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A PHASE 2, RANDOMIZED, OBSERVER-BLINDED, ACTIVE-CONTROLLED TRIAL TO CONFIRM THE DOSE AND FORMULATION OF A RECOMBINANT QUADRIVALENT NANOPARTICLE INFLUENZA VACCINE (QUAD-NIV) WITH OR WITHOUT MATRIX-M1™ ADJUVANT IN HEALTHY ADULTS ≥ 65 YEARS OF AGE

Investigational Materials:	Hemagglutinin Nanoparticle Influenza Vaccine, Quadrivalent (Quad-NIV), representing A/Michigan/45/2015 (H1N1); A/Singapore/INFIMH-16-0019/2016 (H3N2); B/Colorado/60/2017; and B/Phuket/3073/2013; administered with or without Matrix-M1 Adjuvant
Protocol Number:	qNIV-E-201
Sponsor:	Novavax, Inc. (Novavax) 20 Firstfield Road Gaithersburg, MD 20878 USA
Responsible Clinical Operations Manager:	[redacted] Clinical Operations Novavax, Inc. Gaithersburg, MD 20878 Office: 301-591-5067 Email: [redacted]
Version & Date:	Version 3.0 – 21 August 2018
Prior Version(s):	Version 1.0 – 24 May 2018 Version 2.0 – 12 July 2018

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PROTOCOL APPROVAL PAGE

The principal investigator is responsible for ensuring that all trial site personnel, including sub-investigators and other staff members, conduct this trial according to this protocol, Good Clinical Practice (GCP) and International Conference on Harmonisation (ICH) guidelines, the Declaration of Helsinki, and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations during and after trial completion. The principal investigator also agrees not to disclose the information contained in this protocol or any results obtained from this trial without written authorization.

Investigational Material(s):	Hemagglutinin Nanoparticle Influenza Vaccine, Quadrivalent (Quad-NIV), representing A/Michigan/45/2015 (H1N1); A/Singapore/INFIMH-16-0019/2016 (H3N2); B/Colorado/60/2017; and B/Phuket/3073/2013; administered with or without Matrix-M1 Adjuvant
Protocol:	qNIV-E-201
Date of Issue:	21 August 2018

I have read and approve the protocol specified above and agree on its content:

Novavax, Inc.

Signed Electronically

[redacted] Date

Novavax, Inc.

Signed Electronically

[redacted] Date

Novavax, Inc.

Clinical Trial Site

Print Name – Principal Investigator Date

Signature

[redacted] 21 Jun 2022 (GMT-04:00) 2:33:19 PM (GMT-04:00)

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PROTOCOL CHANGE HISTORY

Protocol Version 3.0, 21 August 2018 (revised from Version 2.0, 12 July 2018)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 3.0
Title Page	The Responsible [redacted] has been updated from [redacted] to [redacted]
Synopsis, Section 1.9	Text has been added to the rationale to clarify the method used to evaluate hemagglutination inhibition (HAI) responses in the sponsor's Phase 1/2 trial. Briefly, HAI responses were evaluated by adapting the classical HAI method utilizing recombinant wild-type HA-virus-like particles [VLPs] as the agglutinating agent and human type-O red blood cells (RBCs).
Synopsis, Section 3.1, 3.1.1, Table 1	To ensure safety of trial subjects given this is the first clinical trial of the quadrivalent formulation of the nanoparticle influenza vaccine (Quad-NIV), enrollment has been divided into 3 stages. Stage 1 will enroll a total of approximately 120 subjects (approximately 20 subjects per treatment group, excluding Group D for which no subjects will be enrolled in Stage 1). Stage 2 will enroll a total of approximately 220 subjects (approximately 20 [Groups A, C, D, F, and G] or 60 subjects [Groups B and E] per treatment group). The remainder of the subjects (approximately 1035 subjects total, or 115 [Groups A, C, D, F, and G] or 230 subjects [Groups B and E] per treatment group) will be enrolled in Stage 3. Progression from Stage 1 to Stage 2 and from Stage 2 to Stage 3 will require favorable review of safety data from the previous stage against vaccination holding rules that have been specified in a new Section 3.1.1.1. The total number of trial subjects has been revised to 1375 (previously 1395). Finally, "Site" has been included as a stratification factor.
Synopsis, Section 3.1.1.1	Section has been added to specify vaccination holding rules, which are: 1) The occurrence of more than a single (1) definitely related serious adverse event (SAE) (final assessment by the sponsor per CBER Guidance) in a given MedDRA system organ class (SOC) or more than 2 overall definitely related SAEs per enrollment Stages 1 and 2.

Location of Change	Change/Modification in Version 3.0
	2) The occurrence of any severe (grade 3) solicited (local or systemic) adverse events in > 10% of all subjects.
Synopsis, Section 3.2.2	The secondary endpoints pertaining to any ratios have been modified by repositioning or deleting "Day 0" in the description for clarity.
Synopsis, Section 3.2.3	The exploratory endpoint concerning counts of IFN-γ spot forming units in subjects selected for cellular immune response monitoring has been deleted, as it is not relevant to an objective.
Sections 3.3 – 3.5	It has been indicated that enrollment may be done using a paper-based enrollment system or an integrated web randomization system (IWRS).
Section 3.5	It has been specified that subject trial treatment may be unblinded in the event a vaccination holding rule is met.
Synopsis, Section 5.2	The descriptor "nanoparticle" was deleted from exclusion criterion #2, which now excludes subjects who have participated in any previous Novavax's influenza vaccine clinical trial(s).
Synopsis, Sections 6.1.2, 6.1.4, 7.2, and Appendix	Text has been updated to clarify that, for logistical reasons, selection of the approximately 189 subjects from 3 preselected sites for cell-mediated immune (CMI) testing will be drawn entirely from those enrolled in Stage 3 of the trial.
Section 6.6	Text and Table 2 have updated to only reflect Protocol Deviations (PDs) determined programmatically throughout the trial, and to state that all PDs will be entered into the CRO Clinical Trial Management System (CTMS) by the Clinical Research Associates (CRAs) and/or Clinical Trial Managers (CTMs).
Section 10.1	Analysis of the Intent-to-Treat (ITT) population has been corrected to state "7" treatment groups from the originally stated "6."
Section 10.5	The Sample Size Considerations section has been updated to reflect probabilities for 135, 155, or 310 subjects for each treatment arm.

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Location of Change	Change/Modification in Version 3.0
Section 12	The 2017 Center for Disease Control and Prevention (CDC) reference has been revised from CDC 2017b to CDC 2017, as no other citation from the CDC for the year of 2017 was used in this document.
General	Minor edits and revisions for clarity and readability have been made to the document.

Protocol Version 2.0, 12 July 2018 (revised from Version 1.0, 24 May 2018)
The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 2.0
Synopsis	The Reference Materials and Dosing and Regimen sections have been modified to include Flublok Quadrivalent as a second active comparator (in addition to Fluzone High-Dose).
Section 1.11	The risks associated with Flublok Quadrivalent, based on the Package Insert, have been added.
Section 1.8.1	The total count of SAEs reported in the tNIV-E-101 clinical trial to date has been updated from 12 to 22 in 19 subjects since the finalization of the prior version of this protocol (version 1.0). The distribution of medically-attended AEs for tNIV-E-101 have been updated. Furthermore, Shinde 2018 has been added as a citation to a publication of the trial results in the New England Journal of Medicine. Likewise, the References in Section 12 have been updated.
Synopsis, Sections 2.1, 2.2, and 2.3	The primary, secondary, and exploratory objectives concerning safety and immunogenicity have been modified to add Flublok Quadrivalent as an active comparator.

Location of Change	Change/Modification in Version 2.0
Synopsis, Sections 3.1 and 6.1.10, and Appendix	The Trial Design table and description have been updated to reflect an additional treatment arm (Group G: 2018 - 19 Flublok Quadrivalent injection on Day 0). The total number of treatment arms is now 7 (previously 6), with 155 subjects in Groups A, C, D, F, and G, and 310 subjects in Groups B and E. The total number of trial subjects has been updated to 1395. In addition, the study design description and study visit procedures have been updated to include offering all subjects an injection of a 2019 - 20 licensed seasonal influenza vaccine on the last study visit (Day 364). Finally, the injection volumes (0.5 mL) for each treatment group have been provided.
Section 4.5	Text has been added to specify that Flublok Quadrivalent will be administered based on the manufacturer's instructions, provided in the Pharmacy Manual.
Section 4.6	The manufacturer of the saline placebo has been updated from VWR to Fresenius Kabi.
Synopsis and Section 5.2	Participation in any previous Novavax's nanoparticle influenza vaccine clinical trial has been added as an exclusion criterion. In addition to Fluzone HD and polysorbate 80, exclusion criterion #3 has been updated to exclude subjects who have a history of serious reaction to known components of Flublok Quadrivalent.
Synopsis, Sections 6.1.2, 6.1.4, 7.2, 10.4.2, and Appendix	Text has been updated to clarify that testing for cell-mediated immunity (CMI) responses will be conducted on approximately 189 subjects from 3 preselected sites (or 63 subjects per site; to target a minimum 20 evaluable subjects per treatment group).
Section 6.3	Text has been added to clarify that any influenza vaccines received outside of the study before Day 364 are not permitted and will be considered a protocol deviation. Other routine vaccinations are still permitted for all subjects after completion of the Day 28 visit.
Section 6.4	Text concerning the injections contemplated in this trial has been modified to reflect the addition of Flublok Quadrivalent.
Section 7.2	Immunogenicity assessments have been modified to include Flublok Quadrivalent as an active comparator.

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Location of Change	Change/Modification in Version 2.0
Section 7.2.1	A new section, 7.2.1.1, has been added to clarify the use of 2 different reagents contemplated for use to assess hemagglutination inhibition, ie, egg-based reagents and virus-like particle (VLP)-based reagents as the agglutinating particle.
Synopsis and Section 10.4.2	The pairwise treatment group comparisons for HAI and neutralization endpoints have been updated to include Group G (Flublok Quadrivalent) as a second active comparator.
Synopsis and Section 10.5	The sample size and power calculations have been updated to reflect 155 or 310 subjects for each treatment arm.
General	Minor edits and revisions for clarity and readability have been made to the document.

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TABLE OF CONTENTS

LIST OF TABLES

GLOSSARY OF ABBREVIATIONS

Abbreviation or Term	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APC	Antigen Presenting Cells
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CD	Cluster of Differentiation or Compact Disc
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CMO	Chief Medical Officer
CO_2	Carbon Dioxide
CQA	Clinical Quality Assurance
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTM	Clinical Trial Manager
CTMS	Clinical Trial Management System
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition

Abbreviation or Term	Definition
HD	High-Dose
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMS	Isotope Dilution Mass Spectrometry
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular
IRB	Investigational Review Board
IP	Investigational Product
ITT	Intent-to-treat
IWRS	Interactive Web Randomization System
LLOQ	Lower Limit of Quantitation
mAb	Monoclonal Antibody
MAE	Medically-attended Event
MDCK	Madin Darby Canine Kidney (cells line)
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
MHC	Major Histocompatibility Complex
µL	Microliter
µM	Micromolar
MMP	Methyl-α-D-mannopyranoside
mg	Milligram
mL	Milliliter
mM	Millimolar
MN	Microneutralization
NA	Neuraminidase or Not Applicable
NI	Non-inferiority
NIV	Nanoparticle Influenza Vaccine
nm	nanometer
NP	Nucleoprotein

Abbreviation or Term	Definition
NZW	New Zealand White (rabbits)
OD	Optical Density
PBMC	Peripheral Blood Mononuclear Cell
PD	Protocol Deviation
PP	Per Protocol
PS	Polysorbate
PT	Preferred Term
qNIV or Quad-NIV	Nanoparticle Influenza Vaccine, Quadrivalent
RBC	Red Blood Cell
RDE	Receptor Destroying Enzyme
RSV F	Respiratory Syncytial Virus Fusion
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
Sf	*Spodoptera frugiperda*
SNMC	Significant New Medical Condition
SOC	System Organ Class
SOP	Standard Operating Procedures
SPR	Seroprotection Rate or Surface Plasmon Resonance
SRID	Single Radial Immunodiffusion
TCID	Tissue Culture Infective Dose
TGS	Toxicity Grading Scale
TMAE	Trimethylaminoethyl
TMF	Trial Master File
TNF-α	Tumor Necrosis Factor Alpha
tNIV or Tri-NIV	Nanoparticle Influenza Vaccine, Trivalent
VLP	Virus-Like Particle
VRBPAC	Vaccine and Related Biological Products Advisory Committee
WBC	White Blood Cell
WHO	World Health Organization
w/v	Weight to Volume

CLINICAL PROTOCOL SYNOPSIS

Protocol Number	qNIV-E-201
Title	A Phase 2, Randomized, Observer-blinded, Active-controlled Trial to Confirm the Dose and Formulation of a Recombinant Quadrivalent Nanoparticle Influenza Vaccine (Quad-NIV) with or without Matrix-M1™ Adjuvant in Healthy Adults ≥ 65 Years of Age.
Sponsor and Clinical Phase	Novavax, Inc., 20 Firstfield Road, Gaithersburg, MD 20878 Phase 2
Active Treatment	Hemagglutinin Nanoparticle Influenza Vaccine, Quadrivalent (Quad-NIV), representing A/Michigan/45/2015 (H1N1); A/Singapore/INFIMH-16-0019/2016 (H3N2); B/Colorado/06/2017; and B/Phuket/3073/2013; administered with or without Matrix-M1 Adjuvant.
Reference Materials	Fluzone® High-Dose (HD), egg-derived and formaldehyde-inactivated, seasonal influenza vaccine; and Flublok Quadrivalent®, a recombinant seasonal influenza vaccine, both United States (US)-licensed and manufactured for the 2018 - 2019 influenza season.
Dosing and Regimen	All subjects will receive an intramuscular (IM) injection on Day 0 of their assigned test article. Injections will contain either 240 or 300 µg total hemagglutinin (HA) antigen (differing only in the HA content for the B strains [ie, 60 vs 90 µg HA from each B strain]) with 0, 50, or 75 µg Matrix-M1 adjuvant, either mixed in-clinic or co-formulated in advance of the trial; or the recommended dose of 2018 - 19 Fluzone HD or Flublok Quadrivalent. Subjects who receive the unadjuvanted Quad-NIV will be administered a rescue injection on Day 28 with a licensed 2018 - 19 seasonal influenza vaccine. All other subjects will receive a placebo injection on Day 28. In addition, all subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine at the last study visit (Day 364).
Purpose and Rationale	Data from Novavax's Phase 1/2 clinical trial (tNIV-E-101) of a novel recombinant hemagglutinin (HA) trivalent nanoparticle influenza vaccine (Tri-NIV), containing antigens representing the 3 influenza strains recommended for inclusion in the 2017 - 2018 seasonal influenza vaccine by the Center for Biologics Evaluation and Research (CBER) and the World Health Organization (WHO), and given at a 45 or 180 µg total HA dose (15 or 60 µg HA per strain) with a saponin-based adjuvant (50 µg Matrix-M1), showed that hemagglutination inhibiting (HAI) antibody geometric mean titer (GMT) and ratio of geometric mean titer (GMR) responses (evaluated by adapting the classical HAI method utilizing recombinant wild-type HA-virus-like particles [VLPs] as the agglutinating agent and human type-O red blood cells [RBCs]) against a panel of vaccine-homologous A(H1N1) and A(H3N2) strains, and antigenically-drifted A(H3N2) strains at Day 21, were greater among recipients of 180 µg Tri-NIV than among recipients of the active comparator, Fluzone HD. HAI antibody responses against B/Brisbane were also comparable between 180 µg Tri-NIV and Fluzone HD. Microneutralizing (MN) antibody responses generally supported HAI results, and demonstrated substantially improved responses against circulating antigenically-drifted wild-type A/Singapore (H3N2) virus when comparing 180 µg Tri-NIV to Fluzone HD. Finally, Tri-NIV at both doses was well tolerated by study participants and the safety profile was comparable to that of Fluzone HD, except for slightly elevated counts of severe solicited adverse events among recipients of 180 µg Tri-NIV than among Fluzone HD recipients; however these were overall infrequent and transient. The rationale for the proposed Phase 2 trial and the vaccine formulations to be tested are based on the observations and conclusions derived from the aforementioned Phase 1/2 trial with Tri-NIV; the anticipated requirements of the regulatory pathway to licensure for the nanoparticle influenza vaccine (NIV); and observations regarding the current landscape of licensed seasonal influenza vaccines as follows: • The anticipated licensure pathway for NIV administered with a novel adjuvant, Matrix-M1, will require demonstration of an adjuvant-mediated enhancement of vaccine-induced immunogenicity, and demonstration of an overall favorable risk-benefit profile of NIV formulations containing Matrix-M1, to justify inclusion of an adjuvant.

	• Quadrivalent seasonal influenza vaccine formulations have been widely adopted with the intent of inducing broader protection against co-circulating influenza B viruses of both Victoria and Yamagata lineages and thereby mitigating against the potential for B-lineage vaccine and circulating strain mismatch that may limit the efficacy. • To induce immune responses to influenza B antigens, which are competitive with, and ideally superior to, Fluzone HD or Flublok Quadrivalent, 2 licensed seasonal influenza vaccines deployed among adults ≥ 65 or ≥ 18 years of age in the US, respectively, and represent 2 leading and divergent approaches currently used to develop influenza vaccines with enhanced efficacy (ie, egg-based and recombinant). The immunogenicity of influenza B antigens contained in NIV might be further enhanced either by increasing the dose of B antigens or by increasing the dose of Matrix-M1 adjuvant. • The desired NIV presentation for a future pivotal Phase 3 trial, regulatory licensure, and eventual launch will be a manufactured co-formulation of HA nanoparticle antigen with Matrix-M1 adjuvant. To evaluate the safety and immunogenicity performance of co-formulated NIV, the proposed trial will seek to describe the comparability of co-formulated NIV with Matrix-M1 as compared to in-clinic, bedside-mixed NIV with Matrix-M1 (as examined in the prior Phase 1/2 trial). This Phase 2 trial will evaluate a quadrivalent nanoparticle influenza vaccine (Quad-NIV), containing antigens representing the 4 influenza strains recommended for inclusion in the 2018 - 2019 Northern hemisphere seasonal influenza vaccine [VRBPAC 2018, WHO 2018]. The goals of this trial are to: a) demonstrate a statistically significant Matrix-M1 adjuvant effect on vaccine-induced immunogenicity to vaccine-homologous or antigenically-drifted influenza strains; b) compare the immunogenicity of Quad-NIV prepared by in-clinic mix versus co-formulation prior to vialing; c) describe the effect on Quad-NIV immunogenicity of either increased B antigen dose or increased Matrix-M1 dose with regard to all vaccine-homologous strain immune responses, but especially those to the B viruses; d) describe the immunogenicity to vaccine-homologous and antigenically-drifted influenza strains of all formulations of Quad-NIV relative to the 2 active comparators, Fluzone HD and Flublok Quadrivalent; and e) describe the safety profile of all formulations of Quad-NIV and the active comparators.
Primary Objectives	• To describe the safety and tolerability of Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain) and formulations, without adjuvant or with 1 of 2 different doses of Matrix-M1 adjuvant (mixed in-clinic or co-formulated in advance of the trial), relative to 2 US-licensed comparators, Fluzone HD (Sanofi Pasteur) and Flublok Quadrivalent (Sanofi Pasteur, previously Protein Sciences Corp), in healthy adults ≥ 65 years of age. The safety profile will include solicited short-term reactogenicity; 28-day all adverse event (AE) profile; 1-year post-injection medically-attended adverse event (MAE), serious adverse event (SAE), and significant new medical condition (SNMC) profile; and selected pre- and post-vaccination clinical laboratory parameters. • To demonstrate a Matrix-M1 adjuvant effect by demonstrating the immunogenic superiority of Quad-NIV (60 µg HA per A and B strain) co-formulated with 50 µg Matrix-M1 as compared to Quad-NIV (60 µg HA per A and B strain) without adjuvant. Immunogenic superiority will be demonstrated by excluding values ≤ 1.0 at the lower 95% confidence bound for the baseline-adjusted ratio of Day 28 post-vaccination HAI titers (ie, GMT adjuvant / GMT no adjuvant) for not less than 2 out of 6 influenza strains (ie, any 2 of 4 vaccine-homologous strains and/or 2 antigenically-drifted influenza strains), while no other strain(s) demonstrate a baseline-adjusted ratio of Day 28 post-immunization HAI titers which is significantly < 1.0.
Secondary Objectives	• To compare the immunogenicity of Quad-NIV (60 µg HA per each A and B strain) with 50 µg of Matrix-M1 co-formulated prior to administration relative to a similar formulation mixed in-clinic and also to 2 US-licensed active comparators, Fluzone HD and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, in terms of HAI antibody responses

	against vaccine-homologous A and B strain(s), and antigenically-drifted influenza strains (multiple informative strains may be tested) at Days 0 and 28 post-vaccination. • To describe the immunogenicity of formulations of Quad-NIV with increased B-antigen dose (60 µg HA per A strain and 90 µg HA per B strain; and 50 µg of Matrix-M1) or increased Matrix-M1 dose (60 µg HA per A strain and B strain; and 75 µg of Matrix-M1) relative to the "standard" co-formulated Quad-NIV formulation (60 µg HA per each A and B strain; and 50 µg of Matrix-M1) and also to 2 US-licensed active comparators, Fluzone HD and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, in terms of HAI antibody responses against all vaccine-homologous A and B strain(s), and antigenically-drifted influenza strains (multiple informative strains may be tested) at Days 0 and 28 post-vaccination. • To evaluate the longevity of immune responses to Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain) and formulations, 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 and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, based on HAI responses against vaccine-homologous and antigenically-drifted influenza strains (multiple informative strains may be tested) post-vaccination on Days 0, 28, 56, 182, and 364.
Exploratory Objectives	• To describe the immunogenicity of Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain) and formulations, 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 and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, based on microneutralization (MN) responses to vaccine-homologous and antigenically-drifted influenza strains (multiple informative strains may be tested), at Days 0 and 28 post-vaccination. Note: Due to the time-consuming nature of MN testing, this exploratory objective may be completed in a random subset of participants in each study treatment group after the initial study HAI data are complete and reported in an addendum. Laboratory staff will remain blinded as to treatment assignments until all projected MN tests are complete. Additional time points may also be tested (ie, Days 56, 182, and 364). • To describe the quality and amplitude of cell-mediated immune (CMI) responses in healthy adults ≥ 65 years of age to vaccination with Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain) and formulations, without adjuvant or with 1 of 2 different doses of Matrix-M1 adjuvant (mixed in-clinic or co-formulated in advance of the trial), based on functional T cell responses based on intracellular cytokine analysis. Due to the laborious nature of the cellular assays, they will be performed on subjects drawn from a limited number of preselected sites and results may be reported as an addendum to the main clinical study report. • To describe the vaccine response among subjects with low baseline HAI titers in terms of 2 or 4-fold increases in HAI titers. "Low baseline" will be defined as lowest quintile.
Primary Endpoints:	• Safety and tolerability of Quad-NIV at different doses and formulations: Number and percentage (95% CI) of subjects with solicited local and systemic adverse events over the 7 days post-injection (ie, Day 0 through Day 6, inclusive); all adverse events (including adverse changes in clinical laboratory parameters) through 28 days post-injection (ie, Day 0 through Day 27, inclusive); and MAEs, SAEs, and SNMCs – including

	immunologically-mediated adverse events of special interest (AESIs) - through 1 year post-injection. • HAI antibody titers specific for the HA receptor binding domains of vaccine-homologous A and B strain(s), and at least 2 antigenically-drifted influenza strains, at Days 0 and 28 post-vaccination. 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 Day 28. ○ Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).
Secondary 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: ○ GMT, as described above, on Days 0, 28, 56, 182, and 364. ○ Geometric mean ratio (GMR) – defined as the ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs ($GMR_{Post/Pre}$) on Days 28, 56, 182, and 364. ○ Seroconversion rate (SCR) – defined as proportion of subjects 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 on Days 28, 56, 182, and 364. ○ Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 on Days 28, 56, 182, and 364. ○ Ratio of GMTs between treatment arms at Days 28, 56, 182, and 364 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).
Exploratory Endpoints	• Microneutralization (MN) responses: Neutralizing antibody titers specific to vaccine-homologous A and B strain(s) and antigenically-drifted influenza strains, at Days 0 and 28 post-vaccination, as measured by a microneutralization assay. Note: additional time points may also be assessed. Derived/calculated endpoints based on these data will include: ○ GMT – defined as the antilog of the mean of the log-transformed neutralizing titer for a given treatment group. ○ GMR – defined as the ratio of post-vaccination and pre-vaccination neutralizing GMTs within the same treatment group (designated as $GMR_{Post/Pre}$). ○ SCR – defined as proportion of subjects in a given treatment group with either a baseline reciprocal titer of $<$ lower limit of quantitation (LLOQ) and a post-vaccination reciprocal titer 4-fold higher than the LLOQ, or a baseline reciprocal titer of $\geq$ LLOQ and a post-vaccination reciprocal titer $\geq$ 4-fold higher than the baseline titer. ○ Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). • Proportions of Days 0 and 7 peripheral blood T cell isolates that secrete IL-2, IFN-γ, and TNF-α cytokines following in vitro restimulation with HA in subjects selected for cellular immune response monitoring. • HAI titers, as described above.
Trial Design	This is a Phase 2, randomized, observer-blinded, active-controlled, dose-finding, formulation-optimizing trial in healthy adults $\geq$ 65 years of age to be conducted in the United States. Up to 1375 eligible subjects will be enrolled and randomized into 1 of 7 treatment groups, as shown in the Trial Design table below. The base case groups for demonstration of adjuvant effect, ie, Groups B and E, will each consist of approximately 310 subjects. The remaining groups will consist of approximately 135 (Group D) or 155 (Groups A, C, F, and G) subjects each. All groups will be stratified by site and history of receipt of 2017 - 18 influenza vaccine. On Day 0, all subjects will receive a study treatment as indicated in the Trial Design table by intramuscular (IM) injection. Total injection volumes for each treatment group will be 0.5 mL. On Day 28, subjects in Group E will be administered a rescue injection with a 2018 - 19

	licensed seasonal influenza vaccine. All other subjects will receive a placebo injection on Day 28 to maintain trial blind. Trial follow-up for each subject will span approximately 1 year from the Day 0 injection. It is anticipated that a percentage of the randomized trial subjects will not complete the trial. Subjects who withdraw or are discontinued will not be replaced. In addition, all subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine at the last study visit (Day 364). Enrollment will be divided into 3 stages. Stage 1 will enroll a total of approximately 120 subjects (approximately 20 subjects per treatment group, excluding Group D for which no subjects will be enrolled in Stage 1). Stage 2 will enroll a total of approximately 220 subjects (approximately 20 [Groups A, C, D, F, and G] or 60 subjects [Groups B and E] per treatment group, as per the Trial Design table). The remainder of the subjects (approximately 1035 subjects total, ie, 115 [Groups A, C, D, F, and G] or 230 subjects [Groups B and E] per treatment group, as per the Trial Design table) will be enrolled in Stage 3. Progression from Stage 1 to Stage 2 and from Stage 2 to Stage 3 will require favorable review of safety data from the prior stage against vaccination holding rules as defined in the Safety Monitoring of Enrollment and Vaccinations Section below.
Safety Monitoring of Enrollment and Vaccinations	Vaccination holding rules will be used to govern progression from Stage 1 to Stage 2, and from Stage 2 to full enrollment in Stage 3. Solicited and unsolicited AEs reported from all Stage 1 subjects within 7 days of Day 0 vaccination will be evaluated against vaccination holding rules (see Vaccination Holding Rules below). These AE data will be summarized by the sponsor statistician, reviewed, and provided to an independent medical monitor in aggregate form (without unblinding or subdivision by treatment group). In Stage 1, if vaccination holding rules are not met based on Day 7 data, the independent medical monitor will notify the sponsor's responsible physician to proceed with Stage 2 enrollment of additional subjects in all groups, including 20 subjects in Group D. In Stage 2, if vaccination holding rules are not met based on Day 7 data, the independent medical monitor will notify the sponsor's responsible physician to proceed with enrollment of the balance of subjects in Stage 3. If vaccination holding rules are met in either Stage 1 or 2, the independent medical monitor will notify the sponsor's responsible physician, who will pause enrollment pending further review and request that the sponsor's Chief Medical Officer (CMO) authorize unblinding of the relevant data. Relevant data will include at least the total counts of subjects treated at the time of the hold in each treatment arm; and the treatment assignments, screening history, physical exam(s), concomitant medications, and overall solicited and unsolicited adverse event profiles of the subject(s) triggering the hold. (It is noted that this review may use unmonitored data.) Upon review, the CMO may authorize review of other data. The independent medical monitor and the sponsor's responsible physician and CMO will review the unblinded data and develop a report and recommendation to either: a) resume enrollment, b) amend the protocol and resume enrollment, or c) terminate the protocol. The report, the recommendation, and the amended protocol and ICF (if relevant), will be provided to the IRB and CBER and enrollment will not recommence until IRB approval is obtained, unless the vaccination holding rule was triggered in a comparator arm (ie, Fluzone HD [Group F] or Flublok Quadrivalent [Group G]).
Vaccination Holding Rules	Adverse event reports meeting any 1 of the following 2 criteria will result in a hold being placed on subsequent enrollment and vaccinations, pending further review by the independent medical monitor and sponsor as above: 1) The occurrence of more than a single (1) definitely related serious adverse event (final assessment by the sponsor per CBER Guidance) in a given MedDRA system organ class (SOC) or more than 2 overall definitely related SAEs per enrollment Stages 1 and 2. 2) The occurrence of any severe (grade 3) solicited (local or systemic) adverse events in > 10% of all subjects. If vaccination holding rules are met at any review point, the independent medical monitor and sponsor personnel will review a summary of all individual data of the relevant subject(s),

	including the unblinded treatment assignment, and summary safety data relative to all treatment groups.
	Trial Design for qNIV-E-201

	Day 0 Trial Treatment Injection				Day 28 Injection[2]	Subjects per Enrollment Stage			Subjects Per Group
Treatment Group	Vaccine	HA Dose per Strain, µg (H1N1/H3N2/ B_V/B_Y)	Matrix-M1 Adjuvant Dose, µg	Formulation		Stage 1[3]	Stage 2[3]	Stage 3[3]	
A	Quad-NIV	60, 60, 60, 60	50	In-Clinic Mix	Placebo	20	20	115	155
B		60, 60, 60, 60	50	Co-form	Placebo	20	60	230	310
C		60, 60, 60, 60	75	Co-form	Placebo	20	20	115	155
D		60, 60, 90, 90	50	Co-form	Placebo	0	20	115	135
E		60, 60, 60, 60	0	NA	2018 - 19 Licensed Seasonal Influenza Vaccine	20	60	230	310
F	2018 - 19 Fluzone HD [1]				Placebo	20	20	115	155
G	2018 - 19 Flublok Quadrivalent [1]				Placebo	20	20	115	155
					Total Trial Subjects	120	220	1035	1375

Abbreviations: B_V = B Victoria lineage; B_Y = B Yamagata lineage; Co-form = co-formulated; HA = Hemagglutinin; NA = not applicable.

Note: All subjects will receive 2 vaccinations by IM injection in alternating deltoids on Day 0 and Day 28.

[1] Fluzone HD and Flublok Quadrivalent will be administered at the manufacturer's recommended dose and volume.

[2] On Day 28, subjects in Group E will receive a rescue injection with a licensed seasonal influenza vaccine; all other subjects will receive a placebo injection to maintain trial blind.

[3] Enrollment will be divided into 3 stages. Stage 1 will enroll a total of approximately 120 subjects (approximately 20 subjects per treatment group, excluding Group D for which no subjects will be enrolled in Stage 1). Stage 2 will enroll a total of approximately 220 subjects (approximately 20 [Groups A, C, D, F, and G] or 60 subjects [Groups B and E] per treatment group). The remainder of the subjects (approximately 1035 subjects total, ie, 115 [Groups A, C, D, F, and G] or 230 subjects [Groups B and E] per treatment group) will be enrolled in Stage 3.

Trial Visit Procedures

All subjects will undergo procedures summarized in the Schedule of Events table and described in detail below.

Day 0 – Screening Visit

Clinically stable male and female volunteers, ≥ 65 years of age, who have provided written informed consent to participate in the trial and who are able to comply with trial requirements, will have the following procedures performed: review of inclusion and exclusion criteria; medical history, including influenza vaccination history during the previous 3 years (with emphasis on the 2017 - 18 vaccine) and history of adverse reactions to prior influenza vaccines and allergies; medication history; physical examination of HEENT (head, eyes, ears, nose, and throat), abdomen, extremities, and at least inguinal, cervical, and axillary nodes, gross motor function, and skin; vital signs (heart rate, blood pressure, respiratory rate, and oral temperature), height, and weight; and assessment of concomitant medications. Note that further procedures may be performed at the investigator's discretion in order to adequately screen subjects against eligibility criteria. Potential subjects who meet all inclusion criteria and none of the exclusion criteria (see Inclusion/ Exclusion criteria) may be enrolled. *Note: Subjects should be free of acute illness (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature ≥ 38.0°C) in order to receive the test article injection. Subjects presenting with an acute illness on screening may return to the trial site within the next 7 days to receive their injection provided symptoms have resolved; no repetition of baseline serology or clinical laboratory testing is necessary if the subject returns within 7 days.*

	Day 0 – Trial Treatment Injection Visit All subjects who have eligibility confirmed will be randomized to 1 of 7 treatment groups and will have blood drawn for baseline immunogenicity testing (eg, HAI and MN titers; 20 mL) and clinical laboratory safety parameter assessments (ie, serum chemistry and hematology; 10 mL). Approximately 189 subjects from 3 preselected sites (or 63 subjects per site; to target a minimum 20 evaluable subjects per treatment group) will provide additional blood samples (27 mL) at 2 time points (ie, Days 0 and 7) to support testing of cell-mediated immune responses (CMI). Consent documentation at these sites will be suitably modified. For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3. Subjects will then receive a single IM injection of their assigned treatment into the deltoid muscle of the non-dominant arm. (If the non-dominant arm is not available due to post-surgical changes, skin changes, or prior injury, the dominant arm may be used). Subjects will be monitored in the clinic for approximately 30 to 60 minutes following injection with trial treatment for the occurrence of any local injection site or systemic reactions, including evaluation of vital signs. Starting on vaccination day (Day 0) and for 6 days thereafter (Day 0 through Day 6 inclusive), subjects will maintain diaries for daily recording of their body temperature and any adverse event spontaneously offered. In addition, the following local injection site and systemic reactions will be solicited by diary: injection site (local) events – pain, bruising, redness, and swelling; general systemic events – oral temperature, chills, muscle pain, joint pain, diarrhea, nausea, vomiting, headache, and fatigue; and facial/respiratory systemic events – cough, difficulty breathing, difficulty swallowing, hoarseness, chest tightness, sore throat, wheezing, eye redness, and facial swelling. Subjects will also be asked to record any concomitant medications, physician visits, or hospitalizations associated with these solicited adverse events. ***Follow-up Telephone Contact/In-clinic Visits*** Safety follow-up visits will be performed by scripted telephone contact on Day 3 (± 1 day) to query for any grade 3 solicited or unsolicited event and/or SAE experienced and concomitant medications taken for these events since the last visit. *Subjects who report a grade 3 event and/or SAE may be asked to return to the clinic for an unscheduled visit at the investigator's discretion.* All subjects will have an in-clinic visit on Day 7 (± 1 day) for collection of vital signs, diary review, and query for any AEs and concomitant medications taken. In addition, on Day 7, approximately 189 subjects from 3 preselected sites (or 63 subjects per site) will provide blood samples for post-vaccination CMI responses (27 mL). On Day 28 (± 2 days), subjects will return again for collection of vital signs, to provide blood samples for post-vaccination immunogenicity testing (20 mL) and clinical safety parameters (10 mL), and to report any AEs, MAEs, SNMCs, and SAEs occurring since the last visit, and any concomitant medications taken. Subjects in Group E will be administered a rescue IM injection on Day 28 with a licensed 2018 - 2019 seasonal influenza vaccine. All other subjects will receive placebo. Administration will be performed in the opposite arm used on Day 0. (If the opposite arm is not available due to changes as described above, the same arm used for the Day 0 injection may be used for the Day 28 injection, provided that all local reactogenicity due to the first injection has resolved.) *Subjects should be free of acute illness (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature ≥ 38.0°C) in order to receive the rescue injection. Subjects presenting with an acute illness on Day 28 may return to the trial site within the next 7 days to receive their 2nd vaccination. If a subject has experienced any AEs/SAEs between trial Days 0 and 28, then Day 28 vaccination may be administered or delayed for up to 7 days based on the Investigator's discretion.* Subjects will be monitored in the clinic for approximately 30 to 60 minutes following injection with trial treatment for the occurrence of any local injection site or systemic reactions, including evaluation of vital signs. Subjects will return to the clinic on Days 56 (± 2 days), 182 (± 7 days), and 364 (± 14 days) for collection of vital signs, to provide blood samples for post-vaccination immunogenicity

testing (20 mL), and to report any MAEs, SNMCs, and SAEs occurring since the last trial visit, and any concomitant medications taken for these events.

Additional telephone contacts will occur on Day 90 (± 7 days) and 273 (± 7 days) to query for any MAEs, SNMCs, and SAEs occurring since the last trial visit, and any concomitant medications taken for these events.

Finally, all subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine at the last study visit (Day 364).

Schedule of Events:

Trial Day:	**0**	**3**	**7**	**28**	**56**	**90**	**182**	**273**	**364**
Window (days):		**± 1**	**± 1**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**
Trial Procedures									
Trial Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical/Medication History	X								
Physical Exam	X		X [7]	X [7]	X [7]		X [7]		X [7]
Vital Signs	X [1]		X	X [1]	X		X		X
Clinical Safety Laboratory [2]	X			X					
Serology	X			X	X		X		X
PBMC for CMI	X[8]		X[8]						
Trial Treatment Injection	X								
Injection with a licensed 2018 - 19 seasonal influenza vaccine or placebo [6]				X					
2019 – 20 seasonal influenza vaccine offered to all subjects [9]									X
Adverse Event Review [4]	X	X [3]	X	X	X	X	X	X	X
Concomitant Medications Review [4]	X	X	X	X	X	X	X	X	X
Subject Diary Review		X [3]	X [5]						
End of Trial									X

	Note: Procedures shaded in grey are performed via scripted telephone call. [1] Vital signs to be captured pre-vaccination and between 30 to 60 minutes post-vaccination. [2] Includes assessments for hematology (complete blood count [CBC] with hemoglobin, hematocrit, red blood cell [RBC] count, platelet count, and white blood cell [WBC] count with differential) and serum chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase, creatinine, and blood urea nitrogen [BUN]). [3] Subjects will be asked to report any grade 3 solicited or unsolicited adverse event or SAE experienced since the last visit and may be asked to return to the clinic for an unscheduled visit to evaluate the event(s) at the Investigator's discretion. [4] All adverse events and concomitant medications taken will be collected through Day 28; thereafter, only MAEs, SAEs, and SNMCs and medications taken for these events will be collected. [5] The subject diary will be reviewed by the investigator and collected on Day 7 visit. [6] On Day 28, subjects in Group E will receive a rescue injection with a licensed seasonal influenza vaccine; all other subjects will receive a placebo injection to maintain trial blind. [7] If needed, a physical examination may be performed, based on the investigator's discretion. [8] To be collected from approximately 189 subjects from 3 preselected sites (63 subjects per site). Note: For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3 of the trial. [9] All subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine at the last study visit (Day 364).
Inclusion Criteria	Subjects must meet the following criteria to be eligible to participate: 1) Clinically-stable adult male or female, ≥ 65 years of age. Subjects may have 1 or more chronic medical diagnoses, but should be clinically stable as assessed by: • Absence of changes in medical therapy within 1 month due to treatment failure or toxicity, • Absence of medical events qualifying as serious adverse events within 2 months; and • Absence of known, current, and life-limiting diagnoses which render survival to completion of the protocol unlikely in the opinion of the investigator. 2) Willing and able to give informed consent prior to trial enrollment, and 3) Living in the community and able to attend trial visits, comply with trial requirements, and provide timely, reliable and complete reports of adverse events.
Exclusion Criteria	Subjects will be excluded if they meet any of the following criteria: 1) Participation in research involving investigational product (drug / biologic / device) within 45 days before planned date of first injection. 2) Participation in any previous Novavax's influenza vaccine clinical trial(s). 3) History of a serious reaction to prior influenza vaccination, known allergy to constituents of Fluzone HD, Flublok Quadrivalent, or polysorbate 80. 4) History of Guillain-Barré Syndrome (GBS) within 6 weeks following a previous influenza vaccine. 5) Received any vaccine in the 4 weeks preceding the trial vaccination and any influenza vaccine within 6 months preceding the trial vaccination. 6) Any known or suspected immunosuppressive illness, congenital or acquired, based on medical history and/or physical examination. 7) 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 trial vaccine. 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. 8) Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the trial vaccine or during the trial. 9) 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). 10) Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled or could interfere with evaluation of the vaccine or interpretation of trial results

	(including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting). 11) Known disturbance of coagulation. 12) Suspicion or recent history (within 1 year of planned vaccination) of alcohol or other substance abuse.
Statistical Methods	**General** Continuous variables will be presented by summary statistics (eg, mean and standard deviation [SD] for the non-immunogenicity endpoints; geometric means and their 95% CI for the immunogenicity endpoints). Categorical variables will be presented by frequency distributions (frequency counts and percentages for the non-immunogenicity endpoints; percentages and their 95% CIs for the immunogenicity endpoints). **Analyses Concerning Safety Objectives** Safety analysis will be descriptive and based on the safety population, defined as all subjects who received a dose of trial treatment. Safety will be summarized overall and by individual treatment arms based on solicited short-term reactogenicity post-injection on Day 0, 28-day all AE profile by MedDRA preferred term, and 1-year MAE, SAE, and SNMC profiles post-injection on Day 0. All AEs, including MAEs, SAEs, and SNMCs, will be tabulated by severity, related (possibly, probably, or definitely vs. non-related per investigator assessment), and severe and related. The number and percentage (with 95% CI) of subjects in each treatment group with a given term will be summarized. A listing and narratives of SAEs will also be produced. **Analyses Concerning the Primary Immunogenicity Objective of Adjuvant Effect** The primary immunogenicity analysis will be based on the per-protocol (PP) population. A separate intent-to-treat (ITT) population analysis will not be produced unless > 5% of at least 1 treatment group is excluded from the PP population. For GMTs and GMRs, titers reported below the lower limit of quantitation (LLOQ) (ie, below the starting dilution of assay reported as "< 10") will be set to half that limit (ie, 10 / 2 = 5). Immunogenic superiority of the adjuvanted treatment group (treatment group B) relative to the unadjuvanted Quad-NIV group (treatment group E) will be demonstrated by excluding values ≤ 1.0 at the lower 95% confidence bound for the baseline-adjusted ratio of Day 28 post-vaccination HAI titers (ie, GMT adjuvant / GMT no adjuvant) for not less than 2 out of 6 influenza strains (ie, any 2 of: 4 vaccine-homologous strains and/or 2 antigenically-drifted influenza strains), while no other strain(s) demonstrate a baseline-adjusted ratio of Day 28 post-immunization HAI titers which is significantly < 1.0 (See Sample Size Considerations for details). HAI antibody titers specific for each of the vaccine-homologous and antigenically-drifted influenza strains tested will be summarized by treatment group based on GMT at baseline (screening) and post-vaccination on Day 28 (with 95% CIs), and by ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). **Analyses Concerning the Secondary and Exploratory Immunogenicity Objectives** HAI and neutralization responses will be assessed in terms of GMT, GMR, SCR, and SPR (HAI only) at Days 0, 28, 56, 182, and 364. Note: MN will be assessed at Days 0 and 28 and may include additional time points. P-values may be generated for information and planning of future studies, but will not be adjusted for multiple comparisons. HAI and neutralizing antibody titers specific for each of the virus strains will be summarized by treatment group for each virus stain tested at all time points, including baseline (Day 0) as reference, based on the following parameters (with 95% CIs): • Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed HAI titers at a given time point. • Geometric mean ratio (GMR) – defined as the ratio of post-vaccination to pre-vaccination HAI GMTs ($GMR_{Post/Pre}$) at a given post-vaccination time point.

	• Seroconversion rate (SCR) – defined as proportion of subjects 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 at a given post vaccination time point. • Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 at a given time point (HAI only). • Ratio of GMTs between treatment arms at Days 28, 56, 182, and 364 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). • Proportion of subjects with ≥ 2-fold or ≥ 4-fold increases in HAI titers among those with low baseline titers (ie, lowest quintile) (exploratory endpoint only). For HAI and neutralization endpoints (all strains tested and at all time points), the following treatment group differences will be estimated to address secondary and exploratory objectives: • 60 µg HA per A strain and 90 µg HA per B strain; and 50 µg of Matrix-M1 (Group D) vs Fluzone HD or Flublok Quadrivalent (Group F or G). • 60 µg HA per A strain and B strain; and 75 µg of Matrix-M1 (Group C) vs Fluzone HD or Flublok Quadrivalent (Group F or G). • 60 µg HA per A strain and B strain; co-formulated with 75 µg of Matrix-M1 (Group C) vs 60 µg HA per A strain and B strain; co-formulated with 50 µg of Matrix-M1 (Group B). • 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs a similar formulation mixed bedside (Group A). • 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs Fluzone HD or Flublok Quadrivalent (Group F or G). • 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs 60 µg HA per A and B strain without adjuvant (Group E). • 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs 60 µg HA per A strain and 90 µg HA per B strain; and 50 µg of Matrix-M1 (Group D). Percentages of subjects with immune response will be calculated along with the corresponding 2-sided exact (Clopper-Pearson) binomial CIs. GMTs will be summarized by treatment group and visit day along with the corresponding 2-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. Two-sided 95% CIs for the difference in SCRs and SPRs between treatment groups will be based on the Newcombe hybrid score (METHOD = SCORE riskdiff-option for PROC FREQ in SAS). The comparison of GMTs between treatment groups (ie, the ratio of GMTs) will be conducted on log-transformed titers using the analysis of covariance (ANCOVA) adjusted for the baseline (Day 0) value by including the baseline titer as a covariate. Reverse cumulative distribution displays of HAI and MN titers corresponding to the comparisons described above for each virus strain will be produced in which Day 0 and Days 28, 56, 182, and 364 distributions will be displayed separately by treatment group. Note: MN will be assessed at Days 0 and 28 and may include additional time points. Analysis of exploratory CMI response endpoints will be performed on approximately 189 subjects from 3 preselected sites (63 subjects per site) and results may be reported as an addendum to the main clinical study report.
Sample Size Considerations	For safety endpoints, the probability of observing at least 1 adverse event among 135, 155, or 310 subjects for each Quad-NIV formulation is > 90% if the true rate of such events is 1.7%, 1.5%, or 0.8%, respectively. With 135, 155, or 310 subjects for each treatment group, observing no adverse events of interest (eg, vaccine-related SAE) would represent an upper bound of the 1-sided 95% CI on the percentage of such event is 2.2%, 1.9%, or 1.0%, respectively. This study has a single comparison of 2 treatment groups (Group B vs E) for the primary objective. No formal adjustment for multiple comparisons is planned for the 6 comparisons

associated with the 6 strain-specific GMTs. The demonstration of the superiority of Quad-NIV (60 µg HA per A and B strain) co-formulated with 50 µg Matrix-M1 (Group B) as compared to Quad-NIV (60 µg HA per A and B strain) without adjuvant (Group E) requires simultaneous successes of all 6 tests (at least 2 strains meeting the strain-specific superiority criterion and the non-inferiority criterion for the remaining homologous strains). The non-inferiority for this trial will be carried out without a pre-specified margin. Non-inferiority is defined as the 2-sided 95% CI for the ratio of GMTs (Group B / Group E) containing 1.0 (ie, unadjusted 1-sided p-value ≥ 0.025 against the null hypothesis of H0: Ratio of GMT ≤ 1.0). The superiority is defined as the lower limit of the 2-sided 95% CI for the ratio of GMTs (Group B / Group E) > 1.0 (ie, unadjusted 1-sided p-value < 0.025 against the null hypothesis of H0: Ratio of GMT ≤ 1.0). For other immunogenicity analyses, the purpose is to determine a dose and formulation for the next study based on all available safety and immunogenicity results, including the primary objective analysis. Hence, any statistical analyses (ie, calculations of CIs and p-values) will also be performed without a multiplicity adjustment.

In a previous study using the Tri-NIV formulation (tNIV-E-101), the observed strain-specific standard deviations of $\log_{10}$ HAI titers ranged from approximately 0.4 (B/Brisbane and A/Texas) to approximately 0.6 (A/Switzerland and A/Singapore). The table below summarizes power, unadjusted for multiple comparisons, for the primary objective to demonstrate superiority for pair-wise comparisons of 2 treatment groups. Power calculations also accounted for a 5% attrition rate for the per-protocol population (295 evaluable subjects per treatment group) which is the primary analysis population for all immunogenicity endpoints. For each strain, this study is designed to detect a 1.4-fold increase (40% increase) in GMTs with ≥ 84% power. For 2 strains, this study is designed to detect a 1.5-fold increase (50% increase) in GMTs with ≥ 88% power. For each strain, there will be 97.5% probability of demonstrating a non-inferior GMT for each comparison if 2 treatment groups have an equal GMT. Therefore, demonstrating a superiority against 2 strains with the true difference of 1.5-fold and a non-inferiority against 4 strains with the true difference of 1.0-fold, this study is designed to provide ≥ 80% power.

Power to Detect % Increase in Ratio of GMTs Between 2 Treatment Groups

Per-Protocol N	$\log_{10}$ SD	Fold Increase	Power
295	0.4	1.2	67%
		1.3	93%
		1.4	99%
		1.5	> 99%
		1.6	> 99%
		1.7	> 99%
	0.5	1.2	48%
		1.3	79%
		1.4	94%
		1.5	99%
		1.6	> 99%
		1.7	> 99%
	0.6	1.2	36%
		1.3	63%
		1.4	84%
		1.5	94%
		1.6	98%
		1.7	> 99%

1 INTRODUCTION

1.1 Influenza Virus

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, hemagglutinin (HA) and neuraminidase (NA). 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].

1.2 Influenza Disease Burden in Older Adults

Older adults are at the greatest risk of hospitalization and death due to influenza infection [CDC 2018b]. 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].

1.3 Licensed Vaccines Against Influenza Virus for Older Adults

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 2017 - 18 influenza season, indicated for various populations [FDA 2018, CDC 2018a]. 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 Quadrivalent® (Sanofi Pasteur, previously Protein Sciences). Five trivalent inactivated or recombinant influenza vaccines are also approved and marketed for the 2017 - 18 influenza season in the US. Only 1 influenza vaccine is approved with an adjuvant (FLUAD™ with adjuvant MF59) [CDC 2018a].

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 (ie, FLUAD initially approved in the US in 2015) trivalent inactivated influenza vaccine [CDC 2018a]. 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 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, 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 2018a]. This variability is multifactorial, but likely, in part during several seasons, 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.2a viruses replaced A/Texas/50/12-like clade 3C.1 viruses represented in the vaccines. This mismatch between vaccine and circulating viruses resulted in vaccine effectiveness not different from zero [Skowronski 2016]. Emerging data also demonstrate other mechanisms that may account for reduction in vaccine efficacy, specifically the increasingly-recognized problem of antigenic changes arising from egg-based influenza vaccine production. It has been shown that hemagglutinin proteins produced by viruses replicating in eggs 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 very poor effectiveness of 2017 vaccines against A(H3N2) viruses in Australia [Sullivan 2017]. Thus, there remains a significant need for 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 the 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 hemagglutination inhibiting (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.

1.4 Novavax's Nanoparticle Influenza Vaccines

1.4.1 Trivalent (Tri-NIV)

Novavax's Tri-NIV, a precursor to Quad-NIV, was based on purified, recombinant, full-length HA that self-assembles into distinct nanoparticle structures of approximately 20 to 40 nm [Smith 2017]. A baculovirus/Spodoptera frugiperda (Sf9) insect cell system was used to clone and express 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 [WHO 2017].

The safety and immunogenicity of Tri-NIV have been investigated in a Phase 1/2 clinical trial and the results (see Section 1.8.1) were used to inform the Phase 2 clinical trial design of Quad-NIV.

1.4.2 Quadrivalent (Quad-NIV)

Novavax's Quad-NIV is manufactured in the same manner as Tri-NIV, based on purified, recombinant, full-length HA that self-assemble into distinct nanoparticle structures of approximately 20 to 40 nm [Smith 2017]. 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 2018 - 19 Northern Hemisphere influenza season: A/Michigan/45/2015 (H1N1); A/Singapore/INFIMH-16-0019/2016 (H3N2); B/Colorado/06/2017 (Victoria lineage); and B/Phuket/3073/2013 (Yamagata lineage) [VRBPAC 2018, WHO 2018]. Quad-NIV differs from Tri-NIV mainly in the presence of an additional B strain of the Yamagata lineage, which results in a total HA antigen content 33 to 66% higher than the trivalent formulation. Quad-NIV will be evaluated alone or with 50 µg (the same dose used in Tri-NIV) or 75 µg of Matrix-M1 adjuvant.

1.5 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 1 or more components of the innate immune system, a system that provides a rapid response to infection or tissue damage based on recognition of molecular structures common to large groups of microbial pathogens [Coffman 2010]. Thus, adjuvants may both quantitatively increase the antibody response and also qualitatively broaden its specificity. In addition, some adjuvants may modulate the cellular immune response.

Matrix-M1 is a saponin-based adjuvant, which can be co-administered with an antigen to induce a targeted immune response. Matrix-M1 is manufactured by mixing defined, partially-purified extracts of the bark of the *Quillaja saponaria* Molina tree with cholesterol and phosphatidylcholine in the presence of a detergent. Removal of detergent by diafiltration results in the formation of stable cage-like structures of 2 types, designated Matrix-A and Matrix-C, dependent on the precise *Quillaja* extract incorporated. Matrix-A and -C are blended in an 85:15 ratio, respectively, to yield Matrix-M1. The proposed mode of action of Matrix-M1 does not include a depot effect, but rather is through a combination of activities including recruitment and activation of innate immune cells, rapid antigen delivery to antigen presenting cells (APCs), and enhanced antigen presentation via both Major Histocompatibility Complex (MHC) I and MHC II molecules in the draining lymph nodes.

1.6 Nonclinical Investigations

1.6.1 Matrix-M1-adjuvanted Tri-NIV

A key animal study of Tri-NIV was conducted in an influenza disease model (ferrets) to evaluate its immunogenicity and protective efficacy against both a recent and drifted A/H3N2 challenge strain; and to compare the immune response with that of the 2016 - 17 Fluzone HD and Fluzone Quadrivalent (standard dose) vaccines. In ferrets, Tri-NIV administered with Matrix-M1 adjuvant elicited rapid and robust immune responses in terms of geometric mean hemagglutinin inhibition (HAI) titers, with responses exceeding those induced by Fluzone HD. Secondly, geometric mean 50% microneutralizing (MN) titers against a broad panel of historic H3N2 strains tested, dating to 1999 and spanning a number of clinically-signficant antigenic drift events, showed 2 to 214-fold higher titers among animals given Tri-NIV with Matrix-M1 adjuvant than among animals given Fluzone HD. These data suggest that Tri-NIV may elicit antibodies to broadly-neutralizing epitopes capable of providing greater drift strain protection, even against strains such as A/HongKong/4801/2014, which are associated with impaired influenza vaccine efficacy in humans.

Additionally, a good laboratory practices (GLP)-compliant, repeat-dose toxicology study was conducted in New Zealand White (NZW) rabbits investigating the safety and immunogenicity of a total dose of 60 µg of a nanoparticle influenza vaccine (NIV), a precursor to Tri-NIV (containing 30 µg each of A/Switzerland/9715293/2013 and B/Brisbane/60/2008 [in addition to A/Anhui/1/2013 neuraminidase alone or in combination with RSV F protein, which are not present in the current candidate], and generated using the same baculovirus/Sf9 technology as Tri-NIV and Quad-NIV) was administered to animals on Days 1 and 15, alone or with 50 µg Matrix-M1 adjuvant. Results showed no adverse effects on mortality, physical examinations, cageside observations, dermal Draize observations, body weights, body weight changes, food consumption, body temperatures, ophthalmology, clinical chemistry, hematology, gross pathology, or histopathology, with robust influenza-specific responses observed among actively-immunized animals, when compared to placebo. There were mild inflammatory responses at the vaccine injection sites and hyperplasia of the lymph nodes draining the injection sites, which were accompanied by elevation of serum inflammatory markers (eg, CRP and fibrinogen). These effects were transient and showed rapid resolution and were considered normal, non-adverse responses to immunization. A complete description of these nonclinical studies is provided in the Investigators' Brochure (IB).

1.7 Other Matrix-M1-adjuvanted Vaccines

Additional toxicological studies in NZW rabbits have been performed with 2 different antigens, ie, an influenza virus (H7N9) virus-like particle and an Ebola virus glycoprotein, in which up to 100 µg Matrix-M1 alone or with antigen was evaluated. These toxicological investigations indicated that Matrix-M1 adjuvant in doses up 100 µg was 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 reactions and chemical markers of inflammation, were transient and similar to those reported in the NIV toxicology study and were considered consistent with immune system stimulation consequent to immunization. Reference the Matrix-M™ Adjuvant Safety Data Supplement for details regarding these additional toxicology studies.

1.8 Clinical Investigations

1.8.1 Results of Phase 1/2 Trial (tNIV-E-101) with Tri-NIV and Matrix-M1 Adjuvant

Clinical experience with Tri-NIV is derived from an ongoing Phase 1/2, randomized, observer-blinded, active-controlled clinical trial in 330 subjects. The primary goals of the trial were: 1) to assess the safety of Tri-NIV at 2 different doses as well as of the licensed comparator Fluzone HD (Sanofi Pasteur) in healthy older adults ≥ 60 years of age, in terms of short-term reactogenicity, 21 day all adverse event (AE) profile, and 1 year post dosing medically-attended adverse events (MAE), serious adverse events (SAE), and significant new medical conditions profile (SNMC), as well as pre- and 21 days post-vaccination clinical laboratory parameters; and 2) to describe the immunogenicity of Tri-NIV at 2 different doses and of Fluzone HD, based on HAI responses to vaccine-homologous influenza A and B strains 21 days post-dosing. The secondary objectives of the trial pertained to describing the immunogenicity of Tri-NIV at 2 different doses as well as of Fluzone HD in terms of HAI responses to at least 2 historic and/or drifted A virus strains and MN responses to vaccine-homologous and historic and/or drifted influenza A strains, and the vaccine-homologous B/Victoria lineage strain at 21 days post dosing. An unblinded data review was conducted upon completion of all subject's Day 21 visit; safety follow-up in all subjects through 1 year post-vaccination remains ongoing.

The overall safety profile of Tri-NIV at the 180 µg HA dose was generally comparable to that of Fluzone HD, ie, about 46 - 47% of subjects experienced an AE overall; the 45 µg HA Tri-NIV dose was associated with a lower overall AE rate (37%) driven primarily by the short-term solicited adverse events. While solicited AEs (common vaccine reactogenicity complaints occurring in the first 7 days after exposure) occurred with similar frequency across all treatment groups, severe solicited systemic AEs occurred with slightly higher frequency among Tri-NIV recipients (2 - 4%) as compared with Fluzone HD recipients (0%). These events included typical transient vaccine reactogenicity complaints, and all were transient. More Tri-NIV subjects (5 – 8% by dose) sought medical attention for an AE than Fluzone HD subjects (~2%), but this finding showed an inverse dose response and comprised common intercurrent illnesses distributed across multiple organ systems. Two subjects experienced SAEs through Day 21 post-treatment, and neither was considered related to the test article by the study investigator. As of this writing, a total of 22 SAEs in 19 subjects have been reported to the clinical database,

with none assessed as related to trial treatment. Treatment assignment of these events has not yet been unblinded at the subject level to the safety unit, however, as for medically-attended AEs, the diagnoses span a range of organ systems with no apparent clustering. The subjects are distributed evenly across the 3 treatment groups (6/109 [5.5%], 6/111 [5.4%], and 7/110 [6.4%]). No subject discontinued due to any adverse events at the time of the Day 21 analysis and no deaths have been reported in the trial to date

Tri-NIV with Matrix-M1 adjuvant also proved to be immunogenic in subjects eliciting high HAI titers against both vaccine-homologous and drifted historic strains with a dose-response observed between the 45 and 180 µg total HA doses using an assay based on wild-type sequence virus-like particle (VLP) antigens. Notably, the 180 µg Tri-NIV dose induced higher HAI titers when compared to Fluzone HD against both vaccine-homologous and non-vaccine strains. Specifically, Day 21 HAI titers against A/Michigan (H1N1) among 180 µg Tri-NIV recipients were higher than Fluzone HD (ie, 209.8 vs 170.5, respectively) with a fold rise of 3.2 vs 2.6, respectively. A similar trend was noted with A/HongKong (H3N2) with HAI GMTs among 180 µg Tri-NIV recipients being higher than Fluzone HD (ie, 159.0 vs 115.7, respectively, with a fold rise of 2.7 vs 1.9, respectively). Responses against B/Brisbane were concluded to be comparable among 180 µg Tri-NIV recipients and Fluzone HD recipients (GMTs of 106.2 vs 108.6, respectively, and geometric mean ratio of titers pre and post vaccination [GMR] of 1.9 vs 2.0, respectively); it is also noted that the true HA content of B/Brisbane in the comparator was higher (~90 - 100 µg HA per dose), as measured by isotope dilution mass spectroscopy (IDMS) and single radial immunodiffusion (SRID), than that reported in the manufacturer's label (60 µg HA). All drift strains tested showed the same trend of higher HAI GMTs and GMRs with Tri-NIV at 180 µg total HA content compared to Fluzone HD [Shinde 2018].

A complete description of this clinical study is provided in the IB.

1.8.2 Matrix-M1-adjuvanted Vaccines

Matrix-M adjuvant, in 1 of 2 formulations (ie, Matrix-M1 and Matrix-M2), has been administered with a variety of vaccine antigens to over 1600 human subjects in a total of 15 clinical trials in the US, Europe, and Australia. A total of 1117 subjects have received vaccines containing the Matrix-M1 adjuvant (proposed for use in this trial) and 537 subjects have received vaccines containing Matrix-M2 adjuvant (an adjuvant containing the same active components as Matrix-M1, but in a slightly different ratio). Among all 15 studies, no reported serious adverse events (SAE) have been classified as related to exposure to the Matrix-M adjuvant.

Please refer to the most recent version of the Matrix-M™ Adjuvant Safety Data Supplement for detailed summaries of the clinical experience with Matrix-M1-adjuvanted vaccines.

1.9 Trial Rationale

The influenza virus poses a formidable risk of infection to older adults. Based on estimates by the Centers for Disease Control and Prevention (CDC), in the US alone, up to 85% of all influenza-related deaths and 70% of all influenza-related hospitalizations occur in people 65 years of age or older [CDC 2017]. Novavax, Inc. has developed an insect cell-derived,

egg-free, influenza vaccine (Quad-NIV) based on recombinant hemagglutinin (HA) nanoparticle antigens, which represent the 4 major influenza types/subtypes, recommended for inclusion in the 2018 - 2019 seasonal influenza vaccine by the World Health Organization (WHO) and the Center for Biologics Evaluation and Research (CBER).

Currently, the Advisory Committee on Immunization Practices (ACIP) and CDC recommend that older adults receive an annual vaccination with any seasonal influenza vaccine approved for use in this age group; inactivated influenza (standard or high dose [HD], trivalent or quadrivalent, unadjuvanted or adjuvanted) or recombinant influenza (trivalent) vaccines are considered acceptable options [Grohskopf 2016, CDC 2017]. There are 2 vaccines specifically approved for use in older adults, including high-dose (ie, Fluzone® High-Dose initially approved in the US in 2009) and adjuvanted (ie, FLUAD™ initially approved in the US in 2015) trivalent inactivated influenza vaccines [CDC 2017].

While the efficacy of Fluzone HD, and existing adjuvanted influenza vaccines, is improved in older adults relative to standard-dose, egg-derived inactivated influenza vaccines, it remains suboptimal and also vulnerable to antigenic drift in circulating strains between strain selection in the first quarter of a given year and virus circulation in the following winter season. The latter phenomenon has been particularly troublesome for A(H3N2) strains over the past 10 to 15 years. Accordingly, a vaccine with both strong homologous hemagglutination inhibiting (HAI) and broadly neutralizing antibody responses – which might address drifted strains – could be of added value in older adults.

Data from Novavax's Phase 1/2 clinical trial (tNIV-E-101) of a novel recombinant hemagglutinin (HA) trivalent nanoparticle influenza vaccine (Tri-NIV), containing antigens representing the 3 influenza strains recommended for inclusion in the 2017 - 2018 seasonal influenza vaccine by the Center for Biologics Evaluation and Research (CBER) and the World Health Organization (WHO), and given at a 45 or 180 µg total HA dose (15 or 60 µg HA per strain) with a saponin-based adjuvant (50 µg Matrix-M1), showed that hemagglutination inhibiting (HAI) antibody geometric mean titer (GMT) and ratio of geometric mean titer (GMR) responses (evaluated by adapting the classical HAI method utilizing recombinant wild-type HA-virus-like particles [VLPs] as the agglutinating agent and human type-O RBCs) against a panel of vaccine-homologous A(H1N1) and A(H3N2) strains, and antigenically-drifted A(H3N2) strains at Day 21, were greater among recipients of 180 µg Tri-NIV than among recipients of the active comparator, Fluzone HD. HAI antibody responses against B/Brisbane were also comparable between 180 µg Tri-NIV and Fluzone HD. Microneutralizing (MN) antibody responses generally supported HAI results, and demonstrated substantially improved responses against circulating antigenically-drifted wild-type A/Singapore (H3N2) virus, when comparing 180 µg Tri-NIV to Fluzone HD. Finally, Tri-NIV at both doses was well tolerated by study participants and the safety profile was comparable to that of Fluzone HD, except for slightly elevated counts of severe solicited adverse events among recipients of 180 µg Tri-NIV than among Fluzone HD recipients; however these were overall infrequent and transient.

The rationale for the proposed Phase 2 trial and the vaccine formulations to be tested are based on the observations and conclusions derived from the aforementioned Phase 1/2 trial with Tri-NIV; the anticipated requirements of the regulatory pathway to licensure for the

nanoparticle influenza vaccine (NIV); and, observations regarding the current landscape of licensed seasonal influenza vaccines as follows:

- The anticipated licensure pathway for NIV administered with a novel adjuvant, Matrix-M1, will require demonstration of an adjuvant-mediated enhancement of vaccine-induced immunogenicity, and demonstration of an overall favorable risk-benefit profile of NIV formulations containing Matrix-M1, to justify inclusion of an adjuvant.
- Quadrivalent seasonal influenza vaccine formulations have been widely adopted with the intent of inducing broader protection against co-circulating influenza B viruses of both Victoria and Yamagata lineages and thereby mitigating against the potential for B-lineage vaccine and circulating strain mismatch that may limit the efficacy.
- To induce immune responses to influenza B antigens, which are competitive with, and ideally superior to, Fluzone HD or Flublok Quadrivalent, 2 licensed seasonal influenza vaccines deployed among adults $\geq$ 65 or $\geq$ 18 years of age in the US, respectively, and represent 2 leading and divergent approaches currently used to develop influenza vaccines with enhanced efficacy (ie, egg-based and recombinant). The immunogenicity of influenza B antigens contained in NIV might be further enhanced, either by increasing the dose of B antigens, or by increasing the dose of Matrix-M1 adjuvant.
- The desired NIV presentation for a future pivotal Phase 3 trial, regulatory licensure, and eventual launch, will be a manufactured co-formulation of HA nanoparticle antigen with Matrix-M1 adjuvant. To evaluate the safety and immunogenicity performance of a co-formulated NIV, the proposed trial will seek to describe the comparability of co-formulated NIV with Matrix-M1 as compared to in-clinic, bedside-mixed NIV with Matrix-M1 (as examined in the prior Phase 1/2 trial).

This Phase 2 trial will evaluate a quadrivalent nanoparticle influenza vaccine (Quad-NIV), containing antigens representing the 4 influenza strains recommended for inclusion in the 2018 - 2019 Northern hemisphere seasonal influenza vaccine [VRBPAC 2018, WHO 2018]. The goals of this trial are to: a) demonstrate a statistically significant Matrix-M1 adjuvant effect on vaccine-induced immunogenicity to vaccine-homologous or antigenically-drifted influenza strains; b) describe the immunogenicity of Quad-NIV prepared by in-clinic mixture versus co-formulation prior to vialing; c) describe the effect on Quad-NIV immunogenicity of either increased B antigen dose or increased Matrix-M1 dose with regard to all vaccine-homologous strain immune responses, but especially those to the B viruses; d) describe the immunogenicity to vaccine-homologous and antigenically-drifted influenza strains of all formulations of Quad-NIV relative to the 2 active comparators, Fluzone HD and Flublok Quadrivalent; and e) describe the safety profile of all formulations of Quad-NIV and the active comparators.

1.10 Expected Risks from Vaccination with Quad-NIV with or Without Matrix-M1 Adjuvant

This proposed trial will be the first human exposure to Quad-NIV with Matrix-M1 adjuvant.

Expected risks of vaccination with Quad-NIV in combination with Matrix-M1 adjuvant can be extrapolated from an older adult trial of Tri-NIV with Matrix-M1 adjuvant, which was manufactured using the same baculovirus/Sf9 insect cell system technology used to produce

Quad-NIV (Section 4.2.2). Quad-NIV differs from Tri-NIV principally in the inclusion of HA antigen from a second B virus strain, which results in a 33 - 66% increase in the overall protein dose. In addition, a single formulation of Quad-NIV will contain a 50% increase in the dose of Matrix-M1 adjuvant.

Based on the small sample size available from the clinical trial experience with Tri-NIV with Matrix-M1 adjuvant to date, the following adverse events occurred somewhat more frequently among Tri-NIV vaccinees than active comparator (Fluzone HD) recipients (ie, an excess of 1 – 5 subjects in a 100-subject treatment group): Injection site bruising, injection site redness, headache, fatigue, diarrhea, vomiting, sore throat, eye redness, chest tightness, wheezing, facial swelling, and fever (ie, oral temperature ≥ 38 °C). Other expected AEs may include injection site pain, injection site swelling, muscle pain, joint pain, chills, nausea, cough, hoarseness, eyelid swelling, difficulty breathing, and difficulty swallowing, although these did not occur in greater proportions of Tri-NIV with Matrix-M1 adjuvant subjects when compared to Fluzone HD recipients. Persistence of these signs and symptoms beyond the first 7 days after injection occurs uncommonly and is not expected. Occurrence of these solicited signs and symptoms with characteristics consistent with the definition of a SAE (ie, need for an urgent and significant medical intervention, and/or hospitalization, and/or residual disability) is also not expected.

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 Quad-NIV Investigators' Brochure.

1.11 Risks Associated with Fluzone HD and Flublok Quadrivalent

Fluzone HD has been the subject of several large clinical trials including over 18,500 recipients of Fluzone HD contrasted to over 17,200 subjects concurrently treated with Fluzone, a standard-dose (15 µg of each HA) trivalent inactivated influenza vaccine. In these studies, local injection site solicited adverse events typical of intramuscular vaccine reactogenicity and occurring in the first 7 days after dosing occurred between 1.3- and 1.6-fold more commonly in the Fluzone HD recipients than Fluzone recipients, including a 35.6% incidence of local injection site pain, 14.9% erythema, and 8.9% swelling. Systemic complaints such as myalgia, malaise, and headache were only modestly more common in Fluzone HD recipients, occurring in approximately 17 to 21%. Fever occurred in 3.6% of Fluzone HD vaccinees. The majority of these events were mild in severity. Considering the longer term adverse event profile, Fluzone HD was not distinguishable from standard dose influenza vaccine.

Flublok Quadrivalent has been administered to and safety data collected from 998 adults 18 - 49 years of age and 4328 adults ≥ 50 years of age. In older adults ≥ 50 years of age, the most common local solicited adverse event was tenderness (34%) and pain (19%) at the site of injection. The most common solicited systemic adverse reactions were fatigue (12%) and headache (13%). The majority of these events were mild in severity.

A variety of events have been reported in the post-marketing experience with Fluzone, Fluzone HD, and Flublok Quadrivalent. Information regarding the post-marketing safety data for Fluzone and Flublok Quadrivalent products are available in the corresponding Package Inserts,

which will be supplied to Investigators. Of note, Fluzone HD is produced in eggs, in common with the majority of inactivated vaccines. Therefore, subjects with known history of severe allergic reaction to any influenza vaccine, or allergy to egg proteins, should not receive Fluzone HD. Additionally, subjects with a history of Guillain-Barré syndrome within 6 weeks of any influenza vaccine should not receive Fluzone HD, Flublok Quadrivalent, or be enrolled in this trial (see trial exclusion criteria in Section 5.2).

2 TRIAL OBJECTIVES

2.1 Primary Objectives

- To describe the safety and tolerability of Quad-NIV 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 healthy adults ≥ 65 years of age. The safety profile will include solicited short-term reactogenicity; 28-day all adverse event (AE) profile; 1-year post-injection medically-attended adverse event (MAE), serious adverse event (SAE), and significant new medical condition (SNMC) profile; and selected pre- and post-vaccination clinical laboratory parameters.
- To demonstrate a Matrix-M1 adjuvant effect by contrasting the immunogenic superiority of Quad-NIV (60 µg HA per A and B strain) co-formulated with 50 µg Matrix-M1 as compared to Quad-NIV (60 µg HA per A and B strain) without adjuvant. Immunogenic superiority will be demonstrated by excluding values ≤ 1.0 at the lower 95% confidence bound for the baseline-adjusted ratio of Day 28 post-vaccination HAI titers (ie, GMT adjuvant / GMT no adjuvant) for not less than 2 of 6 influenza strains (ie, any 2 of 4 vaccine-homologous strains and/or 2 antigenically-drifted influenza strains), while no other strain(s) demonstrate a baseline-adjusted ratio of Day 28 post-immunization HAI titers which is significantly < 1.0.

2.2 Secondary Objectives

- To compare the immunogenicity of Quad-NIV (60 µg HA per each A and B strain) with 50 µg of Matrix-M1 co-formulated prior to administration relative to a similar formulation mixed in-clinic and also to 2 US-licensed active comparators, Fluzone HD and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, in terms of HAI antibody responses against vaccine-homologous A and B strain(s), and antigenically-drifted influenza strains (multiple informative strains may be tested) at Days 0 and 28 post-vaccination.
- To describe the immunogenicity of formulations of Quad-NIV with increased B-antigen dose (60 µg HA per A strain and 90 µg HA per B strain; and 50 µg of Matrix-M1) or increased Matrix-M1 dose (60 µg HA per A strain and B strain; and 75 µg of Matrix-M1) relative to the "standard" co-formulated Quad-NIV formulation (60 µg HA per each A and B strain; and 50 µg of Matrix-M1) and also to 2 US-licensed active comparators, Fluzone HD and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, in terms of HAI antibody responses against all vaccine-homologous A and B strain(s), and antigenically-drifted influenza strains (multiple informative strains may be tested) at Days 0 and 28 post-vaccination.
- To evaluate the longevity of immune responses to Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain), 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 and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, based on HAI responses against vaccine-homologous and

antigenically-drifted influenza strains (multiple informative strains may be tested) post-vaccination on Days 0, 28, 56, 182, and 364.

2.3 Exploratory Objectives

- To describe the immunogenicity of Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain) and formulations, 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 and Flublok Quadrivalent, in healthy adults ≥ 65 years of age, based on microneutralization (MN) responses to vaccine-homologous and antigenically-drifted influenza strains (multiple informative strains may be tested), at Days 0 and 28 post-vaccination. Note: Due to the time-consuming nature of MN testing, this exploratory objective may be completed in a random subset of participants in each study treatment group after the initial study HAI data are complete and reported in an addendum. Laboratory staff will remain blinded as to treatment assignments until all projected MN tests are complete. Additional time points may also be tested (ie, Days 56, 182, and 364).
- To describe the quality and amplitude of cell-mediated immune (CMI) responses in healthy adults ≥ 65 years of age to vaccination with Quad-NIV at different doses (ie, 60 µg HA per A and B strain vs 60 µg HA per A strain and 90 µg HA per B strain) and formulations, without adjuvant or with 1 of 2 different doses of Matrix-M1 adjuvant (mixed in-clinic or co-formulated in advance of the trial), based on functional T cell responses based on intracellular cytokine analysis. Due to the laborious nature of the cellular assays, they will be performed on subjects from a limited number of preselected sites and results may be reported as an addendum to the main clinical study report.
- To describe the vaccine response among subjects with low baseline HAI titers in terms of fold increases in HAI titers. “Low baseline” will be defined as lowest quintile.

3 TRIAL OVERVIEW

3.1 Design

This is a Phase 2, randomized, observer-blinded, active-controlled, dose-finding, formulation-optimizing trial in healthy adults ≥ 65 years of age to be conducted in the United States. Up to 1375 eligible subjects will be enrolled and randomized into 1 of 7 treatment groups, as shown in Table 1 below. The base case groups for the demonstration of adjuvant effect, ie, Groups B and E, will each consist of approximately 310 subjects. The remaining groups will consist of approximately 135 (Group D) or 155 (Groups A, C, F, and G) subjects each. Each group will be stratified by site and history of receipt of 2017 - 18 influenza vaccine.

On Day 0, all subjects will receive a study treatment as indicated in Table 1 by intramuscular (IM) injection. Total injection volumes for each treatment group will be 0.5 mL. On Day 28, subjects in Group E will be administered a rescue injection with a 2018 - 19 licensed seasonal influenza vaccine. All other subjects will receive an injection of placebo at Day 28 to maintain trial blind. Trial follow-up for each subject will span approximately 1 year from the Day 0 injection. It is anticipated that a percentage of the randomized trial subjects will not complete the trial. Subjects who withdraw or are discontinued will not be replaced. In addition, all subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine at the last study visit (Day 364).

Enrollment will be divided into 3 stages. Stage 1 will enroll a total of approximately 120 subjects (approximately 20 subjects per treatment group, excluding Group D for which no subjects will be enrolled in Stage 1). Stage 2 will enroll a total of approximately 220 subjects (approximately 20 [Groups A, C, D, F, and G] or 60 subjects [Groups B and E] per treatment group, as per Table 1). The remainder of the subjects (approximately 1035 subjects total, ie, 115 [Groups A, C, D, F, and G] or 230 [Groups B and E] subjects per treatment group, as per Table 1) will be enrolled in Stage 3. Progression from Stage 1 to Stage 2 and from Stage 2 to Stage 3 will require favorable review of safety data from the prior stage, against vaccination holding rules as defined in Section 3.1.1.1.

3.1.1 Safety Monitoring of Enrollment and Vaccinations

Vaccination holding rules will be used to govern progression from Stage 1 to Stage 2, and from Stage 2 to full enrollment in Stage 3. Solicited and unsolicited AEs reported from all Stage 1 subjects within 7 days of Day 0 vaccination will be evaluated against vaccination holding rules (Section 3.1.1.1). These AE data will be summarized by the sponsor statistician, reviewed, and provided to an independent medical monitor in aggregate form (without unblinding or subdivision by treatment group).

In Stage 1, if vaccination holding rules are not met based on Day 7 data, the independent medical monitor will notify the sponsor‘s responsible physician to proceed with Stage 2 enrollment of additional subjects in all groups, including a 20 subjects in Group D. In Stage 2, if vaccination holding rules are not met based on Day 7 data, the independent medical monitor will notify the sponsor’s responsible physician to proceed with enrollment of the balance of subjects in Stage 3.

If vaccination holding rules are met in either Stages 1 or 2, the independent medical monitor will notify the sponsor's responsible physician, who will pause enrollment pending further review and request that the sponsor's Chief Medical Officer (CMO) authorize unblinding of the relevant data. Relevant data will include at least the total counts of subjects treated at the time of the hold in each treatment arm; and the treatment assignments, screening history, physical exam(s), concomitant medications, and overall solicited and unsolicited adverse event profiles of the subject(s) triggering the hold. (It is noted that this review may use unmonitored data.) Upon review, the CMO may authorize review of other data. The independent medical monitor and the sponsor's responsible physician and CMO will review the unblinded data and develop a report and recommendation to either: a) resume enrollment, b) amend the protocol and resume enrollment, or c) terminate the protocol. The report, the recommendation, and the amended protocol and ICF (if relevant), will be provided to the IRB and CBER, and enrollment will not recommence until IRB approval is obtained, unless the vaccination holding rule was triggered in a comparator arm (ie, Fluzone HD [Group F] or Flublok Quadrivalent [Group G]).

3.1.1.1 Vaccination Holding Rules

Adverse event reports meeting any 1 of the following 2 criteria will result in a hold being placed on subsequent enrollment and vaccinations, pending further review by the independent medical monitor and sponsor as above:

1) The occurrence of more than a single (1) definitely related serious adverse event (final assessment by the sponsor per CBER Guidance) in a given MedDRA system organ class (SOC) or more than 2 overall definitely related SAEs per enrollment Stages 1 and 2.

2) The occurrence of any severe (grade 3) solicited (local or systemic) adverse events in > 10% of all subjects.

If vaccination holding rules are met at any review point, the independent medical monitor and sponsor personnel will review a summary of all individual data of the relevant subject(s), including the unblinded treatment assignment, and summary safety data relative to all treatment groups.

Table 1: Trial Design for qNIV-E-201

	Day 0 Trial Treatment Injection				Day 28 Injection [2]	Subjects per Enrollment Stage			Subjects Per Group
Treatment Group	Vaccine	HA Dose per Strain, µg (H1N1/H3N2/B_V/B_Y)	Matrix-M1 Adjuvant Dose, µg	Formulation		Stage 1 [3]	Stage 2 [3]	Stage 3 [3]	
A	Quad-NIV	60, 60, 60, 60	50	In-Clinic Mix	Placebo	20	20	115	155
B		60, 60, 60, 60	50	Co-form	Placebo	20	60	230	310
C		60, 60, 60, 60	75	Co-form	Placebo	20	20	115	155
D		60, 60, 90, 90	50	Co-form	Placebo	0	20	115	135
E		60, 60, 60, 60	0	NA	2018 - 19 Licensed Seasonal Influenza Vaccine	20	60	230	310
F	2018 - 19 Fluzone HD [1]				Placebo	20	20	115	155
G	2018 - 19 Flublok Quadrivalent [1]				Placebo	20	20	115	155
Total Trial Subjects						120	220	1035	1375

Abbreviations: B_V = B Victoria lineage; B_Y = B Yamagata lineage; Co-form = co-formulated; HA = Hemagglutinin; NA = not applicable.
Note: All subjects will receive 2 vaccinations by IM injection in alternating deltoids on Day 0 and Day 28.
[1] Fluzone HD and Flublok Quadrivalent will be administered at the manufacturer's recommended dose and volume.
[2] On Day 28, subjects in Group E will receive a rescue injection with a licensed seasonal influenza vaccine; all other subjects will receive a placebo injection to maintain trial blind.
[3] Enrollment will be divided into 3 stages. Stage 1 will enroll a total of approximately 120 subjects (approximately 20 subjects per treatment group, excluding Group D for which no subjects will be enrolled in Stage 1). Stage 2 will enroll a total of approximately 220 subjects (approximately 20 [Groups A, C, D, F, and G] or 60 subjects [Groups B and E] per treatment group). The remainder of the subjects (approximately 1035 subjects total, ie, 115 [Groups A, C, D, F, and G] or 230 subjects [Groups B and E] per treatment group) will be enrolled in Stage 3.

3.2 Trial Endpoints

3.2.1 Primary Endpoints

- Safety and tolerability of Quad-NIV at different doses: Number and percentage (95% CI) of subjects with solicited local and systemic adverse events over the 7 days post-injection (ie, Day 0 through Day 6, inclusive); all adverse events (including adverse changes in clinical laboratory parameters) through 28 days post-injection (ie, Day 0 through Day 20, inclusive); and MAEs, SAEs, and SNMCs – including immunologically-mediated adverse events of special interest (AESIs) - through 1 year post-injection.
- HAI antibody titers specific for the HA receptor binding domains of vaccine-homologous A and B strain(s), and at least 2 antigenically-drifted influenza strains, at Days 0 and 28 post-vaccination. 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 Day 28.
  - Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).

3.2.2 Secondary 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:
  - GMT, as defined above, on Days 0, 28, 56, 182, and 364.
  - Geometric mean ratio (GMR) – defined as the ratio of post vaccination to pre-vaccination (Day 0) HAI GMTs ($GMR_{Post/Pre}$) on Days 28, 56, 182, and 364.
  - Seroconversion rate (SCR) – defined as proportion of subjects 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 on Days 28, 56, 182, and 364.
  - Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 on Days 28, 56, 182, and 364.
  - Ratio of GMTs between treatment arms at Days 28, 56, 182, and 364 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).

3.2.3 Exploratory Endpoints

- Microneutralization (MN) responses: Neutralizing antibody titers specific to vaccine-homologous A and B strain(s) and antigenically-drifted influenza strains, at Days 0 and 28 post-vaccination, as measured by a microneutralization assay. Note: additional time points may also be assessed. Derived/calculated endpoints based on these data will include:
  - GMT – defined as the antilog of the mean of the log-transformed neutralizing titer for a given treatment group.
  - GMR – defined as the ratio of post-vaccination and pre-vaccination neutralizing GMTs within the same treatment group (designated as $GMR_{Post/Pre}$).
  - SCR – defined as proportion of subjects in a given treatment group with either a baseline reciprocal titer of $<$ lower limit of quantitation (LLOQ) and a post-vaccination reciprocal titer 4-fold higher than the LLOQ, or a baseline reciprocal titer of $\geq$ LLOQ and a post-vaccination reciprocal titer $\geq$ 4-fold higher than the baseline titer.
  - Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).
- Proportions of Days 0 and 7 peripheral blood T cell isolates that secrete IL-2, IFN-γ, and TNF-α cytokines following *in vitro* restimulation with HA in subjects selected for cellular immune response monitoring.
- HAI titers, as described above.

3.3 Randomization and Blinding Procedure

Subject randomization may be conducted using either a paper-based randomization system or an Interactive Web Randomization System (IWRS). Stratification will be by site and history of receipt of 2017 - 18 influenza vaccine. Proportions of subjects in the various strata will not be pre-specified; rather, the goal will be to achieve an approximately equal distribution of subjects with these characteristics across the various treatment groups.

Preparation and administration of each test article dose will be performed by unblinded vaccine pharmacists/administrators. These persons, identified prior to trial dosing, will not perform any trial assessments post-dosing.

3.4 Maintaining the Blinded Randomization Scheme

Randomization procedures may be performed using either a paper-based randomization system or an IWRS, with treatment assignments known only to the responsible unblinded vaccine administrators at the trial center. Subjects and the main trial team clinical staff will remain blinded for the duration of the trial unless emergency unblinding is necessary. Refer to Section 3.5 for information regarding the process for emergency unblinding.

All treatment assignments, vaccine storage and accountability, and/or dosing-related matters will be monitored by a designated "unblinded monitor." Any deviations will be discussed, documented, and resolved by the unblinded monitor and the unblinded site personnel. Reports provided by the unblinded monitor will be reviewed by designated unblinded personnel at either Novavax or the clinical research organization (CRO), not involved with the main trial team. No reports from the unblinded monitor will be released to the Trial Master File (TMF) until database lock for Day 364 and official declaration of unblinding is given by Novavax.

3.5 Procedure for Unblinding Individual Subjects During the Trial

In the event of a medical emergency, or in the event of a triggering of vaccination holding rules, when knowledge of 1 or more subject's treatment assignment may influence his/her clinical care or the conduct of the trial, the sponsor's Chief Medical Officer (CMO) or an investigator or designee may request that the blind be broken for the subject(s) experiencing the emergency or contributing to holding rule activation. Prior to unblinding for individual subjects at site investigator's request, however, the requesting party must use all reasonable efforts to contact the Medical Monitor or designee to discuss the decision to break the blind. In the case of such individual subjects, the investigator will be expected to provide a rationale for the necessity of unblinding based on a meaningful change to the subject's immediate and short-term medical care which will result from knowledge of treatment assignment.

Novavax retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to the test article and that potentially require expedited reporting to regulatory authorities. In addition, the Chief Medical Officer will have the right to request unblinding of Stage 1 or Stage 2 subjects when vaccination holding rules are met (Section 3.1.1.1).

If unblinding of an individual subject is deemed necessary, the unblinded staff member shall obtain subject dose details from the randomization system. The date and time of breaking the blind as well as the reason must be recorded and placed in the Pharmacy Binder by unblinded staff. The individual subject dose details should be revealed only in case of an emergency where further treatment of the subject is dependent on knowing the investigational product he/she has received. The investigator should not otherwise divulge the subject's treatment assignment to site staff, and should provide the information only to those individuals involved in the direct

care of the subject. The date and reasons for breaking the blind must be submitted to the Medical Monitor within 24 hours.

3.6 Trial Duration

The maximum duration of an individual subject's participation in the trial conduct is approximately 1 year.

4 TRIAL TEST ARTICLES

The investigational product (IP) under evaluation in this trial is Quad-NIV alone or adjuvanted with Matrix-M1 adjuvant. Discussions on the IP are presented in this section.

4.1 Overview of Product and Manufacturing Process for Clinical Trial Material

Novavax's Quad-NIV is manufactured in the same manner as Tri-NIV, based on purified, recombinant full-length HA that self-assembles into distinct nanoparticle structures of approximately 20 to 40 nm [Smith 2017]. The baculovirus/*Spodoptera frugiperda* (Sf9) insect cell system is used to clone and express recombinant influenza HAs from the influenza strains recommended for the 2018 - 19 Northern Hemisphere influenza season: A/Michigan/45/2015 (H1N1); A/Singapore/INFIMH-16-0019/2016 (H3N2); B/Colorado/06/2017 (Victoria lineage); and B/Phuket/3073/2013 (Yamagata lineage) [VRBPAC 2018, WHO 2018].

Matrix-M1 is a saponin-based adjuvant, which is co-administered with an antigen to induce an enhanced immune response. Matrix-M1 is manufactured by mixing defined, partially-purified extracts of the bark of the *Quillaja saponaria* Molina tree, termed Fraction-A and Fraction-C, with cholesterol and phosphatidylcholine in the presence of a detergent.

4.2 Manufacture of Bulk Antigen

4.2.1 Recombinant Baculovirus

The recombinant influenza HA genes are cloned into *E. coli* flashBAC GOLD baculovirus transfer vectors (Oxford Expression Technologies, Oxford, UK). The HA genes are under the transcriptional control of the baculovirus AcMNPV polyhedrin promoter at the 5' end and includes a poly (A) sequence at the 3' end. For each influenza strain, recombinant baculovirus expressing a HA gene are identified, plaque-purified, and amplified for use in the manufacture of recombinant influenza HA antigens.

4.2.2 Production and Purification of Quad-NIV

Manufacture of each HA protein antigen is initiated by infecting Sf9 cells in exponential growth with baculovirus containing the strain-specific HA gene. After infection, cells are collected by centrifugation, washed with a detergent-free buffer, and then lysed in the presence of detergent to release membrane-bound HA protein. Leupeptin hemi-sulfate salt is added to the lysis buffer to protect the HA protein from cellular proteases released during the lysis step. The supernatant containing the HA protein is separated from cell debris through the use of depth filtration before it is purified on an ion exchange trimethylaminoethyl (TMAE) column. The B/strain requires an additional chromatography step following TMAE to further remove host cell proteins. The B/strain flow-through fraction is loaded onto a Capto Blue mixed-mode chromatography to capture and remove additional baculovirus and Sf9 host cell proteins, while B/strain HA is recovered in the flow-through fraction. Nanofiltration is then performed to remove viruses from the HA product stream of both A and B strains. The HA protein is then loaded onto a lentil lectin column, which selectively binds the glycosylated protein. After washing, the HA protein is eluted from the column with buffer containing methyl-α-D-mannopyranoside (MMP) and

polysorbate 80 (PS80). Eluted fractions are processed by tangential flow filtration, to concentrate the HA product and exchange it into the final formulation buffer. The product is then diluted to a final formulation containing sodium phosphate and PS80, and then filtered (0.22 μm) to produce bulk drug substance that is clear and colorless, and contains no preservatives. Each HA bulk drug substance is stored at ≤ -60°C until the 4 strains are mixed and diluted to the target concentration with buffer, and filled as drug product. The final composition of the drug product formulation is 25 mM sodium phosphate, 150 mM sodium chloride, 100 mM arginine hydrochloride, 5% w/v trehalose, and 0.03% PS80, pH 7.5.

4.2.3 Manufacture of Matrix-M1 Adjuvant

Matrix-M1 is manufactured by mixing defined, partially-purified extracts of the bark of the *Quillaja saponaria* Molina tree, termed Fraction-A and Fraction-C, with cholesterol and phosphatidylcholine in the presence of a detergent. Detergent removal by diafiltration results in the formation of stable cage-like structures of 2 types, designated Matrix-A and Matrix-C, based on the precise *Quillaja* fraction incorporated. The designation, Matrix-M, refers generically to a blend of Matrix-A and Matrix-C particles together at any ratio. An 85:15 ratio (by weight) of Matrix-A and Matrix-C particles, respectively, yields Matrix-M1. For a more detailed description of the manufacturing process of Matrix-M1 adjuvant, refer to the current Matrix-M Adjuvant Safety Data Supplement.

4.3 Description of Clinical Trial Dosage Formulation

The HA protein content in each purified bulk influenza antigen drug substance is measured and the 4 HA drug substances are mixed and diluted to the target concentration specified in the trial protocol in 25 mM sodium phosphate, 150 mM sodium chloride, 100 mM arginine hydrochloride, 5% w/v trehalose, and 0.03% PS80, pH 7.5. The formulated drug product for Quad-NIV is then filled into 2R single-use glass vials; with or without admixture with Matrix-M1 as appropriate.

Matrix-M1 adjuvant is formulated in phosphate buffer, 150 mM sodium chloride, pH 7.2, and filled into 2.0 mL single-use glass vials.

Quad-NIV drug product co-formulated with Matrix-M1 adjuvant is filled directly into vials at appropriate concentrations. The buffer composition is the same as bulk antigen concentration alone, ie, 25 mM sodium phosphate, 150 mM sodium chloride, 100 mM arginine hydrochloride, 5% w/v trehalose, and 0.03% PS80, pH 7.5. The co-formulated drug product will be filled into 2R single-use glass vials.

For drug products requiring mixing, the Pharmacy Manual will provide detailed instructions for the unblinded pharmacist.

4.4 Fluzone HD – Active Comparator

Fluzone® High-Dose (Sanofi Pasteur) will be administered based on manufacturer's instructions, which will be provided in the Pharmacy Manual.

4.5 Flublok Quadrivalent – Active Comparator

Flublok Quadrivalent® (Sanofi Pasteur, previously Protein Sciences) will be administered based on manufacturer's instructions, which will be provided in the Pharmacy Manual.

4.6 Placebo

Sterile isotonic saline for injection will be used as placebo for recipients in Groups A, B, C, D, F, and G at their Day 28 injection (supplied in single-dose glass vial at a concentration of 9 mg/mL sodium chloride manufactured by Fresenius Kabi).

4.7 Investigational Product Packaging, Storage, and Handling

All IPs (ie, Quad-NIV alone, Matrix-M1 adjuvant alone, Quad-NIV co-formulated with Matrix-M1 adjuvant) will be packaged in validated shipping containers for distribution to the investigational sites under refrigerated conditions. The Quad-NIV and Matrix-M1 vials and cartons will be labeled with the following information: manufacturer's name and address, product name, manufacture date, storage requirements (2 - 8°C), directions for use, and any other investigational product labeling appropriate to the jurisdiction in which the trial is conducted. Fluzone HD, Flublok Quadrivalent, and placebo will be packaged, shipped, and stored based on manufacturer's instructions. All IP and comparator materials should be stored at 2 - 8°C in a temperature-monitored refrigerator. Access to this refrigerator should be limited to designated site personnel.

4.8 Compliance and Drug Accountability

All quantities of the test articles must be reconciled at the completion of enrollment and a written explanation provided for any discrepancies. Unless specific written instructions to the contrary are provided by Novavax, all unused test articles are to be inventoried, and either destroyed or returned to Novavax (or designee) by the clinical site upon notice by Novavax or the site monitor. All used vials will be accounted for on the clinical site's IP Dispensation Log and verified prior to destruction.

5 SELECTION OF TRIAL SUBJECTS

5.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible to participate:

1) Clinically-stable adult male or female, ≥ 65 years of age. Subjects may have 1 or more chronic medical diagnoses, but should be clinically stable as assessed by:
   - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity,
   - Absence of medical events qualifying as serious adverse events within 2 months; and
   - Absence of known, current, and life-limiting diagnoses which render survival to completion of the protocol unlikely in the opinion of the investigator.
2) Willing and able to give informed consent prior to trial enrollment, and
3) Living in the community and able to attend trial visits, comply with trial requirements, and provide timely, reliable, and complete reports of adverse events.

5.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria:

1) Participation in research involving investigational product (drug / biologic / device) within 45 days before planned date of first injection.
2) Participation in any previous Novavax's influenza vaccine clinical trial(s).
3) History of a serious reaction to prior influenza vaccination, known allergy to constituents of Fluzone HD, Flublok Quadrivalent, or polysorbate 80.
4) History of Guillain-Barré Syndrome (GBS) within 6 weeks following a previous influenza vaccine.
5) Received any vaccine in the 4 weeks preceding the trial vaccination and any influenza vaccine within 6 months preceding the trial vaccination.
6) Any known or suspected immunosuppressive illness, congenital or acquired, based on medical history and/or physical examination.
7) 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 trial vaccine. 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.
8) Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the trial vaccine or during the trial.

9) 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).

10) Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled or could interfere with evaluation of the vaccine or interpretation of trial results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).

11) Known disturbance of coagulation.

12) Suspicion or recent history (within 1 year of planned vaccination) of alcohol or other substance abuse.

6 TRIAL ASSESSMENTS AND PROCEDURES

A trial schematic flowchart is provided in Appendix 1. A detailed description of procedures performed at each visit is provided in Section 6.1.

6.1 Trial Visit Procedures

6.1.1 Day 0 – Screening Visit

The following procedures will be performed on the day of the planned vaccination:

- Written informed consent will be obtained in conformance with Section 11.3 of this protocol.
- Inclusion and exclusion criteria review consistent with Section 5.
- Review of medical history, including influenza vaccination history in the previous 3 years (with emphasis on 2017 - 18 vaccine) and history of adverse reactions to prior influenza vaccines and allergies.
- Medication history, including concomitant medications and vaccines within the last year.
- Physical examination including the head, eyes, ears, nose, and throat (HEENT), abdomen, extremities, and at least inguinal, cervical, and axillary nodes, gross motor function, and skin; vital signs (heart rate, blood pressure, respiratory rate, and oral temperature), height, and weight.

Note that further procedures may be performed at the investigator's discretion in order to adequately screen subjects against eligibility criteria and/or to confirm medical history. Potential subjects who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled. *Note: Subjects should be free of acute illness (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature ≥ 38.0°C) in order to receive the test article injection. Subjects presenting with an acute illness on Day 0 may return to the trial site within the next 7 days to receive their injection provided symptoms have resolved; no repetition of baseline serology or clinical laboratory testing is necessary if the subject returns within 7 days.*

6.1.2 Day 0 – Injection 1 Visit

All subjects with confirmed eligibility will have the following procedures performed:

- Randomization to a treatment group.
- Blood draw for baseline immunogenicity testing (20 mL, see Section 7.2) and clinical safety assessments (10 mL).
- Approximately 189 subjects from 3 preselected sites (or 63 subjects per site; to target a minimum 20 evaluable subjects per treatment group) will provide additional blood samples (27 mL) at 2 time points (ie, Days 0 and 7) to support testing of cell-mediated immune responses (CMI). Consent documentation at these sites will be suitably modified. Note: For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3 of the trial.

- Alcohol swab cleansing of the injection site followed by IM injection of the assigned trial treatment into the deltoid muscle of the non-dominant arm. *Note: If the non-dominant arm is not available for the injection due to post-surgical changes, skin changes, or prior injury, the dominant arm may be used.*
- Monitoring for any AEs for approximately 30 - 60 minutes following vaccination.
- Post-injection vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature) at 30 - 60 minutes following vaccination.
- Distribution of the subject diary, thermometer, and a measuring tool to facilitate documentation of any AEs (solicited and unsolicited), concomitant medications, physicians visits, or hospitalizations, occurring from the time of discharge from the trial clinic on Day 0 through Day 6 (inclusive). Subjects will also be instructed to call the trial clinic for any grade 3 (severe) solicited or unsolicited health events, and/or health status changes of concern to the subject.
- Schedule the Day 3 telephone contact and the Day 7 visit before subjects may be dismissed from the clinic.

6.1.3 Day 3 (± 1 day) – Safety Telephone Contact

- Using an Investigational Review Board (IRB)-approved script, the trial staff will contact the subjects using a telephone call to query for any grade 3 solicited or unsolicited adverse event or SAE experienced since their last visit, and any concomitant medications taken for these events. Subjects may be asked to return to the clinic for an unscheduled visit to evaluate the event(s) at the trial investigator's discretion.

6.1.4 Day 7 (± 1 day) – Safety Follow-up Visit

All subjects will return to the clinic on approximately Day 7 for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Review and collection of subject diary.
- Interval history to query for any unsolicited AEs, including MAEs, SNMCs, or SAEs, occurring since the last trial visit, and any concomitant medications taken. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- Blood draw to assess for CMI responses (27 mL) for approximately 189 subjects from 3 preselected sites (63 subjects per site). Note: For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3 of the trial.
- Schedule the Day 28 visit.

6.1.5 Day 28 (± 2 days) – Injection 2 Visit

All subjects will return to the clinic on approximately Day 28 for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Blood draw for immunogenicity assessments (20 mL) and clinical safety assessments (10 mL).

- Interval history to query for any unsolicited AEs, including MAEs, SNMCs, or SAEs, occurring since the last trial visit, and any concomitant medications taken. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- Alcohol swab cleansing of the injection site followed by IM injection into the deltoid muscle of the opposite arm used on Day 0 of a licensed seasonal influenza vaccine or placebo (using the manufacturer's instructions), as appropriate. *Note: If the opposite arm is not available due to post-surgical changes, skin changes, or prior injury, the same arm used for the Day 0 injection may be used for the Day 28 injection. Subjects should be free of acute illness (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature ≥ 38.0°C) in order to receive the second vaccination. Subjects presenting with an acute illness on Day 28 may return to the study site within the next 7 days to receive their 2nd vaccination. If a subject has experienced any AEs/SAE between study Days 0 and 28, then Day 28 vaccination may be administered or delayed for up to 7 days based on the Investigator's discretion.*
- Monitoring for any AEs for approximately 30 - 60 minutes following vaccination.
- Post-injection vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature) at approximately 30 - 60 minutes following vaccination.
- Schedule the Day 56 visit.

6.1.6 Day 56 (± 2 days) – Follow-up Visit

At Day 56, all subjects will return to the clinic for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Blood draw for immunogenicity assessments (20 mL).
- Interval history to query for any MAEs, SNMCs, or SAEs occurring since the last trial visit, and any concomitant medications taken for these events. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- Schedule the Day 90 telephone contact and the Day 182 in-clinic visit.

6.1.7 Day 90 (± 7 days) – Safety Telephone Contact

- Using an IRB-approved script, the trial staff will contact the subjects using a telephone call to query for any MAEs, SAEs, and SNMCs since their last visit, and any concomitant medications taken for these events.

6.1.8 Day 182 (± 7 days) – Follow-up Visit

At Day 182, all subjects will return to the clinic for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Blood draw for immunogenicity assessments (20 mL).
- Interval history to query for any MAEs, SNMCs, or SAEs occurring since the last telephone contact, and any concomitant medications taken for these events. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.

- Schedule the Day 273 telephone contact and the end of the trial visit (Day 364) in-clinic visit.

6.1.9 Day 273 (± 7 days) – Safety Telephone Contact

- Using an IRB-approved script, the trial staff will contact the subjects using a telephone call to query for any MAEs, SAEs, and SNMCs since their last visit, and any concomitant medications taken for these events.

6.1.10 Day 364 (± 14 days) – Follow-up Visit

At Day 364, all subjects will return to the clinic for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Blood draw for immunogenicity assessments (20 mL).
- Interval history to query for any MAEs, SNMCs, or SAEs occurring since the last telephone contact, and any concomitant medications taken for these events. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- All subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine.
- This visit will mark the end of the trial for the subjects.

6.2 Unscheduled Visits

Unscheduled visits are defined as any visits performed to the site outside of the regular visit schedule and can occur at the investigator's discretion for any other trial procedures deemed necessary. Subjects will be encouraged to notify the investigator if any severe (grade 3) local or systemic solicited AEs occur within the 7-day post-dosing period (eg, from Day 0 through Day 6), or if any severe, serious, or otherwise concerning AEs occur at any time following dosing. If symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected.

6.3 Concomitant Therapy

Subjects may receive all concomitant medications and procedures deemed necessary to provide adequate healthcare during the trial, with the exception of those specified in the exclusion criteria. Routine medical standards of care are permitted, including vaccines needed for emergent indications (eg, tetanus booster in response to a penetrating injury). Routine (ie, non-emergent) vaccinations, except the seasonal influenza vaccine, are permitted for all subjects after completion of the Day 28 trial visit. All subjects will be advised to not receive an influenza vaccine outside of the study and will be offered a 2019 – 20 licensed seasonal influenza vaccine at the last study visit (ie, Day 364). Subjects who receive a seasonal influenza vaccine outside of the study before Day 364 will be considered protocol deviations.

Concomitant medications, procedures, and hospitalizations will be recorded throughout the trial including the period from the day informed consent is obtained through the end of trial follow-up. All new or changed concomitant medications taken through Day 28 will be recorded; thereafter, only concomitant medications taken for MAEs, SNMCs, or SAEs will be recorded. The investigator will document the reason for use of the concomitant medication.

6.4 Declining Trial Treatments or Procedures

Subjects have the right to decline trial treatment or other trial procedures for any reason at any time during the trial. This trial contemplates at least 2 injections containing either Quad-NIV with or without Matrix-M1 adjuvant, Fluzone HD, Flublok Quadrivalent, or saline placebo. Refusal of the investigational test article on Day 0 constitutes trial withdrawal without exposure, and no further follow-up is required. If a subject declines trial procedures subsequent to receipt of the investigational product, it should be recorded as a protocol deviation and the reason should be clearly documented in the source document. The subject will be asked to complete all other trial procedures as applicable. If the subject does not wish to remain in the trial, the subject can choose to withdraw consent and discontinue at any time as outlined in Section 6.5.

The investigator may, at his/her discretion, restrict a subject from receiving trial treatment or other trial procedures if he/she considers it to be in the subject's best interest to do so, but can suggest that the subject remain in the trial to be followed for safety if the subject has received a test article. In this situation, the reason for not performing the trial treatment and/or procedure should also be recorded as a protocol deviation and clearly documented in the source document.

6.5 Premature Discontinuation from Trial

Subjects who provide consent but are found to be ineligible on screening will be informed of the reason for ineligibility and may be provided with local medical referral by the investigator as appropriate, but will receive no further trial follow-up.

Subject participation in the trial is strictly voluntary. Subjects have the right to withdraw from the trial at any time and for any reason, without penalty. The investigator may also, at his/her discretion, discontinue subjects from the trial if he/she considers it to be in the participant's best interest to do so, or if the subject is not willing or able to comply with the trial requirements. Novavax will be notified immediately by the investigator if a subject prematurely ends trial participation. The reason for early discontinuation will be clearly documented in the electronic case report form (eCRF). A withdrawal due to an AE will initiate additional reporting requirements as outlined in Section 8.3.

In the event of early termination, investigators will make every reasonable effort to perform trial completion procedures. Trial completion procedures will include a query for any MAEs, SNMCs, or SAEs occurring since the last trial visit, and any concomitant medications taken to treat these events. If the subject discontinues from the trial prior to the Day 28 visit, sites will request the subjects to provide blood samples for serology testing (20 mL) and clinical safety laboratory testing (10 mL). Subjects that terminate from the trial early will not be replaced.

6.6 Protocol Deviations

A protocol deviation (PD) will be defined as a failure to comply with the requirements set forth in the protocol. PDs may be determined programmatically through the course of the trial. Additionally, all PDs will be entered into the CRO Clinical Trial Management System (CTMS) by the Clinical Research Associates (CRAs) and/or Clinical Trial Managers (CTMs). Examples programmatically-determined PDs are provided in Table 2.

Table 2: Programmatically-Determined Protocol Deviations

Missed Visit
Out of Window Visit
Trial Procedure Not Done
Randomization Error

6.7 Trial Termination

Novavax reserves the right to terminate the trial at any time for any reason. If and when the trial is terminated (either prematurely or as scheduled), the investigator will notify the IRB for the trial and other authorities, as required by local regulatory requirements.

The scheduled end of the trial will be the completion of the last Day 364 follow-up visit with the last trial subject.

7 TRIAL LABORATORY REQUIREMENTS

Appendix 3 specifies the maximum amount of blood (up to 174 mL) to be drawn for safety laboratory assessments and immunogenicity laboratory assessments to be completed throughout the trial.

7.1 Clinical Laboratory Testing

The following laboratory tests will be performed by a qualified central laboratory designated by Novavax on blood samples collected from subjects on Days 0 and 28:

- Serum chemistry – alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), creatinine, and blood urea nitrogen (BUN).
- Hematology – complete blood count (CBC) with hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, and white blood cell (WBC) count with differential.

7.2 Serological Assessments of Immunogenicity

Immunogenicity assessments will be made on subject sera collected on Days 0, 28, 56, 182, and 364. The primary measure of immunogenicity for the trial is serum Day 28 HAI antibody titer specific for the HA receptor binding domains of each of the virus strains included in Quad-NIV, Fluzone HD, and Flublok Quadrivalent, as well as antigenically-drifted strains. The secondary and exploratory variables of immunogenicity include HAI titers specific for the HA receptor binding domains of vaccine-homologous and antigenically-drifted strains on Days 0, 28, 56, 182, 364. In addition, neutralizing antibody titers specific for the virus strains included in Quad-NIV, Fluzone HD, and Flublok Quadrivalent, as well as selected antigenically-drifted strains, will be evaluated. Cell-mediated immune responses as reflected in specific antigen-stimulated cytokine production will also be measured for approximately 189 subjects from 3 preselected sites. Note: For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3 of the trial.

7.2.1 Hemagglutination Inhibition (HAI) Assay

7.2.1.1 Egg-based HAI

Briefly, sera will be treated with receptor-destroying enzyme (RDE) to remove non-specific inhibitors of hemagglutination, followed by heat-inactivation, and then plated into microtiter wells, starting with an initial dilution of 1:10 and followed by a series of 2-fold dilutions. The HA antigen (ie, egg-based whole virus) and indicator erythrocyte suspension will be added to designated wells in 2 steps, with mixing and incubation at each step. The titration endpoint will be taken as the highest dilution that demonstrates complete inhibition of hemagglutination. The serum HAI titer will be calculated from the GMT of duplicate test results. The HAI assay will be qualified for this Phase 2 trial in Novavax Clinical Immunology Laboratory under the supervision of Dr. Joyce Plested, Senior Director of Clinical Immunology.

7.2.1.2 VLP-based HAI

Due to the documented inability of recent A(H3N2) strains to agglutinate avian or small mammal red blood cell reagents in hemagglutination inhibition (HAI) assays and, in addition,

the presence of immunologically-significant mutations induced by egg passage in the HA of these strains [Zost 2017], vaccine immunogenicity will be assessed by the classical HAI method adapted with 140 – 190 nm recombinant wild-type hemagglutinin virus-like particles (HA-VLPs), reflecting the amino acid sequence of circulating virus, as the agglutinating agent and human type-O red blood cells (RBCs) as the agglutination target in order to restore assessment of HAI antibody activity. Briefly, sera will be first treated with RDE to remove non-specific inhibitors of hemagglutination, followed by heat-inactivation, and then plated into microtiter wells, starting with an initial dilution of 1:10 and followed by a series of 2-fold dilutions. The HA-VLPs and indicator erythrocyte suspension will be added to designated wells in 2 steps, with mixing and incubation at each step. The titration endpoint will be taken as the highest dilution that demonstrates complete inhibition of hemagglutination. The serum HAI titer will calculated from the GMT of duplicate test results. The HAI assay will be qualified for this Phase 2 trial and performed as described in SOP (P_SOP_02041) using wild-type VLPs and human red blood cells in Novavax Clinical Immunology Laboratory under the supervision of Dr. Joyce Plested, Senior Director of Clinical Immunology.

7.2.2 Microneutralization Assay

The influenza virus microneutralization assay will be based on the WHO manual for the laboratory diagnosis and virological surveillance of influenza, with minor modifications [WHO 2011]. Briefly, subject test sera will be heat-inactivated at 56°C for 30 minutes. Sera will be prepared in 3-fold serial dilutions (starting from 1:10) in singleton, in 96-well plates. Positive and negative virus controls will also be included. An approximate tissue culture infective dose of 100 ($TCID_{50}$) wild type cell-derived virus will be added and incubated for 120 minutes at 37°C ± 2°C in 5.0% ± 1% carbon dioxide (CO_2) for influenza A virus and at 32°C ± 2°C in 5.0% ± 1% carbon dioxide (CO_2) for influenza B virus. After incubation, 100 µL of trypsinized Madin Darby Canine Kidney (MDCK) cells at a concentration of 1.5 x 10^5/mL will be added to each well and incubated for 18 to 22 hours at 37°C ± 2°C in 5.0% ± 1% CO_2 for influenza A virus and at 32°C ± 2°C in 5.0% ± 1% carbon dioxide (CO_2) for influenza B virus. On Day 2, plates will be fixed, blocked, and incubated with mouse anti-influenza A nucleoprotein (NP) monoclonal antibody blend (MAB8251 for influenza A viruses or MAB8661 for influenza B viruses, EMD Millipore, Temecula, CA), followed by washing and incubation with a peroxidase-conjugated goat anti-mouse immunoglobulin G (IgG, Kirkegaard and Perry Laboratories, Gaithersburg, MD). Finally, plates will be washed and incubated with 3,3',5,5'-tetramethylbenzidine substrate (Sigma) and the optical density (OD) will be read after adding the stop solution. A sample titration curve is plotted OD against dilution using a 4-parameter curve fit. The sample neutralizing titer is interpolated on the titration curve as reciprocal of dilution at the OD that 50% of MDCK cells are infected. A 4-parameter fit (SoftMax Pro software) will use the following equation to determine the OD value at which 50% of the MDCK cells are infected:

$$X = [(\text{average OD of virus control wells}) + (\text{average OD of cell control wells})] / 2$$

The MN assay has been qualified (Novavax P_SOP_01866). Assay will be performed in Novavax Clinical Immunology Laboratory under the supervision of Dr. Joyce Plested, Senior Director of Clinical Immunology.

7.3 Assessments of Cell-Mediated Immunity

7.3.1 Assessment of T Cell Responses Based on Intracellular Cytokine Staining

Human PBMCs are cultured in 96-well U-bottom plates at a density of 1 x 10^6 cells/well and treated with the HA peptide, a positive control for T cell activation, or medium (negative control). After incubation at 37°C for 6 to 8 hours in the presence of BD GolgiPlug™ and BD GolgiStop™ (BD Biosciences), cells are labelled for surface markers (CD3, CD4, CD8, CD45RA, and CCR7 [BD Biosciences, San Jose, CA]) and the LIVE/DEAD® indicator dye (Life Technologies, NY) is added. The intracellular cytokines are detected by antibodies specific for IFN-γ, TNF-α, and IL-2. The samples are processed using a LSR-Fortessa flow cytometer (Becton Dickinson, San Jose, CA). Data are analyzed using Flowjo software version Xv10 (Tree Star Inc., Ashland, OR).

7.4 Retention and Use of Archived Specimens

Subject serum samples and frozen peripheral blood mononuclear cell preparations may be archived by Novavax or its contractors for a period not to exceed 25 years. Archived samples may be used for repetition of the assays listed in Sections 7.2 and 7.3 using different influenza antigens, or for other exploratory assays of influenza virus immunity or vaccine response in development. Archived sera may also be used for clinical laboratory testing for safety if needed to evaluate an adverse event, provided that a) sample storage falls within conditions previously validated by the clinical laboratory to yield interpretable results (or an appropriate control strategy can be used to evaluate potential storage impacts), and b) such testing will not include either assays to detect human immunodeficiency virus (HIV) infection, or any human genetic testing. Archived serum samples may also be used to create positive or negative panels for quality control or for assay development related to influenza virus or other infectious diseases (excluding HIV), in which case they will be anonymized.

8 TRIAL ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events (AEs) are defined as any unfavorable or unintended change in the physical, psychological, or biochemical condition of the subject. An AE temporally related to participation in the trial or due to a procedure performed in the trial, will be documented whether or not considered related to the test article. This definition includes intercurrent illnesses and injuries, and exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or severity during the trial are not considered AEs; however, these should be collected as part of the medical history. AEs will be considered treatment emergent from the date and time of the first administration of the investigational product.

Data concerning all classes of adverse events will be collected at scheduled visits from the time informed consent is obtained on Day 0 through Day 28, inclusive. After these specified days, data concerning MAEs, SNMCs, and SAEs will be collected (see Sections 8.1.5 and 8.2 for details of these AEs), as well as additional information regarding outcomes/resolutions of AEs reported prior that had no stop date recorded. In addition to the scheduled visits, subjects will be instructed to notify the investigator and/or return to the clinic if any severe AE (solicited or otherwise) or event fulfilling the definition of an SAE occurs at any time following vaccination. If at a scheduled or unscheduled visit, symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected. Adverse events will be recorded as observed by the investigator, designated personnel, or as provided by the subject on the diary card or during the in-person visit. Full details of the AE (ie, nature, date of onset, and recovery, as well as an assessment of severity, relationship to trial treatment [unsolicited events only], seriousness, treatment, and outcome) will be recorded in the source documentation and captured in the eCRF, and will generally require the investigator(s) causality assessment, except as discussed below.

8.1.1 Solicited Adverse Events/Subject Diary

Subjects will be provided with a diary for the documentation of any AEs, daily recording of their body temperature and certain common post-vaccination symptoms, and concomitant medications and procedures starting on vaccination day and for 6 days following the Day 0 vaccination (ie, from Day 0 through Day 6, inclusive). A series of local injection site and systemic reactions that are reasonably likely to occur in vaccine programs (Table 3) will be solicited daily in the diary and standardized severity grades offered to the subject. Subjects will report injection site events occurring on the deltoid where the test article was administered. A standard tool for the measurement of visible local reactions will be provided (see example provided in Appendix 4) as will a digital oral thermometer. Subjects will also be asked to record any physician visits or hospitalizations, and any unsolicited AEs experienced during Day 0 through Day 6. In addition to reporting Grade 3 solicited adverse events in the diary card, subjects should be encouraged to contact the investigator by telephone if these occur. The investigator may request an *ad hoc* clinic visit at his/her judgment, and should enter any Grade 3 solicited adverse events reported by telephone in the Subject Diary promptly, even if the balance of diary data is not yet available.

Table 3: Listing of Diary Solicited Events

Injection Site (Local) Events:	Systemic Events		
	General	Gastrointestinal	Respiratory/Facial
Pain	Oral temperature	Nausea	Eye redness
Bruising	Chills	Vomiting	Facial swelling
Redness	Muscle pain	Diarrhea	Eyelid swelling
Swelling	Joint pain		Hoarseness
	Headache		Sore throat
	Fatigue		Cough
			Difficulty breathing
			Wheezing
			Chest tightness
			Difficulty swallowing

Note: All events listed will be solicited by diary for 7 days post-dosing. Subjects will report injection site events occurring on the arm where the test article was administered. Events reported outside the solicitation window will be categorized and reported as unsolicited AEs.

Standard severity grading definitions will be provided in the diary. Grading of visible, measurable injection site reactions will be based on the Food and Drug Administration (FDA) Guidance for Industry, Toxicity Grading Scale (TGS) for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). Definitions are summarized in Table 5. Oral temperatures will be collected as a continuous variable and graded by the investigator based on ranges provided in the TGS as shown in Table 6.

Investigators will not be required to assess causality of solicited adverse events specifically named in the diary if onset is during the solicitation period (these will be presumed to be treatment-related). Adverse events consistent with the solicited adverse events listed in the diary, but with onset after the solicitation period (ie, Day 7 thereafter), will be captured as unsolicited AEs and are subject to all procedures for unsolicited AE data.

Solicited AEs, collected from the subject diary, which continue after the collection period (ie, on or after Day 7 for vaccination-emergent events) will be followed to resolution. The continuing, solicited AE will be captured by verbatim term on an "AE eCRF" page. The investigators will be required to assess severity of the continuing solicited adverse event(s) starting from the time after the last diary entry until resolution.

8.1.2 Unsolicited Adverse Events

Any AEs reported spontaneously by subjects will be categorized as unsolicited events and Medical Dictionary for Regulatory Activities (MedDRA) coded by system organ class (SOC) and preferred term (PT). Solicited events with an onset after the solicitation period will also be classified as unsolicited AEs. Unsolicited events that occur within 7 days following vaccination should also be recorded in the subject diary. If any Grade 3 unsolicited event is reported during this period, subjects should be encouraged to contact the investigator by telephone. The investigator may request an *ad hoc* clinic visit at his/her judgment, and should enter any Grade 3 unsolicited adverse event reported by telephone in the unsolicited AE eCRF promptly, even if the balance of diary data is not yet available. All unsolicited AEs will be assessed for severity

(as defined in Section 8.1.2) and for causality (as discussed in Section 8.5), and will be documented in the source documents and captured in the eCRF.

8.1.3 Vital Sign Abnormalities as Adverse Events

For purposes of reporting vital sign abnormalities as AEs, those values that show an increase in the toxicity grade relative to the baseline values (in the same subject) 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 repeated 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 sign abnormalities which are the logical consequence of another diagnosis (eg, irregular tachycardia in a subject with atrial fibrillation or fever in a subject with pneumonia) need not be reported separately.

8.1.4 Clinical Laboratory Findings as AEs

Clinical laboratory parameters will be tabulated in trial reports by grades using the TGS provided in the **Trial Operations Manual**, which is based on the FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). Minor adaptations may be made to the grade ranges for some parameters to conform with the normal, high, and low reference ranges established at the central laboratory selected for the trial.

Laboratory values that show an increase in the toxicity grade relative to baseline values in the same subject, and *attain* at least Grade 2 (eg, normal or Grade 1 to Grade 2 or higher) will be reported as AEs. Repeat testing will be conducted as defined below until the laboratory parameter returns to baseline, becomes stable, or an explanatory diagnosis is available:

- Grade 2 events - weekly, from the time the investigator becomes aware of the abnormal laboratory parameter.
- Grade 3 events - every 72 hours, from the time the investigator becomes aware of the abnormal laboratory parameter.

The investigator may also elect to report less severe abnormalities as AEs, at his/her discretion, if the abnormality is of sufficient concern to trigger, or should have triggered, a diagnostic evaluation (including repeat testing).

8.1.5 Medically-attended Events and Significant New Medical Conditions

These classes of events will be collected at all trial visits, and if offered spontaneously by the subject at any time.

Medically-attended events (MAEs) are adverse events which result in an unscheduled visit to a healthcare provider due to symptomatic illness or injury. These may include office visits, clinic visits, home consultations, or emergency room evaluations for non-life-threatening events that

do not result in hospitalization (life-threatening events or hospitalizations are SAEs, see Section 8.2).

Significant new medical conditions (SNMCs) are adverse events that are new (that is, not present at baseline), clinically significant (meaning that they imply an important change in the subject's long-term health status), and typically chronic (requiring an ongoing change in the subject's medical management). This category is not meant to include minor or transient diagnoses or age-related changes. For example, while new diagnoses of presbyopia or tinea versicolor are chronic conditions, they are not SNMCs because no significant change in health status is implied. Similarly, adverse events which are isolated, treatable events that resolve and do not require chronic therapy are also not SNMCs (examples could include an uncomplicated acute urinary tract infection or a simple fracture resolved with conservative treatment and with no residual disability). In contrast, new diagnoses of rheumatoid arthritis or coronary artery disease are SNMCs because they imply a long-term change in health status and require ongoing medical management. Additionally, 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 AESIs listed in Table 4. Note that this regulatory request is not specific to Novavax's Quad-NIV or Matrix-M1 adjuvant; and there is no current evidence to suggest that the trial drugs 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 AESIs.

Table 4: Adverse Events of Special Interest

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), 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

Table 4: Adverse Events of Special Interest

Categories	Diagnoses (as MedDRA® Preferred Terms)
Vasculidities:	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 anti-neutrophil cytoplasmic antibody [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 glomerulo-nephritis, membranoproliferative glomerulonephritis, and mesangio-proliferative glomerulonephritis
Cardiac Disorders:	Autoimmune myocarditis/cardiomyopathy
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
Metabolic Disorders:	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, sarcoidosis, pernicious anemia

The eCRF will provide a field in which the investigator may designate AEs as MAEs, SNMCs, or both. Because of the significance of the designation for the subject's health, long-term medical management, and for evaluation of vaccine safety, SNMCs are expected to be substantiated diagnoses, not isolated symptoms which might or might not be a SNMC, and the investigator should record sufficient data in the eCRF to support the diagnosis.

Full details of MAEs and SNMCs (ie, nature, date of onset, and recovery (if applicable) as well as an assessment of severity, relationship to trial agent, seriousness, treatment, and outcome) will be recorded in the source documentation and captured in the eCRF, and will require the investigator(s) causality assessment.

8.2 Serious Adverse Events

A SAE is defined as an AE that results in any of the following outcomes:

- Death,
- An immediate threat to life,
- In-patient hospitalization or prolongation of an existing hospitalization. (Hospitalization is defined as an actual admission, not a 24-hour stay or emergency room visit; *note that elective surgeries, undertaken for conditions present prior to receipt of trial drug and without complication, should not be considered SAEs*),
- A persistent or significant disability/incapacity (substantial disruption of an ability to conduct normal life functions), or
- A congenital anomaly or birth defect (*not relevant to this protocol*).

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 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 in-patient hospitalization. Events which could have led to the above outcomes had they occurred with greater severity are not SAEs, but should be reported as AEs, MAEs, or SNMCs, as appropriate.

The eCRF will provide a field for designating an AE as an SAE. SAEs are associated with enhanced reporting requirements (see Section 8.3).

8.3 Safety Reporting Requirements and Timelines for SAEs and Certain Other Events

Any SAE must be reported (using the SAE Report Form) to Novavax Product Safety **within 24 hours** of the investigator's first knowledge of the event, regardless of the presumed relationship to the investigational product. The investigator or qualified designee must complete the SAE Report Form, sign, and transmit the completed form to Novavax Product Safety.

Initial reports of SAEs may be reported via fax or e-mail. Initial reports **must** be signed (physically or electronically) by the investigator or a qualified sub-investigator and transmitted to Novavax Product Safety **within 24 hours** of site awareness. When additional follow-up information becomes available, a written follow-up SAE Report Form must be completed, signed by the investigator or a qualified sub-investigator, and transmitted as soon as possible. The investigator is responsible for obtaining detailed information to support all SAE reports, including records of inpatient and outpatient care, laboratory reports, and autopsy or medical examiner reports.

The following events must be reported to the Medical Monitor **within 24 hours** of the investigator's first knowledge of the event:

- Any withdrawal of consent after dosing due to an AE.
- Overdose (of a test article as specified in the protocol with or without an AE).
- Inadvertent or accidental exposure to the test article with or without an AE.
- Medication error (includes the administration of an incorrect treatment, an expired test article, a test article that has deviated from its required storage or refrigeration requirements, or any test article prior to documentation of informed consent).

Novavax will be responsible for notifications of SAEs to the relevant regulatory authorities; investigators will be responsible for IRB notification.

8.4 Severity

All AEs will be assigned severity by the subject and/or investigator (as applicable) according to the TGS. Subjects will also be able to indicate severity for any AEs experienced and record this in their diary according to the same scale. For quick reference, an abbreviated grading scale is provided in Table 5 for visible and non-visible local AEs and for systemic AEs for which severity is based on interference with daily activities and not numeric ranges, and in Table 6 for fever and gastrointestinal adverse events of nausea, vomiting, and diarrhea.

The severity of visually-evaluated local AEs will be a function of size. During the diary period, subjects will monitor the size of visible local AEs at the injection site using the Subject Measurement Tool (Appendix 4) which has concentric circles that correspond to the diameters specified in Table 5. For the purposes of reporting during the solicitation period (ie, Day 0 through 6) the subjects' observations will form the primary data. During clinic visits, investigators may measure any persisting local AEs with a ruler, documenting the size of the reaction at its widest diameter, using the numeric scale provided in Table 5 to assess for severity.

Non-visible local AEs (eg, pain) will be assigned a severity based primarily on interference with daily activities.

Systemic solicited AEs and unsolicited AEs will be assigned a severity grade based primarily on disruption of normal daily activities, with the exception of fever and select solicited gastrointestinal AEs that have their own distinct toxicity grades (Table 6). Medical care-seeking is typically absent for grade 1 (mild) and often present for grade 3 (severe) events, but is not the primary determinant of severity, since individuals behave differently in this regard.

Severity of vital sign abnormalities (including oral temperature, which is captured as a continuous variable) will be graded based on established ranges provided in the TGS and reported as an AE using the criteria outlined in Section 8.1.3.

Table 5: Definition of Severity Grading for Adverse Events

Severity Grade	Definitions for Local Adverse Events		Definitions for Systemic Adverse Events
	Visual Local AE Size Grading Description	Non-Visual Local AE Grading Description	Systemic AE Grading Description
0 – Normal	Reaction size (greatest single diameter) < 2.5 cm	No noticeable symptom	No noticeable symptom or finding
1 – Mild	Reaction size (greatest single diameter) 2.5 to 5.0 cm	Discomfort or tenderness noticeable, but does not interfere with normal daily activities	Mild symptoms or diagnostic observations; intervention not indicated; no interference with normal activity
2 – Moderate	Reaction size (greatest single diameter) > 5.0 to 10.0 cm	Moderate discomfort or tenderness on firm pressure; causes some limitation of normal daily activities	Moderate symptoms or diagnostic observations; some interference with normal activity, not requiring medical intervention
3 – Severe	Reaction size (greatest single diameter) > 10.0 cm	Severe pain at rest, pain or tenderness immobilizes the injected limb and prevents normal daily activities	Severe symptoms, significantly disrupts or prevents normal daily activities, generally requires medical attention/intervention

Table 6: Severity Grade Definitions for Solicited Gastrointestinal Adverse Events and Fever

Severity Grade	Gastrointestinal Adverse Event			Fever
	Nausea	Vomiting	Diarrhea	
0 – Normal	No noticeable symptom	No noticeable symptom	No noticeable symptom	< 38.0
1 – Mild	No interference with activity, or 1 to 2 episodes/ 24-hour period	No interference with activity, or 1 to 2 episodes/ 24-hour period	1 to 3 unformed (loose) stools/24-hour period	38.0 to 38.4
2 – Moderate	Some interference with activity, or > 2 episodes/ 24-hour period	Some interference with activity, or > 2 episodes/ 24-hour period	4 to 5 unformed (loose) stools/24-hour period	38.5 to 38.9
3 – Severe	Prevents daily activity, or requires intravenous hydration	Prevents daily activity, or requires intravenous hydration	≥ 6 loose stools/24-hour period, or requires intravenous hydration	> 38.9

8.5 Relationship (Causality)

The relationship of an AE to the test article must be assessed and documented by the investigator or a qualified sub-investigator. Based on the criteria described below, the investigator must classify the AE according to the following categories shown in Table 7.

Table 7: Definition of Relationship for Adverse Events

Relationship	Relationship Description
Unrelated / Unlikely	• May or may not follow a reasonable temporal sequence from administration of the test article; • No plausible mechanism based on known or suspected actions of the test article or product class; • Readily explained by known characteristics of the subject's clinical state, common intercurrent illnesses, or other treatments administered to the subject.
Possibly	• Follows a reasonable temporal sequence from administration of the test article; • Based on known or suspected actions of the test article or product class, a plausible mechanism could exist; • May be reasonably explained by known characteristics of the subject's clinical state, common intercurrent illnesses, or other treatments administered to the subject; but the investigator deems this less likely than test article effect.
Probably	• Follows a reasonable temporal sequence from administration of the test article; • Based on known or suspected actions of the test article or product class, a plausible mechanism could exist; • Cannot be reasonably explained by known characteristics of the subject's clinical state, common intercurrent illnesses, or other treatments administered to the subject.
Definitely	• Follows a reasonable temporal sequence from administration of the test article; • Consistent with known actions of the test article or product class; • Cannot be reasonably explained by known characteristics of the subject's clinical state, common intercurrent illnesses, or other treatments administered to the subject. • May be confirmed by rechallenge (if applicable).

9 TRIAL DATA MANAGEMENT

9.1 Recording and Collection of Data

Novavax will provide sites with source documents for the recording and collection of subject data. Data will be entered into an electronic data capture (EDC) system by site staff. All source documents and EDC entries will be completed as soon as possible after the subject's visit. Corrections to data in the EDC system will be documented in the electronic audit trail that is compliant to US FDA regulations (21 Code of Federal Regulations Part 11). The investigator will review data resident in the EDC and indicate by electronic signature that, to his/her knowledge, the data are complete and accurate. If further changes are made after this, the investigator will need to again sign the Investigator Signature Page electronically. Designated source documents will be signed and dated by the appropriate trial personnel. The investigator must agree to ensure completion and maintenance of source documents for each subject participating in the trial.

9.2 Data Quality Assurance

All trial data will be entered by clinical trial site staff with trial-specific EDC training into a computerized data management system via EDC. Statistical analyses of data will only be performed after all clinical monitoring and data queries have been resolved. A quality audit may be performed to assure the quality and integrity of the clinical data generated and the accuracy of its reporting following Novavax clinical quality assurance (CQA) processes.

9.3 Monitoring

Novavax, as the Sponsor of this trial, is responsible for ensuring the proper conduct of the trial, in accordance with the Declaration of Helsinki (Amended Fortaleza, Brazil, 2013) and Good Clinical Practices (GCP) including, but not limited to, protocol adherence and the validity of the data recorded in the database. For the purposes of this trial, Novavax may transfer responsibility for the clinical monitoring to independent clinical monitors or a CRO who may monitor on-site or remotely. Novavax and/or independent clinical monitors are responsible for ensuring that the site(s) prepare complete, accurate, legible, and well-organized clinical trial data. On-site monitoring inspections will be routinely performed in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely. In addition, clinical monitors will provide ongoing support to ensure the investigator's continued understanding of all applicable regulations concerning the clinical evaluation of the investigational vaccine, and the proper execution of the protocol, as well as the investigator's reporting responsibilities.

The clinical trial sites will be monitored periodically for database accuracy and completeness, adherence to the protocol, regulatory compliance, safety reporting, clinical trial material accountability, and the maintenance of comprehensive source documents. Where applicable, the database will be checked against applicable source documents to verify completeness and accuracy. When data entry has been completed by the appropriate trial staff, source documents verified and monitored by Novavax and/or CRO representatives, and reviewed by the investigator, the investigator should sign and date the *Investigator Signature Page*.

9.4 Audit and Inspection

Novavax CQA reserves the option to develop a Quality Assurance plan to ensure the integrity of the conduct of the clinical trial. CQA visits may be performed during the trial and post-trial by Novavax CQA or other personnel authorized by Novavax. Regulatory authorities reserve the right to audit trial sites following submission of data in regulatory applications. By signing this protocol, the investigator acknowledges that these inspection procedures may take place and agrees to provide access to the required subject records and other trial documentation. Further, the investigator agrees to inform Novavax and the IRB immediately of any scheduled or unscheduled inspection by regulatory authorities.

9.5 Adherence to and Changes to the Protocol

Any change or addition to this protocol will only be made when a protocol amendment has been written, approved, and signed by Novavax and the investigator before the change or addition can be considered effective, unless immediate implementation of a change is necessary to ensure the safety of subjects. This amendment must also be submitted to the IRB for approval and, when necessary, regulatory authority approval before implementation. Protocol amendments may affect consent forms of current and future subjects. Novavax will clearly specify when a protocol amendment includes safety, procedural, and/or efficacy information that will require specific informed consent form (ICF) text changes.

9.6 Retention of Records

It is the responsibility of the investigator and trial staff to maintain a comprehensive and centralized filing system of all trial-related documentation, which is suitable for inspection at any time by Novavax, its designees, and regulatory agencies. These should minimally include:

- Subject files including the completed eCRF (based on output from clinical database) on compact disc (CD), supporting source documentation, and the informed consent and any other subject information.
- Trial files (essential documents and regulatory files) including the protocol with all amendments, the IB, safety and protocol deviations meeting IRB reportable criteria, copies of all regulatory documentation, and all correspondence with the IRB, regulatory authority, and Novavax.
- Pharmacy files including all investigational vaccine shipment, receipt, storage, dispensing, and accountability records, and pharmacy-related correspondence.

In addition to the eCRF, the investigator will maintain adequate records that fully document the progress of the trial. Copies of these trial records and related documents must be kept on file by the investigator for a period of no less than 15 years (or longer if mandated by relevant local regulations). ALL DOCUMENTATION AND MATERIAL PROVIDED BY NOVAVAX OR A NOVAVAX REPRESENTATIVE FOR THIS TRIAL (CASE REPORT FORMS, PROTOCOL, ETC) ARE TO BE RETAINED IN A SECURE PLACE AND TREATED AS CONFIDENTIAL MATERIAL.

10 TRIAL STATISTICAL CONSIDERATIONS

This section includes a brief description of the statistical analyses that will be performed in this trial.

10.1 Subject Populations

The following subject populations will be used in all analyses:

- Safety Population - Includes all trial subjects that provide consent, are randomized, and receive the test article. The Safety Population will be used for all safety analyses; and will be analyzed as actually treated.
- Per-Protocol Population (PP) - Includes all subjects in the Safety Population that received the assigned dose of the test article according to protocol, have HAI serology results for Day 0 and Day 28, and have no major protocol deviations affecting the primary immunogenicity outcomes as determined by Novavax prior to database lock and unblinding. The PP Population will be the primary population used for immunogenicity analyses.
- Intent-to-Treat (ITT) Population - Includes all subjects in the Safety Population that provide any HAI serology data. The ITT Population will be the secondary population used for any immunogenicity analyses and will be analyzed according to treatment as randomized. Analysis using the ITT population will not be performed if it differs from the PP population by less than or equal to 5% of the subjects for each of the 7 treatment groups.

10.2 General

Continuous variables will be presented by summary statistics (eg, mean and standard deviation [SD] for the non-immunogenicity endpoints; geometric means and their 95% CI for the immunogenicity endpoints). Categorical variables will be presented by frequency distributions (frequency counts and percentages for the non-immunogenicity endpoints; percentages and their 95% CIs for the immunogenicity endpoints).

10.3 Demographics and Protocol Compliance

Demographic parameters and other baseline characteristics (eg, age, sex, race, and ethnicity) will be summarized by treatment group for all subjects in the safety population. The number and description of protocol deviations will be summarized for all enrolled subjects who signed the ICF and were randomized in to the study.

10.4 Analyses Addressing Protocol Objectives

10.4.1 Analyses of Primary Objectives

10.4.1.1 Safety

Safety analysis will be descriptive and based on the safety population, defined as all subjects who received a dose of trial treatment. Safety will be summarized overall and by individual treatment arms based on solicited short-term reactogenicity post-injection on Day 0, 28-day all AE profile by MedDRA preferred term, and 1-year MAE, SAE, and SNMC profiles

post-injection on Day 0. All AEs, MAEs, SAEs, and SNMCs will be tabulated by severity, related (possibly, probably, or definitely vs. non-related per investigator assessment), and severe and related. The number and percentage (with 95% CI) of subjects in each treatment group with a given term will be summarized. Clinical laboratory data will be summarized by means and 95% confidence interval (CI), minima and maxima, at Day 0 and Day 28 in each treatment group, as well as means and 95% CI of change from baseline at Day 28. Changes from baseline will also be summarized at Day 28 for each treatment group in terms of the proportion of subjects with no change in toxicity grade versus proportions with 1, 2, or 3 grade changes. A listing and narratives of SAEs will also be produced.

10.4.1.2 Immunogenicity

The primary immunogenicity analysis will be based on the PP population. A separate ITT population analysis will not be produced unless > 5% of at least 1 treatment group is excluded from the PP population. For GMTs and GMRs, titers reported below the lower limit of quantitation (LLOQ, ie, below the starting dilution of assay reported as "< 10") will be set to half that limit (ie, 10 / 2 = 5). Immunogenic superiority of the adjuvanted treatment group (treatment group B) relative to the unadjuvanted Quad-NIV group (treatment group E) will be demonstrated by excluding values ≤ 1.0 at the lower 95% confidence bound for the baseline-adjusted ratio of Day 28 post-vaccination HAI titers (ie, GMT adjuvant / GMT no adjuvant) for not less than 2 out of 6 influenza strains (ie, any 2 of: 4 vaccine-homologous strains and/or 2 antigenically-drifted influenza strains), while no other strain(s) demonstrate a baseline-adjusted ratio of Day 28 post-immunization HAI titers which is significantly < 1.0 (See Section 10.5 for details).

HAI antibody titers specific for each of the vaccine-homologous and antigenically-drifted influenza strains tested will be summarized by treatment group based on GMT at baseline (screening) and post-vaccination on Day 28 (with 95% CIs), and by ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).

10.4.2 Analysis of Secondary and Exploratory Immunogenicity Objectives

HAI and neutralization responses will be assessed in terms of GMT, GMR, SCR, and SPR (HAI only) at Days 0, 28, 56, 182, and 364. Note: MN will be assessed at Days 0 and 28 and may include additional time points. P-values may be generated for information and planning of future studies, but will not be adjusted for multiple comparisons.

HAI and neutralizing antibody titers specific for each of the virus strains will be summarized by treatment group for each virus stain tested at all time points, including baseline (Day 0) as reference, based on the following parameters (with 95% CIs):

- Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed HAI titers at a given time point.
- Geometric mean ratio (GMR) – defined as the ratio of post vaccination to pre-vaccination (Day 0) HAI GMTs ($GMR_{Post/Pre}$) at a given post vaccination time point.

- Seroconversion rate (SCR) – defined as proportion of subjects 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 at a given post vaccination time point.
- Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 at a given time point (HAI only).
- Ratio of GMTs between treatment arms at Days 28, 56, 182, and 364 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).
- Proportion of subjects with ≥ 2-fold or ≥ 4-fold increases in HAI titers among those with low baseline titers (ie, lowest quintile) (exploratory endpoint only).

For HAI and neutralization endpoints (all strains tested and at all time points), the following treatment group differences will be estimated to address secondary and exploratory objectives:

- 60 µg HA per A strain and 90 µg HA per B strain; and 50 µg of Matrix-M1 (Group D) vs Fluzone HD or Flublok Quadrivalent (Group F or G).
- 60 µg HA per A strain and B strain; and 75 µg of Matrix-M1 (Group C) vs Fluzone HD or Flublok Quadrivalent (Group F or G).
- 60 µg HA per A strain and B strain; co-formulated with 75 µg of Matrix-M1 (Group C) vs 60 µg HA per A strain and B strain; co-formulated with 50 µg of Matrix-M1 (Group B).
- 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs a similar formulation mixed bedside (Group A).
- 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs Fluzone HD or Flublok Quadrivalent (Group F or G).
- 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs 60 µg HA per A and B strain without adjuvant (Group E).
- 60 µg HA per A strain and B strain with 50 µg of Matrix-M1 co-formulated (Group B) vs 60 µg HA per A strain and 90 µg HA per B strain; and 50 µg of Matrix-M1 (Group D).

Percentages of subjects with immune response will be calculated along with the corresponding 2-sided exact (Clopper-Pearson) binomial CIs. GMTs will be summarized by treatment group and visit day along with the corresponding 2-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. Two-sided 95% CIs for the difference in SCRs and SPRs between treatment groups will be based on the Newcombe hybrid score (METHOD = SCORE riskdiff-option for PROC FREQ in SAS). The comparison of GMTs between treatment groups (ie, the ratio of GMTs) will be conducted on log-transformed titers using the analysis of covariance (ANCOVA) adjusted for the baseline (Day 0) value by including the baseline titer as a covariate.

Reverse cumulative distribution displays of HAI and MN titers corresponding to the comparisons described above for each virus strain will be produced in which Day 0 and Days 28, 56, 182, and 364 distributions will be displayed separately by treatment group. Note: MN

will be assessed at Days 0 and 28 and may include additional time points. Analysis of exploratory CMI response endpoints will be performed on approximately 189 subjects from 3 preselected sites (63 subjects per site) and results may be reported as an addendum to the main clinical study report.

10.5 Sample Size Considerations

For safety endpoints, the probability of observing at least 1 adverse event among 135, 155, or 310 subjects for each Quad-NIV formulation is > 90% if the true rate of such events is 1.7%, 1.5%, or 0.8%, respectively. With 135, 155, or 310 subjects for each treatment group, observing no adverse events of interest (eg, vaccine-related SAE) would represent an upper bound of the 1-sided 95% CI on the percentage of such event is 2.2%, 1.9%, or 1.0%, respectively.

This study has a single comparison of 2 treatment groups (Group B vs E) for the primary immunogenicity objective. No formal adjustment for multiple comparisons is planned for the 6 comparisons associated with the 6 strain-specific GMTs. The demonstration of the superiority of Quad-NIV (60 µg HA per A and B strain) co-formulated with 50 µg Matrix-M1 (Group B) as compared to Quad-NIV (60 µg HA per A and B strain) without adjuvant (Group E) requires simultaneous successes of all 6 tests (at least 2 strains meeting the strain-specific superiority criterion and the non-inferiority criterion for the remaining homologous strains). The non-inferiority for this trial will be carried out without a pre-specified margin. Non-inferiority is defined as the 2-sided 95% CI for the ratio of GMTs (Group B / Group E) containing 1.0 (ie, unadjusted 1-sided p-value $\geq$ 0.025 against the null hypothesis of H0: Ratio of GMT $\leq$ 1.0). The superiority is defined as the lower limit of the 2-sided 95% CI for the ratio of GMTs (Group B / Group E) > 1.0 (ie, unadjusted 1-sided p-value < 0.025 against the null hypothesis of H0: Ratio of GMT $\leq$ 1.0). For other immunogenicity analyses, the purpose is to determine a dose and formulation for the next study based on all available safety and immunogenicity results, including the primary objective analysis. Hence, any statistical analyses (ie, calculations of CIs and p-values) will also be performed without a multiplicity adjustment.

In a previous study using the Tri-NIV formulation (tNIV-E-101), the observed strain-specific standard deviations of $\log_{10}$ HAI titers ranged from approximately 0.4 (B/Brisbane and A/Texas) to approximately 0.6 (A/Switzerland and A/Singapore). Table 8 summarizes power, unadjusted for multiple comparisons, for the primary objective to demonstrate superiority for pair-wise comparisons of the 2 treatment groups. Power calculations also accounted for a 5% attrition rate for the per-protocol population (295 evaluable subjects per treatment group) which is the primary analysis population for all immunogenicity endpoints. For each strain, this study is designed to detect a 1.4-fold increase (40% increase) in GMTs with $\geq$ 84% power. For 2 strains, this study is designed to detect a 1.5-fold increase (50% increase) in GMTs with $\geq$ 88% power. For each strain, there will be 97.5% probability of demonstrating a non-inferior GMT for each comparison if 2 treatment groups have an equal GMT. Therefore, demonstrating a superiority against 2 strains with the true difference of 1.5-fold and a non-inferiority against 4 strains with the true difference of 1.0-fold, this study is designed to provide $\geq$ 80% power.

Table 8: Power to Detect Percentage Increase in Ratio of GMTs Between 2 Treatment Groups

Per-Protocol N Group	Log_{10} SD	Fold Increase	Power
295	0.4	1.2	67%
		1.3	93%
		1.4	99%
		1.5	> 99%
		1.6	> 99%
		1.7	> 99%
	0.5	1.2	48%
		1.3	79%
		1.4	94%
		1.5	99%
		1.6	> 99%
		1.7	> 99%
	0.6	1.2	36%
		1.3	63%
		1.4	84%
		1.5	94%
		1.6	98%
		1.7	> 99%

10.6 Plan for Statistical Summaries and Analyses

10.6.1 Day 28 Unblinded Data Review

An unblinded review will be conducted of all available immunogenicity and safety data (inclusive of clinical laboratory safety assessments) upon completion of Day 28 visits for all subjects and at least the completion of HAI data concerning all four vaccine-homologous virus strains and at least 2 antigenically-drifted influenza strains at Days 0 and 28. For the review, treatment codes will only be unblinded after the data are deemed ready for the analysis after all subjects have completed the Day 28 visit and the data are monitored. The determination of the readiness will be based on the blinded review of outstanding queries of critical data points. Given the time-consuming nature of the microneutralization and cellular response assays, these data may be presented only in the final CSR (see Section 10.6.2).

In order to execute this review, a select group of trial staff will be unblinded at the CRO and at Novavax. All personnel unblinded to the trial data will be documented. No individual unblinded at a subject treatment level will be involved in follow-up safety monitoring. Specifically, personnel at the clinical trial site including, investigators and trial staff, research site, immunology laboratory, and trial subjects will remain blinded to treatment assignments until the end of trial (ie, Day 364).

Since trial procedures and monitoring practices will not change following the review and the trial will not be terminated prematurely on the basis of these data, no decision cut points or stopping rules will be stipulated.

Immunogenicity and safety analyses from the unblinded review may be presented in an abbreviated unblinded clinical study report (CSR) drafted by the Sponsor that may be submitted to regulatory authorities as needed.

10.6.2 Final Clinical Study Report

The final CSR will present the balance of all safety and immunogenicity (if any) data through Day 364 (the scheduled end of trial). The database will be locked and the final CSR prepared, when all of the above data have been entered, reviewed, and all queries related to the data have been addressed. Any decisions to deviate from the planned analyses will be described in detail in the final CSR.

10.7 Computer Methods

Statistical analyses will be performed using SAS® version 9.3 or greater under a Windows operating system.

11 TRIAL LEGAL AND ETHICAL REQUIREMENTS

11.1 Compliance with Regulatory Requirements

This trial will be conducted in accordance with the protocol, the Declaration of Helsinki (amended Fortaleza, Brazil, 2013), International Conference on Harmonisation (ICH) GCP Guidelines, and the US FDA regulatory requirements.

11.2 Ethics Committee

This trial will be conducted under the auspices of a properly-constituted IRB, as defined by US regulatory requirements, and in accordance with the Declaration of Helsinki (amended Fortaleza, Brazil, 2013). This committee will review and approve all aspects of the trial, including the protocol and ICF to be used, any and all advertising or informational materials, and any modifications made to the protocol and ICF, prior to, or during the trial. Prior to initiation of clinical activity, investigators will provide Novavax with a copy of the communication from the IRB indicating approval of the protocol and ICF. In the event that a central IRB is used, Novavax will provide copies of correspondence to the investigators. All changes to the protocol or ICF must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

If applicable, the investigators will be responsible for obtaining annual IRB renewal throughout the duration of the trial. Copies of the investigators' annual report to the IRB and copies of the IRB continuance of approval must be furnished to Novavax.

11.3 Informed Consent

The investigators or designated site trial staff members will be responsible for obtaining written informed consent (and any applicable local or state regulatory documentation), signed and dated by each subject, prior to his/her participation in the trial. Informed consent will be obtained from a subject after a full explanation of the purpose of the trial, the risks and discomforts involved, potential benefits, etc, have been provided by the investigators, both verbally and in writing. The original signed copy of the ICF must be maintained in the institution's records and will be subject to inspection by a representative of Novavax and/or regulatory agencies. The subject will also be given a copy of the signed consent form.

11.4 Required Site Documentation

The following documents must be provided to Novavax or its designee prior to the start of the trial:

- Current *Curriculum Vitae* and medical licenses (as applicable) for the principal investigator and all sub-investigators,
- Financial Disclosure Forms from the principal investigator and all sub-investigators,
- Signed protocol and amendments (if any),

- Copy of correspondence from the IRB indicating approval of the protocol, ICF, and any site-specific trial advertisements, signed by the IRB chairperson or designee, and containing the name and address of the IRB,
- Membership roster of the IRB, listing names and occupations. If an investigator participating in this trial is an IRB member, documentation should be provided of his/her abstention from voting on this protocol,
- ICF reviewed and approved by the IRB, or a revised document if changes were requested by the committee with the IRB stamp and date, and
- Reference ranges for all safety tests required in the protocol and documentation of laboratory licensure if the trial site's local clinical laboratory will be used.

11.5 Subject Confidentiality

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties, other than those cited below, is prohibited. Subject confidentiality will be further ensured by utilizing a subject identification code and subject initials. Relevant US national and local jurisdictions governing privacy rules and protection of human subjects will be followed in this trial.

In compliance with regulatory guidelines regarding the monitoring of clinical studies, and in fulfillment of the investigator's obligations to Novavax, it is required that data generated as a result of the trial be available for inspection, on request, by personnel from Novavax, CRO monitors representing Novavax, and/or regulatory agencies. These shall include all trial relevant documentation, including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, and admission/discharge summaries for hospital admissions occurring while the subject is on-trial.

As part of the required content of the informed consent, subjects must be informed that their records will be reviewed by Novavax and/or regulatory agencies. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the trial.

11.6 Disclosure of Information

Information concerning the investigational Quad-NIV and patent application processes, scientific data, or other pertinent information is confidential and remains the property of Novavax. The investigator may use this information for the purposes of the trial only. It is understood by the investigator that Novavax will use information developed in this clinical trial in connection with the development of the investigational vaccine and therefore may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical trial, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to Novavax. Authorization to publish or otherwise publically disclose the results of this trial is strictly governed by the terms set forth in the clinical trial agreement.

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APPENDIX 1 – QNIV-E-201 TRIAL PROCEDURES SCHEDULE

Trial Day:	**0**	**3**	7	**28**	**56**	**90**	**182**	**273**	**364**
Window (days):		**± 1**	**± 1**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**
Trial Procedures									
Trial Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical/Medication History	X								
Physical Exam	X		X [7]	X [7]	X [7]		X [7]		X [7]
Vital Signs	X [1]		X	X [1]	X		X		X
Clinical Safety Laboratory [2]	X			X					
Serology	X			X	X		X		X
PBMC for CMI	X[8]		X[8]						
Trial Treatment Injection	X								
Injection with a 2018 - 19 licensed seasonal influenza vaccine or placebo [6]				X					
2019 - 20 licensed seasonal influenza vaccine offered to all subjects [9]									X
Adverse Event Review [4]	X	X [3]	X	X	X	X	X	X	X
Concomitant Medications Review [4]	X	X	X	X	X	X	X	X	X
Subject Diary Review		X [3]	X [5]						
End of Trial									X

Note: Procedures shaded in grey are performed via scripted telephone call.

[1] Vital signs to be captured pre-vaccination and between 30 to 60 minutes post-vaccination.

[2] Includes assessments for hematology (complete blood count [CBC] with hemoglobin, hematocrit, red blood cell [RBC] count, platelet count, and white blood cell [WBC] count with differential) and serum chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase, creatinine, and blood urea nitrogen [BUN]).

[3] Subjects will be asked to report any grade 3 solicited or unsolicited adverse event or SAE experienced since the last visit and may be asked to return to the clinic for an unscheduled visit to evaluate the event(s) at the Investigator's discretion.

[4] All adverse events and concomitant medications taken will be collected through Day 28; thereafter, only MAEs, SAEs, and SNMCs and medications taken for these events will be collected.

[5] The subject diary will be reviewed by the investigator and collected on Day 7 visit.

[6] On Day 28, subjects in Group E will receive a rescue injection with a licensed seasonal influenza vaccine; all other subjects will receive a placebo injection to maintain trial blind.

[7] If needed, a physical examination may be performed, based on the investigator's discretion.

[8] To be collected from approximately 189 subjects from 3 preselected sites (63 subjects per site). Note: For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3 of the trial.

[9] All subjects will be offered a 2019 - 20 licensed seasonal influenza vaccine at the last study visit (Day 364).

APPENDIX 2 – QNIV-E-201 SUBJECT DIARY CARD (DRAFT)

Daily Diary Entries

Subject ID US ____-____	Subject Initials ____	Day of Vaccination (Day 0)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Ongoing after Day 6?
ORAL TEMPERATURE		Date: __/__/__ ____°F	Date: __/__/__ ____°F	Date: __/__/__ ____°F	Date: __/__/__ ____°F	Date: __/__/__ ____°F	Date: __/__/__ ____°F	Date: __/__/__ ____°F	Tick the box if symptom is still continuing after Day 6
		❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	
GENERAL SYMPTOMS	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	
Chills									❒
Muscle Pain									❒
Joint Pain									❒
Diarrhea**									❒
Nausea ***									❒
Vomiting ***									❒
Headache									❒
Fatigue									❒
RESPIRATORY/FACIAL SYMPTOMS	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	
Cough									❒
Difficulty Breathing									❒
Chest Tightness									❒
Wheezing									❒
Sore Throat									❒
Difficulty Swallowing									❒
Hoarseness									❒
Eye Redness									❒
Eyelid Swelling									❒
Facial Swelling									❒
INJECTION SITE SYMPTOMS	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	
Pain									❒
Bruising*									❒
Redness*									❒
Swelling*									❒
Please complete the questions below by choosing either "Yes" or "No." Circle your response. *Any box marked with a "YES" will require additional information/explanation.*									
Have your medications changed or are you taking any new medications? *If yes, please record in the Medication Log.*		YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	
Did you visit a doctor? *If yes, please record the reason for seeking medical attention in the Doctor Visit Log.*		YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	
Did you have any other symptoms? *If yes, please list them in the "Other Symptoms Log" on page 9.*		YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	

** GRADING FOR DIARRHEA
0 = Normal
No noticeable symptom
1 = Mild
1 to 3 unformed (loose) stools within a 24-hour period
2 = Moderate
4 to 5 unformed (loose) stools within a 24-hour period
3 = Severe
6 or more loose stools within a 24-hour period, or requires intravenous hydration

*** GRADING FOR NAUSEA AND VOMITING
0 = Normal
No noticeable symptom
1 = Mild
No interference with activity or 1 to 2 episodes within a 24-hour period
2 = Moderate
Some interference with activity or ≥2 episodes within a 24-hour period
3 = Severe
Prevents daily activity or requires intravenous hydration

0 = NORMAL
No noticeable symptom or finding
1 = MILD
Noticeable discomfort/pain, or symptom that does not interfere with activities of daily living
2 = MODERATE
Moderate discomfort/pain, or symptom that limits but does not stop activities of daily living
3 = SEVERE
Severe pain of symptoms that stop activities of daily living and may require medical treatment

0 = NORMAL
No noticeable symptom
1 = MILD
Noticeable discomfort or tenderness that does not interfere with normal activity
2 = MODERATE
Moderate discomfort or tenderness that causes some limitation of normal activity
3 = SEVERE
Severe pain at rest, immobilizes the injected arm and prevents normal daily activity

*SEE SUBJECT MEASUREMENT TOOL INSTRUCTIONS

*A subject diary will be provided to all subjects to record solicited and unsolicited adverse events experienced, concomitant medications used, and any medical visits/procedures sought, within the first 7 days following Day 0 vaccination. The above is a sample excerpt from such a diary. **It is provided for informational purposes only and may differ from the actual diary issued to subjects.**

APPENDIX 3 – QNIV-E-201 BLOOD DRAW SCHEDULE

Trial Visit Day	Amount of Blood Drawn for Immunogenicity Assessment (mL)	Amount of Blood Drawn for Clinical Safety Assessment (mL)	Amount of Blood Drawn for CMI Assessment (mL)
Day 0 *(pre-vaccination)*	20	10	27[1]
Day 7 *(± 1 day)*	--	--	27[1]
Day 28 *(± 2 days)*	20	10	--
Day 56 *(± 2 days)*	20	--	--
Day 182 *(± 7 days)*	20	--	--
Day 364 *(± 14 days)*	20	--	--
TOTAL FOR ENTIRE TRIAL (mL)	120 – 174 [2]		

[1] To be collected from approximately 189 subjects from 3 preselected sites (63 subjects per site). Note: For logistical reasons, these subjects will be drawn entirely from those enrolled in Stage 3 of the trial.
[2] Most subjects will provide up to 120 mL of blood in the trial. Approximately 189 subjects from 3 preselected sites will provide up to 174 mL.

APPENDIX 4 – QNIV-E-201 SUBJECT MEASUREMENT TOOL

(Do not use this page in clinic, as it may not be to exact scale)

The Subject Measurement Tool consists of a transparent set of concentric circles with diameters that correspond to the ranges in the toxicity grading scale (2.5, 5, and 10 cm, in diameter). Subjects are instructed to overlay the template over the injection site for any reaction that can be visually observed (eg, redness, swelling, bruising). An assessment of severity is then made by determining the circle that best describes the size of the reaction: reactions that are smaller than Circle A (2.5 cm) are considered Grade 0; reactions larger than Circle A but equal to or smaller than Circle B (5 cm) are considered Grade 1; reactions larger than Circle B but equal to or smaller than Circle C (10 cm) are considered Grade 2; reactions larger than Circle C are considered Grade 3. The table below summarizes the severity grading for visible injection site reactions based on size.

Definition of Severity Grading for Visible Local Adverse Events

Severity Grade	Injection Site Grading Description
0 - Normal	Reaction size fits inside Circle A
1 - Mild	Reaction size larger than Circle A, but fits inside Circle B
2 - Moderate	Reaction size larger than Circle B, but fits inside Circle C
3 - Severe	Reaction size larger than Circle C

Approved

Signature Page

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