenance of Blinding

This is an observer-blinded study. To maintain the blind, predetermined unblinded study site personnel will manage vaccine logistics, preparation, and potentially administration according to the Pharmacy Manual so as to maintain the blind from the remainder of the study site personnel and participants. The unblinded study site personnel may administer study vaccine if qualified to do so but will not be involved in study related assessments or have participant contact for data collection after administration of study vaccine.

A participant's vaccine assignment will not be revealed to the study site study team until the end of the study unless medical treatment of the participant depends on knowing the study vaccine the participant received.

7.2.4 Unblinding Procedures

7.2.4.1 Planned Unblinding

A participant's vaccine assignment will not be revealed to the site study team until the end of the study.

7.2.4.1.1 Participants Receiving Approved and/or Authorized COVID-19 Vaccines

Participants are asked not to receive approved/authorized COVID-19 vaccines for the duration of study follow-up, and in particular, through Day 84, so as not to cofound assessment of immune responses to ICC vaccine. However, for participants who received the Novavax investigational vaccine and who nonetheless wish to receive an approved/authorized COVID-19 vaccine from another manufacturer will be advised to discuss this plan with their healthcare provider given the current lack of safety data regarding the sequential administration of vaccines made by different manufacturers. Participants who want to receive an approved/authorized vaccine in this manner will be strongly encouraged do so only after Day 84 and will encouraged to remain in study for safety follow-up as defined in the protocol. However, participants also have the right to discontinue participation in the study at any time.

7.2.4.2 Unplanned or Unintentional Unblinding

A participant's vaccine assignment will not be revealed to the site study team until the end of the study unless medical treatment of the participant depends on knowing the study vaccine the participant received. Should a situation arise where unblinding is required, the investigator at that study site has the sole authority to obtain immediate unblinding via the IWRS. Prior to unblinding, or as soon thereafter as possible, the investigator should contact the PPD Medical Monitor to discuss the medical emergency and the reason for revealing the actual vaccine received by that participant. Emergency code breaks performed using the IWRS must be clearly explained and justified in the eCRF. The date on which the code was broken must also be documented.

When the investigator contacts the IWRS system to break a treatment code for a participant, they must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the study treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Protocol safety Review Team, PPD Site Monitor, the PPD Medical Monitor, and the PPD Project Manager that the code has been broken, but no treatment assignment will be communicated.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IWRS in case of emergency. The investigator will inform the participant how to contact their backup in cases of emergency when they are unavailable. The investigator will provide the protocol number, study vaccine name if available, participant number, and instructions for

contacting the local entity which has responsibility for emergency code breaks to the participant in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

7.3 Assessment and Verification of Compliance

All doses of the study vaccine should be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the participant has received the entire dose.

The location (right or left arm, or other location if required), if the full dose was administered, date, and timing of all doses of study vaccine will be recorded in the participants' eCRF. If a participant is not administered study vaccine, the reason for the missed dose will be recorded.

7.4 Prior and Concomitant Therapies

Administration of medications, therapies, or vaccines will be recorded in the eCRF. Concomitant medications will include all medications (including vaccines) taken by the participant from the time of signing the ICF through 182 days after the first vaccination (or through the early termination visit if prior to that time). Prescription and over-the-counter (OTC) drugs will be included. Do not record herbals, vitamins, and supplements.

Concomitant medications will be collected through Day 70 for all unsolicited AEs, and through EoS for all MAAEs, SAEs, or AESIs (including PIMMCs). Receipt of any approved or deployed COVID-19 or influenza vaccine should also be recorded through EoS. Sites will record the date(s) and brand of the approved or deployed COVID-19 vaccine received.

7.4.1 Prohibited Therapies

Subjects may receive all concomitant medications and procedures deemed necessary to provide adequate health care during the study, with the exception of those specified in the exclusion criteria and as indicated below. Routine medical standards of care are permitted, including vaccines needed for emergent indications (eg, tetanus booster in response to a penetrating injury).

The following therapies are prohibited within the specified timeframes of study conduct:

- No routine (non-emergent) vaccines will be allowed until after study Day 70 (ie, 14 days after the second dose of test vaccine).
- No influenza vaccine will be allowed within 2 months prior to first study vaccination until after the last study visit (Day 182).
- No investigational product (drug/biologic/device) within 90 days prior to first study vaccination until after the last study visit (Day 182).
- No chronic administration (defined as more than 14 continuous days) of any immunosuppressant medication within 3 months of first study vaccination until the last study visit (except topical, inhaled, or intranasal steroids or short-term oral steroids with course lasting ≤ 14 days). Topical tacrolimus and ocular cyclosporine are permitted.

8 SAFETY MONITORING

The timing and frequency of all safety assessments are listed in the SOE (Table 1). Solicited and unsolicited AEs will be graded for severity using the provided criteria (Appendix 2). Recording of solicited and unsolicited AEs will be conducted by electronic data capture (EDC). AESIs, including PIMMCs, will also be monitored (see Appendix 1 for details).

8.1 Definitions

- **AE** – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related. Any abnormal laboratory test results or other safety assessments (eg, physical exam, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease) will be considered AEs.
- **SAE** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (An event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained, usually involving an overnight stay, at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- **Causality or relatedness** – For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality as follows.
  - Not Related: There is no reasonable possibility of relationship to study vaccine. The AE does not follow a reasonable temporal sequence from administration of study

vaccine or can be reasonably explained by the participant's clinical state or other factors (eg, concurrent diseases, and concomitant medications).
  - Related: There is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the participant's clinical state or other factors (eg, concurrent diseases, or concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the study vaccine, and/or resolves with discontinuation of the study vaccine (and/or recurs with re-challenge, if applicable).

- **Adverse reaction** – An AR is any AE caused by a drug.
- **Suspected adverse reaction (SAR)** – An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.
- **Unexpected** – An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.
- **Severity or intensity** – The severity (or intensity) of an AE/SAE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:

  - Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
  - Moderate: These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
  - Severe: These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

  If the severity of an AE/SAE changes, the most intense severity should be reported. An AE/SAE characterized as intermittent does not require documentation of the onset and duration of each episode.

8.2 Documenting Adverse Events

At every study visit, participants will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to participant observations, AEs will be documented from any data collected on the AE page of the eCRF or other documents that are relevant to participant safety.

Care will be taken not to introduce bias when detecting AEs, MAAEs, AESIs (including PIMMCs) and SAEs. Open ended and non-leading verbal questioning of the participant is the preferred method to enquire about AE occurrences. AESIs (including PIMMCs) will be inquired about according to the specific diseases listed in Appendix 1.

When an AE/AESI/SAE occurs, it is the responsibility of the investigator to review all available documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the eCRF.

It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity, seriousness, causality, whether the AE caused the participant to not receive the second dose of study vaccine, any other action taken, and the outcome. A new AE must be recorded if the severity of the AE changes.

Should an SAE have an outcome of death, the report should contain a comment regarding the co involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

8.2.1.1 Assessment of Causality

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator should consider the following, before reaching a decision on causality assessment:

- Time relationship between study vaccine injection and event's onset.
- Re-challenge following second vaccination, if applicable.
- Medical history.
- Study treatment.
- Mechanism of action of study vaccine.
- Class effect.
- Concomitant treatments in use.
- Withdrawal of study treatment.
- Lack of efficacy/worsening of existing condition.
- Possible vaccine enhancement of COVID-19.

- Erroneous treatment with study medication or concomitant medication.
- Protocol-related process.

8.2.1.2 Action Taken with Study Vaccine Due to AE

The action taken with study vaccine should be recorded using one of the following:

- No action taken.
- Next dose delayed.
- Permanently discontinued/withdrawn from further study vaccination (with date).
- Not applicable.

8.2.1.3 Other Action Taken

Details of any other actions taken should be specified:

- Specific therapy/medication.
- Surgical or medical procedure.
- Prolonged hospitalization.

8.2.1.4 AE Outcome

Each AE should be rated according to one of the following outcomes:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal.
- Unknown.

8.2.2 Time Frame for Collection

All AEs reported or observed during the study will be recorded on the AE page of the eCRF.

Medical occurrences that begin prior to the first dose of study vaccine will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All unsolicited AEs of any severity will be collected from the time of first study vaccination through Day 70 (ie, until 14 days after the second vaccination). Any relevant observations made prior to the first dose of study vaccine are to be recorded on the AE eCRF but will not be considered TEAEs and will be reported separately from TEAEs.

MAAEs and AESIs (including PIMMCs) will be collected from the time of first study vaccination until EoS.

All SAEs will be collected from signing of informed consent until completion of the EoS.

Participants who receive an approved/authorized vaccine (see Section 7.2.4.1), will be encouraged to remain in the study for safety follow-up and safety assessments will be performed via the timelines and mechanisms as described herein. In addition, all vaccine administration errors, AEs, SAEs, cases of multisystem inflammatory syndrome, and hospitalized or fatal cases

of COVID-19 following vaccination with the approved/authorized must be reported following local regulatory reporting guidance for safety events that occur in subjects who receive approved/authorized vaccines within the study.

At any time after completion of the EoS visit, if an investigator learns of an SAE that could reasonably be considered related to study vaccine, they should promptly notify the Sponsor.

8.2.3 Classification of Events

8.2.3.1 Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of study vaccine.

8.2.3.2 Adverse Event of Special Interest

Participants will be assessed for diagnosis of an AESI at all study contacts. AESIs include PIMMCs, AEs specific to complications of COVID-19 (listed in Appendix 1), or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. Listings of AESI are presented in Appendix 1.

An AESI must be reported as if it is an SAE (Section 8.3).

8.2.3.3 Medically Attended Adverse Events

A MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

8.2.3.4 Reactogenicity Symptoms

On vaccination days, participants will remain in clinic (or under observation) for at least 30 minutes to be observed for any severe reactogenicity.

Participants will utilize their eDiary to record reactogenicity following each vaccination. All participants will record reactogenicity starting on the same day of the vaccinations and for a total of 7 days thereafter inclusive of the day of vaccination (ie, through Day 6 or Day 62). Study site personnel will regularly review the eDiary for completeness. Should any reactogenicity event extend beyond 7 days after vaccination (toxicity Grade ≥ 1), then it will be recorded as an AE with a start date that matches Day 7 or Day 63 of the reactogenicity event and followed to resolution per ICH guidelines for AE capture. Such AEs should be reported and managed as described in Section 8.3. The toxicology grading scale implemented in the electronic diary for the study is included in Appendix 2.

8.3 Reporting Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. Investigators and other study site personnel must inform appropriate PPD representatives of any SAE that occurs during the course of the study, from the time of informed consent until the EOS visit, regardless of whether it is judged to be causally related to study vaccine or procedures. Notification must occur within 24 hours of when they become aware of it. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered resolved, chronic and/or stable.

SAE reports received that may be attributed to a combination of the Novavax vaccine and an approved/authorized vaccine from a different manufacturer will be reported to local regulatory authorities as applicable. SAE reporting forms allow for the notation of other factors that may have impacted the investigator's assessment of causality. Investigators will be instructed to utilize this section of the reporting form to note the impact of an approved/authorized vaccine from a different manufacturer on the event, if applicable. Investigators will be required to report any SAEs in subjects who received a different manufacturer's approved/authorized vaccine to local health care and/or regulatory authorities as per the local regulatory guidelines.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to PPD within 24 hours as described above. The date when the AE becomes serious should be notated in the eCRF or on the SAE form.

All SAEs will also be recorded in the eCRF. The investigator is responsible for informing the HREC/IRB of the SAE as per local requirements. Paper SAE forms should be completed at the study site and emailed within 24 hours of study site awareness of the event to the Central Receipt mailbox:

PPD Pharmacovigilance:

24-Hour Safety Hotline Fax:

24-Hour Safety Hotline:

The report form should be attached to the email; a notification email of the event describing it in the email text is not sufficient. There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial SAE report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE report form.

Minimum criteria for a reportable event are:

- Identifiable patient (participant number)
- A suspect product (ie, study vaccine)
- An identifiable reporting source (investigator/study site identification), and
- An event or outcome that can be identified as serious.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

8.3.1.1 Safety Reporting to Sponsor

PPD Pharmacovigilance and Safety Services (PVSS) will forward the SAE and Pregnancy reports to the Sponsor's safety representative(s) within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

8.3.1.2 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards, and Investigators

PPD will notify the Sponsor of any SAE and will perform follow-up activities with the concerned study site. PPD will retain responsibility of expedited and periodic reporting according to national requirements. Procedure and timelines for safety reporting are provided in the Safety Management Plan as agreed by PPD and the Sponsor. The investigator must comply with any applicable study site-specific requirements related to the reporting of SAEs (particularly deaths and suspected unexpected serious adverse reactions) to the HREC/IRB that approved the study. Investigators should provide written documentation of HREC/IRB notification for each report to the PPD PVSS. In accordance with ICH GCP, PPD PVSS will inform the investigators of findings that could adversely affect the safety of participant, impact the conduct of the study, or alter the HREC's/IRB's approval/favorable opinion to continue the study, as assessed by the Sponsor. In particular and in line with respective regulations, PPD PVSS will inform the investigators of SAEs. The investigator should place copies of Safety Reports in the Investigator Site File. National regulations with respect to Safety Report notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the PPD Safety Reporting Group (SRG) will provide appropriate Safety Reports directly to the concerned lead HREC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or study site-specific regulations, the investigator will be responsible for promptly notifying the concerned HREC/IRB of any Safety Reports provided by the PPD SRG and of filing copies of all related correspondence in the Investigator Site File.

8.3.1.3 24/7 Medical Emergency Coverage for Urgent Protocol related Medical Questions

In a study-related health emergency, when assigned medical monitors for a study cannot be reached by a caller, for discussion of urgent medical related questions an on-call physician can be reached 24 hours 7 days a week (24/7) via PPD pharmacovigilance.

On this internet page, a list of country specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, there may be restrictions when dialing toll-free numbers from a mobile phone.

8.4 Adverse Events of Special Interest

Participants will be assessed for diagnosis of an AESI at all study visits. AESIs include PIMMCs, AEs specific to COVID-19, or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. Listings of AESI are presented in Appendix 1.

8.5 Pregnancy

Pregnancy is not considered an AE unless there is a suspicion that an investigational vaccine may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To

ensure participant safety, each pregnancy must be reported to PPD Pharmacovigilance & Safety Services within 24 hours of learning of its occurrence. If pregnancy occurs, further vaccination will be discontinued. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of both mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any pregnancy brought to the investigator's attention before the study is completed should be reported to PPD Pharmacovigilance & Safety Services using the pregnancy reporting forms provided to sites.

Any pregnancy brought to the investigator's attention after the participant has completed the study but occurring while the participant was in the study must be promptly reported to:

Sponsor Safety Monitor [redacted]

8.6 Overdose or Misuse

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than is normally used. Every overdose must be reported to PPD PVSS within 24 hours of awareness, using the details provided in Section 8.3 if the overdose was associated with an SAE. Other overdoses and those associated with non-serious AEs should be reported in the eCRF AE page. Only overdoses associated with a clinical SAE needs to be reported as an SAE. The quantity and duration of the excess dose should be documented in the eCRF.

Overdose in this study is specifically defined as any dose greater than the intended protocol dose (Section 7). In case of overdose, it is recommended that the participant be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be administered immediately. Note that administration of the "wrong" vaccine is a protocol deviation, but not, in the absence of associated AE, an SAE.

8.7 Vital Signs Measurements

Vital signs measurements will include oral temperature (or via forehead/ear reader), pulse rate, diastolic and systolic blood pressure (after participant is seated for at least 5 minutes), and respiratory rate. Temperature will be recorded and graded during general systemic reactogenicity evaluation. The other vital signs measurements will be recorded as continuous variables prior to each vaccination.

On vaccination days, vital signs measurements will be collected once before vaccination to ensure the participant has controlled blood pressure and heart rate and no evidence of fever prior to vaccination and once at 30 to 60 minutes (± 15 minutes) after vaccination to check for any reactions to the vaccine. The investigator will only apply standard toxicology grading on the day of vaccination, both before and after vaccination (Table 8). If individual vital signs measurements are considered clinically significant by the investigator, vaccination may be withheld that day, and participants may return on a subsequent day for re-evaluation and vaccination within 7 days.

For purposes of reporting vital signs abnormalities as AEs, those values that show an increase in the toxicity grade relative to the baseline values (in the same participant) and ***attain*** at least a Grade 2 (eg, normal or Grade 1 to Grade 2, or Grade 2 to Grade 3) should be reported as an AE, at the investigator's judgement. Investigators may report lesser abnormalities as AEs if indicated based on clinical judgment. Abnormal vital signs may be reported at the investigator's discretion, and because these measures are highly labile, should only be reported as AEs when the investigator believes there is a persistent and meaningful and clinically significant physiologic change. If multiple assessments of vital signs are made, then only the most recent measurement will be reported. Vital signs abnormalities that are the logical consequence of another diagnosis (eg, irregular tachycardia in a participant with atrial fibrillation or fever in a participant with pneumonia) need not be reported separately.

8.8 Physical Examinations

A physical examination will be performed at screening (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes of the upper extremities and neck, and musculoskeletal system/extremities) (Section 6.1.1). Height and weight will be measured and BMI will be calculated at screening only.

After physical examination at baseline determines eligibility (Section 6.1.1), subsequent physical examination assessments are symptom directed as triggered by AE or symptom reports at the time points specified in the SOE (Table 1).

9 ANALYSIS

This section includes a description of the statistical strategy and considerations for the study. Further detailed specifications for the analysis of data from the study will be presented in a Statistical Analysis Plan (SAP).

9.1 Hypothesis

There are no formal statistical hypotheses evaluated in this study. The analysis will descriptively characterize the safety and immunogenicity profiles for the various vaccine formulations administered to participants. The immunogenicity data generated from the study will also serve as input into a response surface modeling analysis conducted under a DoE analysis approach (details below).

9.2 Population

9.2.1 Sample Size Rationale

The sample size of 40 participants per group for this study is based on clinical and practical considerations and not on a formal statistical power calculation. This distribution of participants would provide a sufficient number of replicates per set of factor levels studied in the DoE approach to account for expected variability in the immune responses due to elements such as subject and assay variability. There were no formal power calculations based on the DoE analysis methods. As an informal way to measure the approximate number of replicates (ie, participants) needed per vaccine formulation, the data from HAI testing with VLP reagents from the qNIV-E-301 study for eleven vaccine-homologous and vaccine-nonhomologous strains will be used to average the fold rise at Day 28 to provide input to a sample size calculation to detect a two-fold difference in response relative to baseline. This calculation showed that a sample size of 40 would provide > 99% power to differentiate the immune response between two formulations.

With 40 participants in each treatment group, there is 87% probability to observe at least 1 participant with an AE if the true incidence of the AE is 5%. With 560 participants receiving a combination formulation of influenza and SARS-CoV-2 vaccine, an AE with true incidence of 0.534% can be detected with 95% probability.

9.2.2 Analysis Sets

The following analysis sets are identified for analysis.

9.2.2.1 All Randomized Participants Analysis Set

The Randomized Subjects Analysis Set will include all participants who are randomly assigned to treatment, regardless of whether they actually received any study vaccine. The Randomized Subjects Analysis Set will be used for participant disposition summaries and will be analyzed according to the treatment as randomized.

9.2.2.2 Full Analysis Set

The Full Analysis Set (FAS) will include all participants who are randomized and received at least 1 dose of study vaccine, regardless of protocol violations or missing data. The FAS will be

the secondary analysis set used for immunogenicity analyses and will be analyzed according to the treatment as randomized.

9.2.2.3 Safety Analysis Set

The Safety Analysis Set will include all participants who provide consent, are randomized, and receive at least 1 dose of study vaccine. Participants in the Safety Analysis Set will be analyzed as actually treated.

9.2.2.4 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set for immunogenicity will be determined for each study visit. The PP Analysis Set will include all participants who receive the full prescribed regimen of the study vaccine according to the protocol, have blood collected for immunogenicity assessment for baseline and at least 1 post-vaccination time point, and have no major protocol violations that are considered clinically relevant to impact immunogenicity response as determined prior to database freeze for analysis. The PP Analysis Set is further subsetted according to immunogenicity measures such as the humoral serology subset and CMI assay subset.

Within the PP Analysis Set there are 3 subsets defined:

9.2.2.4.1 Humoral Serology Subset

All participants in the PP Analysis Set who were tested for HAI and anti-rS protein serology (ELISA) prior to study vaccination will be included in this subset.

This includes both the HAI as well as MN_{50} assay testing for homologous and/or heterologous strains.

9.2.2.4.2 Cell-mediated Assay Subset

All participants in the PP Analysis Set who have their CMI response assessed by ICCS and/or ELISpot prior to study vaccination will be included in this subset. CMI assessments are at Days 0, 7, 63 and 182 for all participants for a preselected subset of study sites.

9.3 Testing Procedures

9.3.1 Analysis of the Primary Endpoints

The analysis of the primary safety endpoints will be descriptive with no formal statistical testing. The numbers and percentages (with 95% CIs) of participants with the event(s) relevant to the endpoint will be computed. The analysis will be based on the Safety Analysis Set. 95% CIs will be computed using the method of Clopper and Pearson.

Numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of subjects with solicited local and systemic AEs through 7 days after each vaccination will be summarized by treatment group and the maximum toxicity grade over 7 days after each vaccination. The duration of solicited local and systemic AEs after each vaccination will also be summarized by treatment group.

Unsolicited AEs will be coded by Preferred term (PT) and System Organ Class (SOC) using the latest version of Medical Dictionary of Regulatory Activities (MedDRA) and summarized (numbers, percentages, 95% CI) by treatment group as well as by severity and relationship to study vaccine. Unsolicited AEs through 70 days after first vaccination; all MAAEs through Day 182 after first vaccination; and any MAAEs related to vaccine, SAEs, or AESIs (including PIMMCs) through 182 days after first vaccination will be listed separately and summarized by treatment group.

9.3.2 Analysis of Secondary Endpoints of Immunogenicity (Traditional Approach)

The analysis of secondary immunogenicity endpoints will be descriptive with no formal statistical testing. The immune response will be described using geometric mean, within-group geometric mean ratio of post-vaccination to pre-vaccination (GMFR), SCR, and SPR; and between-group GMTR or GMEUR.

The immunogenicity analyses will be performed using the PP analysis set.

For the serum IgG antibody levels specific for the rS / HA antigen(s) as detected by ELISA, the geometric mean at each study visit, and the geometric mean titer ratio compared to baseline (Day 0) at each post-vaccination study visit, along with 95% CI will be summarized by treatment group. The 95% CI will be calculated based on the t distribution of the log transformed values, then back transformed to the original scale for presentation. The seroprotection (HAI only) and seroconversion/seroresponse rate along with 95% CIs based on the Clopper Pearson method will be summarized by treatment group at each post vaccination study visit. GMTR or GMEUR will be summarized for selected treatment arms (to be articulated in the SAP), where an analysis of covariance model will be constructed at each post-vaccination study visit on the log transformed titer, including the treatment group as a fixed effect and the baseline log transformed titer as a covariate. This will enable comparisons of selected treatment groups within each visit, although no adjustment for multiplicity will be made.

Results from neutralization assays specific for the influenza HA and SARS-CoV-2 wild-type (or variant) will be summarized in a similar manner to assess functional antibody response.

Cell-mediated response for both Th1 and Type 2 T helper (Th2) cell pathways will be assessed by cytokine profiling (eg, IL-1, TNFα, IFNγ, and CD40L) with flow cytometry and ICCS after in vitro antigen re-stimulation of harvested PBMCs. To describe the quality and amplitude of CMI response, descriptive statistics (mean, median, geometric mean, interquartile range, minimum, maximum, and 95% CI) will be computed by treatment group at Days 0, 7, 63 and 182 in the participants allocated to the CMI analysis subset.

9.3.3 Analysis of Secondary Immunogenicity Endpoint Using the DoE Approach

The study's 12 unique vaccine formulations (excluding reference formulations) arose from a DoE approach with the objective to construct one or more response surface models that can provide information on a combination of antigen (both HA and rS) that when combined with 50 μg of Matrix-M1 adjuvant will maximize HAI and anti-S immune responses. The combination(s) identified may or may not be the formulations that are studied. The results are intended to inform selection of potential dose levels for further study.

With the analysis to be performed in the PP population (ie, receiving both doses of study material), there are 2 factors studied. These are the nominal amount (in μg) of SARS-CoV-2 rS protein in each dose, and the nominal amount (in μg) of each of four (4) HA strains for influenza strains in each dose. The levels within each factor are as follows:

Factor	Levels
SARS-CoV-2 rS (μg)	2.5, 7.5, 22.5
HA per strain (μg)	5, 10, 35, 60

These levels will be treated as continuous values. The mean reportable values of anti-spike and HAI antibody responses from each vaccine group will be used to build predictive model(s). The regression model(s) will include all main effects, interactions, and quadratic effects that are found to be statistically significant.

Computer software will be used to fit the model(s) for response(s) of interest. Statistical significance of each model parameter (using p-value) will be assessed in constructing a final response surface. The SAP will contain further theoretical and practical issues related to this methodology.

9.3.4 Analysis of Exploratory Endpoints of Immunogenicity

9.3.4.1 Cell-mediated Immunity

To describe the quality and amplitude of CMI response, descriptive statistics (mean, median, geometric mean, interquartile range, minimum, maximum, and 95% CI) will be computed at Days 0, 7, 63 and 182 in the participants allocated to the CMI analysis subset.

9.3.5 Population Analysis

9.3.5.1 Disposition and Protocol Compliance

The number of participants consented, randomized, and vaccinated will be presented by the study vaccine group for all Randomized Subjects Analysis Set.

The number (percentage) of participants in Randomized Subjects Analysis Set, FAS, Safety Analysis Set, and PP Analysis Set who have completed the study up to the time of analysis will be summarized by the study vaccine group (eg, at Day 70 analysis, count how many participants completed through Day 70. End of study analysis would include counts on participants completing the entire study).

The number (percentage) of participants who discontinue the study prior to the time point of analysis and the reason for discontinuation (eg, AE, investigator decision, lost to follow-up, non-compliance, etc.) will be presented by the study vaccine group. A listing of all participants discontinued the study will be presented by the study vaccine group, reason for discontinuation, and day of last study contact. Day of last study contact will be calculated as follows: date of study discontinuation (as recorded on EoS eCRF) minus date of Day 0 vaccination.

The number (percentage) of participants with a major protocol deviation recorded up to time of analysis will be summarized by the study vaccine group and protocol deviation category. A listing of all participants with one or more major protocol deviations will also be provided.

9.3.5.2 Demographics and Baseline Characteristics

Baseline demographic and background characteristics (eg, age, gender, ethnicity, race, height, weight, and BMI) will be summarized by the study vaccine group on both FAS and Safety Analysis Set. Frequencies and percentages will be presented for categorical variables. Continuous variables will be summarized using descriptive statistics (total number of participants, mean and standard deviation, median, minimum, and maximum).

Medical history and physical examination diagnoses/abnormalities will be coded using the MedDRA terms. Baseline medical history and physical examination findings recorded on Day 0 (prior to vaccination) will be summarized separately by the vaccine group and by MedDRA SOC/PT on the Safety Analysis Set. Within each SOC and PT, the number and percentage of participants with at least one abnormality will be presented, respectively. Multiple abnormalities within a given SOC and PT for a participant will be counted once.

9.3.6 Safety Analysis

All safety analyses will be conducted using the Safety Analysis Set according to the methodology outlined in Section 9.3.1.

9.3.6.1 Solicited Adverse Events

Data will be summarized on participants experiencing at least 1 solicited AE during the 7-day period after first dose and after second dose separately as well as overall. The summaries will also break down by local injection site symptoms and systemic symptoms/signs as well as at the individual reaction level. Denominator for the analyses will count participants who provide data for at least one reaction for one day. Missing data will not be imputed.

9.3.6.2 Unsolicited Adverse Events

Unsolicited AEs will be coded by SOC and PT using MedDRA terms. Unsolicited AEs will be summarized overall and by the vaccine group and by SOC/PT, as well as by severity and relationship to the study vaccine to present the number and percentage with its corresponding exact 95% CIs using Clopper-Pearson method. For multiple occurrences of an AE in the same participant, a participant will be counted only once, using the most severe or most related occurrence for the summarization by severity or relationship to the study vaccine, respectively. Unsolicited AEs will be summarized through Day 70.

All MAAEs, AESIs (predefined list), and SAEs, throughout the study will be collected from the first vaccination through Day 182 after first vaccination and summarized overall and by the study vaccine group as well as by severity.

A listing of participants with unsolicited AEs, MAAEs, AESIs, and SAEs will also be produced from the first vaccination through Day 182.

The denominator is based on the Safety Analysis Set. Missing data will not be imputed while handling of partial dates will be described in the SAP.

9.3.6.3 Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and vaccinations will be summarized overall and by the vaccine group and preferred drug name as coded using the WHO drug dictionary for all participants on the Safety Analysis Set.

9.3.7 Immunogenicity Analysis

Analysis of non-CMI immunogenicity parameters by a "traditional" approach will be performed with the methods outlined in Section 9.3.2. Analysis of CMI data will be done with the method described in Section 9.3.4.

9.3.7.1 HAI and MN Titers for Influenza Strains

For both homologous and heterologous (ie, antigenically drifted) influenza strains, and for both results arising from HAI assay and MN assay, titer data will be summarized by calculating geometric mean, geometric mean of individual ratio of post-baseline to baseline value (GMFR), SCRs and SPRs.

The definition of seroconversion is either a baseline titer of < 10 and post-vaccination titer ≥ 40 or a baseline titer ≥ 10 and post-vaccination titer $\geq$ 4-fold higher than baseline. The definition of seroprotection is only applicable to HAI and is a titer value ≥ 40.

Values below the lower limit of quantification of the assay will be set to half for use in computations.

The between group ratio of GMT (GMTR) is the antilog of the difference of means of log-transformed titers between 2 groups.

Data will be summarized for Days 0 (GMT and SPR only), 28, 56, 70, 84 and 182. Missing data will not be imputed.

Analyses will exclude subjects who have a lab-confirmed case of influenza between vaccination and time point(s) of analysis.

9.3.7.2 ELISA (IgG) Concentration and MN_{50} Titers for SARS-CoV-2

Both concentration and titer data will be computed by calculating geometric mean, GMFR, and SCR.

The definition of seroconversion is a post-vaccination concentration/titer $\geq$ 4-fold higher than baseline.

Values below the lower limit of quantification of the assay will be set to half for use in computations.

The between group ratio of GMEU or GMT (GMEUR or GMTR) is the antilog of the difference of means of log-transformed concentrations/titers between two groups. It will be calculated for selected treatment arms (to be articulated in the SAP).

Data will be summarized for Days 0 (GMEU/GMT only), 28, 56, 70, 84 and 182. Missing data will not be imputed.

Analyses will exclude subjects who have a PCR-confirmed case of COVID-19 between vaccination and time point(s) of analysis.

9.3.8 Predictive Modeling of the Measured Responses

The Day 70 immune responses will be the primary set of data to use for stepwise multi-regression analysis. Participants with non-missing Day 70 responses will be included in the modeling. The PP Analysis Set will be used, meaning participants receiving both doses of study material. Treatment group is not part of the model independent variables ("factors" and their higher order terms), but rather the factors account for the amount of each antigen or adjuvant received, treated mathematically as continuous quantities.

Participants having a lab-confirmed case of influenza or COVID-19 between Day 0 and Day 70 may have data excluded for the modeling to reduce the extra variability arising from such data. The input data may be assessed for extent and nature of variability to determine which data points to exclude. Sensitivity analyses may need to be performed during the modelling exercise to assess impact of selected data points on the conclusions.

Response measures of interest will be defined in the SAP. Each of these responses will be modelled with the levels of nominal antigen/adjuvant for the formulation as independent variables. The significance of each model parameter will be assessed to determine whether to keep the parameter in the model (eg, interaction terms). The end result will include predictive models, a list of significant terms, and optimized dosage of antigen/adjuvant combinations that maximize the desirable responses.

9.4 Interim Analysis

As all analyses are descriptive, there are no interim analyses planned that require adjustment to Type I error. After all participants have completed Day 70, and their data are cleaned, an analysis of the primary and relevant secondary endpoints will be conducted. Data will also be used in the response surface modeling covered under the exploratory analysis.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor (or designee) and an appropriate ethics committee. Any amendment to the protocol or consent materials must also be approved by the study sponsor (or designee) and HREC/IRB and must be submitted/notified to the regulatory authority, as required, before they are implemented.

10.2 Ethics Review

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant HREC/IRB. The HREC/IRB shall be appropriately constituted and perform its functions in accordance with ICH GCP and local requirements as applicable.

The HREC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, participant recruitment procedures (eg, advertisements), written information to be provided to the participants, IB, available safety information, information about payment and compensation available to participants, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the HREC/IRB and Regulatory Authority (Competent Authority) as applicable.

10.3 Informed Consent

The nature and purpose of the study shall be fully explained to each participant. They must be informed that participation is voluntary.

Documentation of informed consent (either written or via eConsent) must be obtained from each participant prior to any study procedures being performed. The process of obtaining informed consent must be documented in the participant's source documents. The authorized person obtaining the informed consent must also sign the ICF, and a copy of the ICF must be provided to the participant. Participants must be re-consented to the most current version of the ICF during their participation in the study.

Participants will be requested to provide the name and contact information for an emergency contact and to provide consent for serum banking for future testing to support establishment of correlates of protection against SARS-CoV-2 infection and disease (see Section 6.2 regarding sample retention).

The consent documents to be used for the study shall include all the elements of informed consent as outlined in accordance with ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate HREC/IRB prior to use.

10.4 Data Privacy

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, relevant regulatory authority(ies), or the HREC/IRB.

The investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11 OVERSIGHT

11.1 Quality Control and Assurance

The Sponsor/designee shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013) and ICH GCP (CPMP/ICH/135/95 and updates).

The investigator will be responsible for the following:

Providing written summaries of the status of the study to the IRB/HREC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/HREC.
Notifying the IRB/HREC of SAEs or other significant safety findings as required by IRB/HREC procedures.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate HREC/IRB, except when necessary to eliminate immediate hazards to the participant or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the participant having to be withdrawn from the study and render that participant non-evaluable.

The identification and reporting of serious breaches of ICH GCP or the protocol to the Regulatory Authorities and Ethics Committees will be conducted according to local SOPs and regulations.

11.1.1 Monitoring

The clinical research organization clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel. The monitor will be blinded to study vaccine assignment. A separate unblinded study monitor will be responsible for drug accountability.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

11.1.2 Audits

The investigator and institution involved in the study will permit study-related monitoring, audits, HREC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or the regulatory authority access to all study records.

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.1.3 Protocol Deviations

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the HREC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a participant being discontinued from the study or significantly affects the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to regulatory authority including ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The HREC should be notified of all protocol deviations, if appropriate, in a timely manner.

Review and categorization of protocol deviations will occur prospectively during the study prior to database lock(s).

11.1.4 Records

11.1.4.1 Data Capture and Management

All required study data will be entered by study site personnel in the eCRF or by study participants in the eDiary created for the study. These data collection tools are a validated EDC system that contains a system generated audit trail. Data required according to this protocol are recorded by study site personnel via data entry into the internet-based EDC software system or by study participant via the eDiary on their personal electronic device (smartphone). The investigator shall ensure that all data from participant visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal PPD and external study site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the investigator on CD ROM for archiving at the study site.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

11.1.4.2 Source Documentation

The investigator must maintain source documents, such as laboratory reports, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the participant's source documents.

The investigator/institution shall provide direct access to source data/documents for study related monitoring, audits, HREC/IRB review, and regulatory inspection.

11.1.4.3 Records Retention

The investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study vaccine or per local regulation, whichever is longer. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

11.2 Study Termination or Study Site Closure

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last study visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

12 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities.

The Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator may be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship agreements. Authors will be provided reasonable access to all study data, statistical tables, figures, and relevant reports and will have the opportunity to review complete study results. All proposed publications based on this study must be participant to the Sponsor's approval requirements.

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 FINANCING AND INSURANCE

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54 and local regulations. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD nor the study site is financially responsible for further treatment of the disease under study.

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15 APPENDICES

APPENDIX 1 LISTINGS OF ADVERSE EVENTS OF SPECIAL INTEREST

Because it has been hypothesized that immunizations with or without adjuvant may be associated with autoimmunity, regulatory authorities have requested that Novavax instruct investigators to be especially vigilant regarding the PIMMC listed below (Table 5). Note that this regulatory request is not specific to Novavax's qNIV or SARS-CoV-2 rS or Matrix-M1 adjuvant; and there is no current evidence to suggest that the study vaccines in this protocol are, or are not, associated with these illnesses. The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 5 Potential Immune-Mediated Medical Conditions

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory Disorders:	Acute disseminated encephalomyelitis (including site-specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (eg, Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis.
Musculoskeletal and Connective Tissue Disorders:	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome.
Vasculitides:	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal Disorders:	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis.
Hepatic Disorders:	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis.
Renal Disorders:	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
Cardiac Disorders:	Autoimmune myocarditis/cardiomyopathy.

Table 5 Potential Immune-Mediated Medical Conditions

Categories	Diagnoses (as MedDRA Preferred Terms)
Skin Disorders:	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome.
Hematologic Disorders:	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia.
Metabolic Disorders:	Autoimmune thyroiditis, Grave's or Basedow's disease, new onset Hashimoto thyroiditis[a], diabetes mellitus type 1, Addison's disease.
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

Abbreviations: ANCA = anti-neutrophil cytoplasmic antibody; IgA = immunoglobulin A; MedDRA = Medical Dictionary for Regulatory Activities.

AEs specific to COVID-19 are listed below (Table 6). The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 6 Adverse Events Representing Complications Specific to of COVID-19[1]

Categories	Diagnoses (as MedDRA System Organ Class/Preferred Term)
Respiratory/Infectious Disorders:	ARDS, pneumonitis, septic shock-like syndrome.
Cardiac Disorders:	Acute cardiac injury, arrhythmia.
Coagulopathy	Deep vein thrombosis, myocardial infarction, stroke.
Renal Disorders:	Acute kidney injury.
Hematologic Disorder	Thrombocytopenia, septic shock-like syndrome.
Inflammatory Disorders:	Cytokine Release Syndrome related to COVID-19 infection[2], multisystem inflammatory syndrome in children (MIS-C).
Neurologic Disorders:	Generalized convulsions.

Abbreviations: AIDS = acquired immune deficiency disease syndrome; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DAIDS = Division of AIDS, NIAID, NIH; MedDRA = Medical Dictionary for Regulatory Activities; NIAID = National Institutes of Allergy and Infectious Diseases; NIH = National Institutes of Health.

1. COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential. The current listing is based on Coalition for Epidemic Preparedness Innovations /Brighton Collaboration Consensus Meeting (12/13 March 2020) and expected to evolve as evidence accumulates (Lambert 2020).
2. Cytokine release syndrome related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath (DAIDS 2017).

APPENDIX 2 TOXICITY GRADING SCALE FOR CLINICAL ABNORMALITIES (LOCAL AND GENERAL SYSTEMIC REACTOGENICITY, AND VITAL SIGNS)

Table 7 Modified FDA Toxicity Grading Scale for Clinical Abnormalities (Local and General Systemic Reactogenicity)

Local Reaction to Injectable Product				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-prescription pain reliever >24 hours or interferes with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Requires ER visit or hospitalization
Erythema/redness[a]	25 − 50 mm	551 − 100 mm	>100 mm	Necrosis or exfoliative dermatitis[b]
Induration/swelling[a]	2.525 − 50 mm	5.151 − 100 mm	>100 mm	Necrosis[b]
Systemic (General)				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever[c] (°C) (°F)	38.0 − 38.4 100.4 − 101.1	38.5 − 38.9 101.2 − 102.0	39.0 − 40 102.1 − 104	>40 >104
Nausea/vomiting	Does not interfere with activity or 1 − 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires IV hydration outside of hospital	Requires ER visit or hospitalization
Headache	Does not interfere with activity	Repeated use of non-prescription pain reliever >24 hours or interferes with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires ER visit or hospitalization
Fatigue/Malaise	Does not interfere with activity	Some interference with activity	Significant, prevents daily activity	Requires ER visit or hospitalization
Myalgia	Does not interfere with activity	Some interference with activity	Significant, prevents daily activity	Requires ER visit or hospitalization
Arthralgia	Does not interfere with activity	Some interference with activity	Significant, prevents daily activity	Requires ER visit or hospitalization

[a] The measurements should be recorded as a continuous variable.

[b] These events are not participant reported through the eDiary and will be monitored through the AE pages of the study database.

[c] Oral temperature if participant collected, sites may collect temperature using local clinic practices/devices. Toxicity grade will be derived.

Source: DAIDS 2017

Table 8 FDA Toxicity Grading Scale for Clinical Abnormalities (Vital Signs)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia (bpm)	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia (bpm)[a]	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths per minute)	17 – 20	21 – 25	>25	Intubation

Note: Participant should be at rest for all vital signs measurements.

[a] When resting heart rate is between 60 – 100 bpm. Use clinical judgement when characterizing bradycardia among some healthy participant populations (eg, conditioned athletes).

Source: DAIDS 2017