21 Firstfield Road Gaithersburg, MD 20878 USA

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

Novavax Protocol Number: qNIV-E-201

STATISTICAL ANALYSIS PLAN (SAP) for Unblinded and Final Analysis of Safety and Immunogenicity Data

SAP Version and Date: Version 2.0 - 04 March 2020

Investigational Product: 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.

APPROVAL SIGNATURE PAGE

Protocol Number:	qNIV-E-201
Protocol Version and Date:	Version 3.0 – 21 August 2018
Protocol 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.
SAP Version and Date:	Version 2.0 - 04 March 2020

☐ Original Statistical Analysis Plan

☒ Amended Statistical Analysis Plan

SAP Originated By: [redacted] Aug.31, 2018
Date

Signatures below indicate the SAP has been reviewed and approved by the following personnel:

[redacted]

Medical Lead Date

[redacted]

Statistician Lead Date

SAP CHANGE HISTORY

SAP Version 2.0, 04 March 2020 (revised from Version 1.1, 15 October 2018)

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

Location of Change	Change/Modification in Version 2.0
Section 8.1.1	Visual Local AE Size Grading Description for 2 – Moderate has been updated from '5.0 to 10.0 cm' to '> 5.0 to 10.0 cm' in Table 4.
Section 12	• Between treatment comparisons for the CMI results were performed at 2-sided 0.1 Type I error rate level and 2-sided 90% CIs for inference. • For the CMI measurements that require log transformation will be assigned a value of 1 count per million cells for those reported as 0 (section 12).
Appendix 1	The table note #9 numbering error has been corrected.

SAP Version 1.1, 15 October 2018 (revised from Version 1.0, 15 August 2018)

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

Location of Change	Change/Modification in Version 1.1
Section 7.2 Section 7.3	The method of p-value calculation for the difference in SCRs/SPRs between treatment groups has been updated.
Section 8.1.1	'Normal ≤ 38.0ºC' has been updated to 'Normal < 38.0ºC' to be consistent with Table 5.

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LIST 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
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CRO	Contract Research Organization
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold-rise
GMR	Ratio of Geometric Mean Titer
GMT	Geometric Mean Titer
HAI	Hemagglutination Inhibition
IC	Informed Consent
IIV	Inactivated Influenza Vaccine
IM	Intramuscular
IP	Investigational Product
ITT	Intent-to-treat
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Liter
LLOQ	Lower Limit of Quantitation

Abbreviation or Term	Definition
MAE	Medically-attended Event
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MN	Microneutralization
NIV	Nanoparticle Influenza Vaccine
PBMC	Peripheral Blood Mononuclear Cell
PP	Per Protocol
PPE	Per Protocol for Efficacy
PT	Preferred Term
qNIV or Quad-NIV	Nanoparticle Influenza Vaccine, Quadrivalent
RBC	Red Blood Cell
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
SNMCs	Significant New Medical Conditions
SOC	System Organ Class
SPR	Seroprotection Rate
TGS	Toxicity Grading Scale
TNF-α	Tumor Necrosis Factor Alpha
tNIV or Tri-NIV	Nanoparticle Influenza Vaccine, Trivalent
VRBPAC	Vaccine and Related Biological Products Advisory Committee
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

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 ≥ 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 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.

1.1 Study 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.

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.

1.2 Randomization and Treatment Assignments

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.

1.3 Unblinding

Treatment assignments are known only to the responsible unblinded vaccine administrators at the trial center. Personnel at the clinical study site including, investigators and study staff, immunology laboratory, and study subjects will remain blinded to individual subject treatment assignments until after the database lock for the final analysis unless emergency unblinding is necessary.

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.

1.4 Scope of the Analysis Plan

This statistical analysis plan (SAP) provides a detailed outline of the safety and immunogenicity analyses in accordance with Study Protocol qNIV-E-201Version 3.0, dated 21 August 2018, and will address the analysis presentation of the unblinded data as well as the final review of all data for the completed study.

An unblinded data review will be conducted upon completion of all Day 28 visits, which will include all available immunogenicity data through Day 28 and safety data (inclusive of clinical laboratory safety assessments for hematology and serum chemistry) through Day 28. Day 364 final analysis will be conducted when all available immunogenicity and safety data through Day 364 have been entered, reviewed, and all queries related to the data have been addressed.

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 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.

2.1.2 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.

2.1.3 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.

2.2 Study Endpoints

2.2.1 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 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).

2.2.2 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).

2.2.3 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 ≥ LLOQ and a post-vaccination reciprocal titer ≥ 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 ANALYSIS POPULATIONS

3.1 Safety Population

The 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.

3.2 Intent-to-Treat Population

The 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.

3.3 Per-Protocol Population

The Per-Protocol (PP) Population 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.

3.4 Discussion of Populations to be Used for Various Analyses

Subject demographic, baseline data, and safety AE summaries will be based on the Safety Population. All subjects enrolled (randomized) will be used for subject disposition. Immunogenicity summaries and associated statistical analyses will be based primarily on the PP Population and secondarily on the ITT Population.

3.4.1 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. This file will provide a description of each protocol deviation and will clearly identify whether or not a deviation warrants exclusion from the PP analysis set. All protocol deviations will be presented in a data listing, with a flag to indicate if a deviation was considered major and resulted in the exclusion of the subject from the PP analysis set.

Table 2: Programmatically-Determined Protocol Deviations

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

The following rules will be applied to capture programmatically determined PDs.

- Missed Visit information in protocol deviation from the eCRF will be subservient to those programmatically-determined and will not be used for formal CSR. Missed Visit will not be triggered by “Subject Diary Review” procedure. Missed Visit applies to planned in-clinic visits at Days 0, 7, 28, 56, 182 and 364. Telephone contacts will not be counted as missed visits, though the presence or absence of these visits will be apparent in the data listings. If a subject withdraws from the study early, no subsequent protocol deviations will be checked.
- Out of Window visit will be determined by comparing the actual visit day to the intended visit day. If a subject missed a particular visit (s), (s)he will not be considered as “Out of Window” for that visit but will be counted as “Missed Visit”. Out of Window visit applies to all planned trial visits at Days 0, 7, 28, 56, 182 and 364. Telephone contacts will not be reviewed for visit windows, however the date of occurrence will be present in the data listings.
- Trial Procedure Not Done will include trial procedures (“Physical Exam”, “Vital Signs”, “Clinical Safety Laboratory”, “Serology”, “Trial Treatment Injection” and “Rescue Injection with a licensed seasonal influenza vaccine”) listed in Appendix 1 "Trial

Procedures Schedule" in the protocol. If a subject had "Missed Visit" or "Out of Window Visit", (s)he will not be counted as "Procedure Not Done" again for the intended visit.

- Randomization Error will be determined by programmer to compare the stratification factors in the EDC to those in the randomization file generated by IWRS vendor. If a subject has discrepancy between the two data sources, (s)he will be flagged as randomization error.

3.4.1.1 Major Protocol Deviations Assessment

Prior to unblinding, the medical and operational leads will jointly assess protocol deviations and create a consensus final protocol deviations assessment file. Protocol deviations deemed to indicate clear violations of GCP and/or subject consent; or to have a likely effect on the primary immunogenicity outcomes will exclude those subjects from the PP analysis set. In general, the following will be deemed "major":

- Failure to obtain completely executed and documented informed consent.
- Failure to receive, or document receipt of, the study treatment as randomized.
- For inclusion in the PP Population, failure to provide a sample for serologic analysis on Day 0 and on Day 28.
- Receipt of immunosuppressive medication from Day 0 until the Day 28 visit.
- Documented receipt of any non-protocol influenza vaccine between 6 months prior to Day 0 and the Day 28 visit.
- Other deviations deemed likely by the Sponsor to degrade the immune response to the test article.

4 SUBJECT DISPOSITION

The number of subjects consented, randomized, and vaccinated will be presented by treatment group for all subjects.

The number (percentage) of subjects in the Safety Population, ITT Population, PP Population who have completed the study through Day 28 and through Day 364 will be summarized by treatment group.

The number (percentage) of subjects who discontinue the study prior to Day 364 and the reason for discontinuation (eg, adverse event, investigator decision, lost to follow-up, non-compliance, etc.) will be presented by treatment group. A listing of all subjects in the Safety Population who are discontinued will be presented by treatment group, reason for discontinuation, and day of last study contact. Day of last study contact will be calculated as follows: date of study discontinuation (as recorded on EOS eCRF) minus date of Day 0 vaccination.

The number (percentage) of subjects in the Safety Population with Major Protocol Deviation will be summarized by treatment group. A listing of all subjects in the Safety Population with one or more protocol deviations recorded through Day 28 and through Day 364, will be

provided and will include: treatment group, study day associated with the deviation, protocol deviation category and a description of the deviation as recorded by the site.

5 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and other baseline characteristics (age at Day 0 vaccination, gender, ethnicity, race, height [cm], weight [kg], as well as history of receipt of 2017 - 18 influenza vaccine) will be summarized by each treatment group for all subjects in the Safety Population and ITT Population.

Descriptive statistics (total number of subjects [n], mean and standard deviation, median, minimum and maximum values) will be summarized for weight (kg) and height (cm) measurements recorded at Study Day 0. Age (years) at the Day 0 vaccination will be calculated as the closest lower integer result of (Date of Study Day 0 – Date of Birth) / 365.25, and will be summarized using above descriptive statistics.

The number and percentage of subjects for Gender (eg, “Male”, “Female”), Ethnicity (ie, Hispanic or Latino, not Hispanic or Latino), Race (ie, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White) will be summarized.

Medical history and physical examination diagnoses/abnormalities will be coded using MedDRA version 20.0. Baseline medical history and physical examination findings recorded on Day 0 (prior to vaccination) will be summarized separately, by MedDRA system organ class (SOC) preferred term (PT), treatment group for all subjects in the Safety Population. Within each SOC and PT, the number and percentage of subjects with at least one abnormality will be presented, respectively. Multiple abnormalities within a given SOC and PT for a subject will be counted once.

6 EXTENT OF EXPOSURE

6.1 Study Vaccine

Subject vaccination exposure will be summarized as the number and percentage of subjects who received test article at Day 0 by treatment group.

6.2 Concomitant Medication

The assessment of concomitant medication use by the subject during the study will coincide with the collection period of adverse events. Concomitant medications recorded on the Concomitant Medications CRF will be summarized by WHO-DRUG Anatomical Therapeutic Chemical **(**ATC) Term and standardized (generic) medication name version September 2019. The number (percentage) of subjects who record one or more concomitant medications will be presented by treatment group for all subjects in the Safety Population. Multiple occurrences of medication usage for a subject will be counted only once within an ATC term and standardized medication name. The presentation of concomitant medications will include all medications recorded on the Concomitant Medications CRF, including medications with a missing or partial

start date or a start date prior to Study Day 0 vaccination. A separate listing of treatment-emergent new concomitant medications will be presented.

7 ANALYSES ADDRESSING PROTOCOL OBJECTIVES

7.1 Analyses of Primary Objectives of 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. No missing data will be imputed.

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. 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.
- Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers) and two-sided 95% CI will be calculated on log-transformed titers using the analysis of covariance (ANCOVA) with treatment group and baseline (Day 0) measurement as the covariates under two-sided type I error rate of 0.05. No type I error rate will be adjusted. The primary comparison to evaluate the Matrix-M1 adjuvant effect by demonstrating the immunogenic superiority of Quad-NIV is:
  - Group B - qNIV CF A60/B60/M50 (New) vs. Group E - qNIV Unadj A60/B60/M- (Ref)

    Note: CF = co-formulated; A = A strain; B = B strain; M = Matrix-M1 Adjuvant.

    Note: Two antigenically-drifted influenza strains maybe A/Wisconsin/19/2017 and A/Switzerland/9715293/2013

  ➢ A sample SAS code for between-group geometric mean ratio ($GMR_{new/ref}$) is given below:

```
proc mixed data= fludata;
      by Visit;
      class Treatment;
      model log(HAI_28) = log(HAI_D0) Treatment/noint;
      lsmeans Treatment/cl diff e alpha=0.05;
run;
```

7.2 Analyses of Secondary Objectives of Immunogenicity

HAI antibody titers specific for each of the virus strains will be assessed in terms of GMT, GMR, SCR, and SPR (HAI only) at Days 0, 28, 56, 182, and 364. Derived/calculated endpoints based on these data will include:

- Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed HAI titers on Days 0, 28, 56, 182, and 364.

- Geometric mean ratio (GMR) – defined as the ratio of post-vaccination to pre-vaccination HAI GMTs ($GMR_{Post/Pre}$) on Days 28, 56, 182, and 364.
  - Within-group geometric mean ratio ($GMR_{post/pre}$) for each arm will be conducted using paired t distribution. A sample SAS code is given below:

```
proc ttest data= fludata alpha=0.05;
      by Group Visit;
      PAIRED log(HAI_D28)*log(HAI_D0);
run;
```

- 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 on Days 28, 56, 182, and 364.
  - SCR and corresponding 2-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method with the following sample SAS code:

```
proc freq data=fludata noprint;
      by treatment;
      tables seroconvind / binomial(exact) alpha=.05;
      output out=out1 binomial;
run;
```

  - Pearson Chi-Square p-value will be derived for testing the equality of SCRs between two groups; otherwise Chi-Square p-value will be derived with continuity adjustment if small sample size. The Newcombe method will be used to construct its 95% confidence interval with the following sample SAS code:

```
proc freq data = fludata noprint;
      tables trt*seroconvind / riskdiff (column=2 cl=(newcombe))
      chisq;
run;
```

- Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 on Days 28, 56, 182, and 364 (HAI only). SPR and corresponding 2-sided exact binomial 95% CIs will be constructed similarly using the Clopper-Pearson method. Chi-Square p-value will be derived for testing the equality of SPRs between two groups similarly as SCR described above. The Newcombe method will be used to construct its 95% confidence interval.
- Ratio of GMTs between treatment arms at Days 28, 56, 182, and 364 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). P-values may be generated for information and planning of future studies, but will not be adjusted for multiple comparisons. The following treatment group differences will be estimated to address secondary objectives.
  - Ratio of GMTs between treatment arms at Days 0 and 28 post-vaccination using ANCOVA 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 include:

- Group B - qNIV CF A60/B60/M50 vs. Group A - qNIV Ref A60/B60/M50
- Group B - qNIV CF A60/B60/M50 vs. Group F - FHD3
- Group B - qNIV CF A60/B60/M50 vs. Group G - FBK4

– Ratio of GMTs between treatment arms at Days 0 and 28 post-vaccination using ANCOVA to compare the immunogenicity of Quad-NIV with increased B-antigen dose or increased Matrix-M1 dose relative to the "standard" co-formulated Quad-NIV formulation and also to 2 US-licensed active comparators include:

- Group C - qNIV CF A60/B60/M75 vs. Group B - qNIV CF A60/B60/M50
- Group C - qNIV CF A60/B60/M75 vs. Group F - FHD3
- Group C - qNIV CF A60/B60/M75 vs. Group G - FBK4
- Group D - qNIV CF A60/B90/M50 vs. Group B - qNIV CF A60/B60/M50
- Group D - qNIV CF A60/B90/M50 vs. Group F - FHD3
- Group D - qNIV CF A60/B90/M50 vs. Group G - FBK4

– Ratio of GMTs between treatment arms on Days 0, 28, 56, 182, and 364 using ANCOVA to evaluate the longevity of immune responses to Quad-NIV at different doses and formulations, with 1 of 2 different doses of Matrix-M1 adjuvant, and of 2 US-licensed comparators includes above comparisons and below comparison for each strain.

- Group C - qNIV CF A60/B60/M75 vs. Group D - qNIV CF A60/B90/M50

7.3 Analyses of Exploratory Objectives of Immunogenicity

The following exploratory antibody titers will be summarized using the same statistical approaches as the primary and secondary immunogenicity 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 ≥ LLOQ and a post-vaccination reciprocal titer ≥ 4-fold higher than the baseline titer. SCR and corresponding

2-sided exact binomial 95% CIs will be constructed by Clopper-Pearson method. Two-sided 95% CIs for the difference in SPRs between treatment groups will be based on the Newcombe hybrid score. Chi-Square p-value will be derived similarly as above.

- Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). Note: Same comparisons as HAI antibody titers between treatment arms will be conducted using ANCOVA.
- 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. 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.
- HAI titers, as described above. Proportion of subjects with ≥ 2-fold or ≥ 4-fold increases in HAI titers among those with low baseline titers (ie, lowest quintile) and corresponding 2-sided exact binomial 95% CIs will be constructed similarly by Clopper-Pearson method.
- 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.

8 SAFETY ANALYSES

All safety analyses will be based on the safety population. Adverse events 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 study 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 study 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.

8.1 Analyses of Primary Objectives of Safety

Safety analysis will be descriptive and based on the safety population, defined as all subjects who received a dose of trial treatment. Safety data will be summarized overall and by individual treatment group for solicited short-term reactogenicity events on Day 0-6, all unsolicited AE profile by MedDRA preferred term and SOC, 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 2-sided exact 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. For multiple occurrences of an adverse event in the same subject, a subject will be counted only once, using the most severe or most related occurrence for the summarization by severity or relationship to test article, respectively.

8.1.1 Solicited Adverse Events

Solicited AEs for this study are pre-specified in Section 8.1.1 of the protocol and include both injection site reactions (ie, bruising, pain, redness, and swelling) and systemic events (ie, chills, diarrhea, fatigue, headache, joint pain, muscle pain, nausea, oral temperature [for assessment of fever], vomiting) that are reported within seven days following the Day 0 vaccination and are solicited by diary. These events are considered related to the test article and are collected using a severity rating of 0 (Normal), or 1, 2, or 3 (mild, moderate or severe, respectively), using the maximal severity observed for the specific symptom post-vaccination.

Notable exceptions include oral temperature, which is collected as a continuous variable and that uses temperature grade ranges established in the toxicity grading scale (TGS), and events of injection site redness and swelling, which will be measured using a Subject Measurement Tool (Appendix 2). Oral temperature (fever) will be summarized by severity according to regulatory guidance, eg, Normal < 38.0ºC, Mild = 38.0 – 38.4ºC, Moderate = 38.5 – 38.9ºC, Severe > 38.9ºC. The Subject Measurement Tool is a transparent acetate sheet imprinted with a set of concentric circles with diameters that correspond to TGS ranges that are also used to assign severity.

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.

Table 4: 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 5: Severity Grade Definition 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

The following summaries of solicited AEs will be presented by treatment group as part of the primary analysis of safety:

- Summary of solicited treatment-emergent AEs by the verbatim terms specified in the diary and within the post-vaccination window (Days 0-6).
- Summary of all local/systemic solicited AEs by severity (mild, moderate, severe), and within the post-vaccination window (Days 0-6).

8.1.2 Unsolicited Adverse Events

Unsolicited adverse events are defined as any adverse events occurring within the 7-day window following vaccination and not specifically solicited in the diary, or any solicited event that occurs outside the 7-day diary solicitation period. The number (percentage) of subjects with unsolicited AEs will be summarized by MedDRA SOC and PT. All unsolicited AEs will be assessed for severity (Section 8.1.2 in Protocol) and for causality (Section 8.5 in Protocol).

The following summaries of unsolicited AEs will be presented for all subjects in the Safety Population as part of the primary analysis of safety:

- Overall summary of unsolicited AEs by treatment group (Days 0 - 28).
- A summary by severity (normal, mild, moderate, or severe), MedDRA SOC, PT, and treatment group (Days 0 - 28).
- A summary by relationship (causality) to test article of an AE (unlikely/unrelated, possibly, probably, or definitely) to test article, MedDRA SOC, PT, and treatment group (Days 0 - 28).
- A summary of severe and related (unlikely/unrelated, possibly, probably, or definitely) AEs, MedDRA SOC, PT, and treatment group (Days 0 - 28).
- A summary of any AEs including MAEs, SNMCs and SAEs, by MedDRA SOC, PT, and treatment group (Days 0 - 28).

The final analysis will include the following summaries of unsolicited AEs.

- Overall summary of unsolicited AEs by treatment group (Days 0 - 364).
- A summary by severity (normal, mild, moderate, or severe), MedDRA SOC, PT, and treatment group (Days 0 - 364).
- A summary by relationship (causality) to test article of an AE (unlikely/unrelated, possibly, probably, or definitely) to test article, MedDRA SOC, PT, and treatment group (Days 0 - 364).
- A summary of severe and related (unlikely/unrelated, possibly, probably, or definitely) AEs, MedDRA SOC, PT, and treatment group (Days 0 - 364).
- A summary of any AEs including MAEs, SNMCs and SAEs, by MedDRA SOC, PT, and treatment group (Days 0 - 364).

8.2 Medically-Attended Events and Significant New Medical Conditions

These classes of events will be collected at all study 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 8.3).

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.

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.

MAEs and SNMCs will be recorded and summarized from Day 0 to Day 28 for the unblinded data review and from Day 0 to Day 364 following study completion for the final analysis, for all subjects in the Safety Population. Note that MAEs and SNMCs are also included in the overall summary of AEs.

8.3 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 study 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).

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

A listing of subjects with SAEs will be summarized from Day 0 to Day 28 for the unblinded analysis, and from Day 0 to Day 364 following study completion for the final analysis, for all subjects in the Safety Population.

8.4 Vital Signs

Descriptive statistics for vital signs (blood pressure, heart rate, oral temperature, respiratory rate) at Days 0, 7, 28, 56, 182 and 364 will be presented by treatment group for all subjects in the Safety Population.

9 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 4 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 log10 HAI titers ranged from approximately 0.4 (B/Brisbane and A/Texas) to approximately 0.6 (A/Switzerland and A/Singapore). Table 6 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 ≥ 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.

Table 6: 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 PRELIMINARY UNBLINDED AND FINAL ANALYSES

An unblinded analysis will be conducted upon completion of all Day 28 visits, which will include all available immunogenicity data through Day 28 at the time of the analysis and safety data (inclusive of clinical laboratory safety assessments) through Day 28. For the review, treatment codes will only be unblinded after all subjects have completed the Day 28 visit, the data are monitored, all applicable queries are resolved, and the database locked.

In order to execute this review, a select group of study staff will be unblinded at the CRO and at Novavax. No individual unblinded at a subject treatment level will be involved in follow-up safety monitoring or immunogenicity determination. Specifically, personnel at the clinical study site including, investigators and study staff, research site, immunology laboratory, and study subjects will remain blinded to treatment assignments until the end of study (ie, Day 384).

Immunogenicity and safety analyses from the Day 28 unblinded analysis may be presented in an abbreviated Unblinded CSR drafted by the Sponsor that will be submitted to regulatory

authorities as needed. The final CSR will present the balance of all disposition, immunogenicity and safety data (inclusive of concomitant medications) through Day 364 (the scheduled end of study.

Any decisions to deviate from the planned analyses stated in SAP will be described in detail in the final study report.

11 COMPUTER METHODS

Statistical analyses will be performed using SAS® version 9.4 or higher in a Windows environment.

Sample size calculations based on two-sample t-test were performed using PASS 12, version 12.0.3 released on August 6, 2013.

12 DATA HANDLING CONVENTIONS

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

All statistical analyses will be 2-tailed and assessed at the 5% significance level. For all analyses except for the CMI data, p-value of < 0.05 will be considered statistically significant. After unblinding, post hoc between treatment comparisons for the CMI endpoints which were exploratory endpoints of the study were performed at 2-sided 0.1 Type I error rate and 2-sided 90% CIs for inference.

Tabulations will be produced for appropriate demographic, baseline, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean and standard deviation (SD), median, minimum, and maximum values will be presented.

All references to analysis of GMT will be interpreted as analysis of the $\log_{10}$ of titer values or of the reciprocal titers (eg, the reciprocal titer of 1:160 is the number 160) or of concentrations.

The individual immunogenicity titer values recorded as below the LLoQ of the assay will be set to half LLoQ for the purposes of GMT and GMR analyses, except for the CMI analysis. After unblinding, for the CMI measurements that require log transformation will be assigned a value of 1 count per million cells for those reported as 0. The LLoQ values will be provided by corresponding lab or CRO as part of the data transfer.

Medical history and AEs will be coded using the MedDRA Version 20.0.

Each parameter will be reported with below defined decimal numbers in Table 7.

Table 7: Decimal Numbers for Parameters

Parameter	Number of Decimals
Number of subjects (e.g. N, N1, N2)	0
Percentage (%)	1
Mean	1 more decimal than raw data
Standard Deviation (SD)	1 more decimal than mean
Median, Min, Max	as same decimal as raw data
GMT, $GMR_{Post/Pre}$, their corresponding 95% CIs	1
Ratio of GMTs, its corresponding 95% CIs	2
SPR (%), SCR (%), SPR difference, SCR difference, their corresponding 95% CIs	1
P value for $GMR_{Post/Pre}$ and Ratio of GMTs	3

Note: For analysis of exploratory CMI response, up to 5 decimal numbers will be presented depending on number of significant digits for each parameter.

12.1 Baseline Definitions

For all analyses, baseline will be defined as the last non-missing measurement prior to the first administration of the study material. For immunogenicity analysis, baseline will be the sample drawn prior to the first vaccination, on the day of vaccination.

12.2 Adjustments for Covariates

Comparison of GMTs between treatment groups will be adjusted for pre-vaccination titer.

12.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment will be applied for the secondary endpoints.

12.4 Withdrawals, Dropouts, Loss to Follow-up

The Investigator may withdraw any subject from the study at any time for medical reasons or if the subject is unable or unwilling to comply with the protocol. A subject may elect to discontinue his/her participation and withdraw from the study at any time. A subject withdrawing from the study may do so without detriment to access to medical care. See Sections 6.5 - 6.6 of the protocol for more details on withdrawal of subjects.

Any subject discontinuing from the trial at any time other than the screening period will not be replaced. A subject who receives the investigational product but withdraws for any reason will be encouraged to return for the safety assessments according to the Schedule of Procedures (Appendix 1). If the subject does not wish to remain in the study, the subject can choose to withdraw consent and discontinue at any time as outlined in Section 6.5 of the protocol.

12.5 Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

When tabulating AE, Concomitant Medications and Hospitalizations data, partial dates of event onset will be handled as follows:

- If the day of the month is missing, the onset date will be assumed to be the date of the Day 0 vaccination or first of the month, whichever is later, in order to conservatively report the event as vaccine-emergent.
- If the month or year (or both) of the onset date is missing, impute month or year (or both) which makes the imputed date most adjacent to the first dosing date.
- If the onset day and month are both missing, the event onset will be coded to the date of the Day 0 vaccination or 1st January of the year, whichever is later, in order to conservatively report the event as vaccine-emergent.
- A completely missing onset date will be coded as the date of the Day 0 vaccination, unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
- When imputing a start date ensure that the new imputed date is prior to the end date of the AE or med.

A conservative approach will be taken to assess the relationship of an event to test article: if the relationship of an event is missing, it will be considered treatment-related. Missing severity for an AE will not be imputed.

13 CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

NA

14 CHANGES TO THE SAP

14.1 List of Changes from Version 1.1 to Version 2.0

The following changes post unblinding were made to be consistent with previously published data (Couch 2014) from Version 1.1 to Version 2.0 of the Statistical Analysis Plan.

Reason for Changes:

- Between treatment comparisons for the CMI results were performed at 2-sided 0.1 Type I error rate level and 2-sided 90% CIs for inference (Section 12).)
- For the CMI measurements that require log transformation will be assigned a value of 1 count per million cells for those reported as 0 (section 12).

15 REFERENCES

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Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza with Vaccines. MMWR Recomm Rep 2016; 65(5): 1-54.

VRBPAC. (2018). Summary Minutes: 151st Vaccines and Related Biological Products Advisory Committee. Retrieved 29 March 2018. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM602610.pdf.

WHO. (2018). Recommended composition of influenza virus vaccines for use in the 2018-2019 northern hemisphere influenza season. Retrieved 29 March 2018.

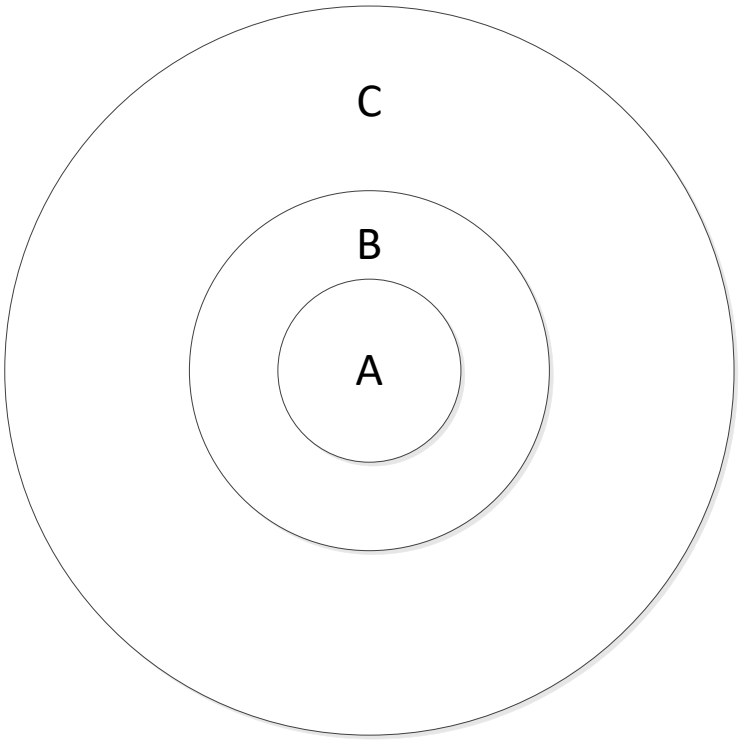
Appendix 1 – QNIV-E-201 TRIAL PROCEDURES SCHEDULE

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 subjects from a limited number of preselected sites.
[9] All subjects will be offered a 2019 - 20 seasonal influenza vaccine at the last study visit (Day 364).

Appendix 2 – 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