NOVAVAX | Creating Tomorrow's Vaccines

21 Firstfield Road, Gaithersburg, MD 20878 USA

A PHASE 3, RANDOMIZED, OBSERVER-BLINDED, ACTIVE-CONTROLLED TRIAL TO EVALUATE THE IMMUNOGENICITY AND SAFETY OF A RECOMBINANT QUADRIVALENT NANOPARTICLE INFLUENZA VACCINE (QUAD-NIV) WITH MATRIX-M1™ ADJUVANT AGAINST FLUZONE® QUADRIVALENT IN CLINICALLY STABLE ADULTS ≥ 65 YEARS OF AGE

Novavax Protocol Number: qNIV-E-301

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

SAP Version and Date: Version 3.0 - 01 November 2019

Investigational Product: Hemagglutinin Nanoparticle Influenza Vaccine, Quadrivalent (Quad-NIV), representing the strains recommended for inclusion in quadrivalent vaccines for the 2019 - 2020 northern hemisphere influenza season, ie, A/Brisbane/02/2018 (H1N1) pdm09; A/Kansas/14/2017 (H3N2); B/Maryland/15/2016; B/Phuket/3073/2013; administered with Matrix-M1 Adjuvant

APPROVAL SIGNATURE PAGE

Protocol Number:	qNIV-E-301
Protocol Version and Date:	Version 4.0 – 31 October 2019
Protocol Title:	A Phase 3, Randomized, Observer-blinded, Active-controlled Trial to Evaluate the Immunogenicity and Safety of a Recombinant Quadrivalent Nanoparticle Influenza Vaccine (Quad-NIV) with Matrix-M1™ Adjuvant Against Fluzone® Quadrivalent in Clinically Stable Adults ≥ 65 Years of Age
SAP Version and Date:	Version 3.0 - 01 November 2019

☐ Original Statistical Analysis Plan

☒ Amended Statistical Analysis Plan

SAP Originated By: [redacted] 01 November 2019
Project Statistician Date

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

Signed Electronically

[redacted] Date
Novavax, Inc.

Signed Electronically

[redacted] Date
Novavax, Inc.

SAP CHANGE HISTORY

SAP Version 3.0, 01 November 2019 (revised from Version 2.0, 06 September 2019)

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

Location of Change	Change/Modification in Version 3.0
Version and date for Protocol in SAP	Protocol version and date have been updated to Protocol Version 4.0, 31 October 2019.
Section 1.4	Section 1.4 in SAP has been updated based on the changes in Section 10.6.1 and Section 10.6.2 in Protocol Version 4.0, 31 October 2019.
Section 10	Section 10 in SAP has been updated based on the changes in Section 10.6.1 and Section 10.6.2 in Protocol Version 4.0, 31 October 2019.
Section 14	Link for 1st reference CDC. (2017) has been updated.

SAP Version 2.0, 06 September 2019 (revised from Version 1.0, 16 August 2019)

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

Location of Change	Change/Modification in Version 2.0
Version and date for Protocol in SAP (Approval Signature Page and Section 1.4)	Protocol version and date have been updated to Protocol Version 3.0, 03 September 2019.
Appendix 1	The Day 28 Study Visit window has been expanded from ± 2 days to ± 4 days.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
C	Celsius
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
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
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HEENT	Head, Eyes, Ears, Nose, Throat
ICH	International Conference on Harmonisation
IM	Intramuscular
IP	Investigational Product
ITT	Intent-to-treat
IWRS	Interactive Web Randomization System
LLOQ	Lower Limit of Quantitation
MAE	Medically-attended Event
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram

Abbreviation or Term	Definition
µL	Microliter
mL	Milliliter
µM	Micromolar
mM	Millimolar
MN	Microneutralization
NA	Neuraminidase or Not Applicable
NI	Non-inferiority
NIV	Nanoparticle Influenza Vaccine
nm	Nanometer
NP	Nucleoprotein
PBMC	Peripheral Blood Mononuclear Cell
PD	Protocol Deviation
PP	Per Protocol
PT	Preferred Term
qNIV or Quad-NIV	Nanoparticle Influenza Vaccine, Quadrivalent
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 Procedure
SPR	Seroprotection Rate or Surface Plasmon Resonance
TGS	Toxicity Grading Scale
TMF	Trial Master File
tNIV or Tri-NIV	Nanoparticle Influenza Vaccine, Trivalent
VLP	Virus-Like Particle
WHO	World Health Organization
w/v	Weight to Volume

1 INTRODUCTION

The influenza virus poses a formidable risk of infection resulting in serious illness in 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]. During the current influenza season (2018-19), interim estimates indicate that vaccine efficacy in older adults (≥ 50 years of age) remains relatively low at 24% (-15% to 51%) against all influenza types [Doyle 2019].

In light of the continued suboptimal effectiveness of seasonal influenza vaccines, particularly in older adults, Novavax has developed a novel recombinant hemagglutinin (HA) quadrivalent nanoparticle influenza vaccine (Quad-NIV) for the prevention of disease due to influenza virus in adults ≥ 65 years of age, using a recombinant baculovirus and insect cell technology. With a nanoparticle structure, recombinant wild-type sequenced HAs, and use of Matrix-M1 adjuvant, Quad-NIV may offer several important advantages over existing licensed egg-derived seasonal influenza vaccines, including avoidance of antigenic mismatch due to egg-adaptive mutations; induction of both broadly cross-reactive antibody responses against emerging drift variants of seasonal influenza viruses [Shinde 2018]; and potent cross-reactive polyfunctional CD4+ T cells.

In a recent Phase 2, dose-finding, formulation-optimizing trial in adults ≥ 65 years of age, multiple formulations of Quad-NIV, containing HA-based antigens representing the 4 influenza strains recommended for inclusion in the 2018-2019 Northern hemisphere seasonal influenza vaccine [VRBPAC 2018, WHO 2018] and co-formulated with Matrix-M1 adjuvant, given intramuscularly, induced robust hemagglutination inhibition (HAI) antibody responses against both homologous A/B and drifted H3N2 strains. Three formulations in particular: formulation A (60 µg HA of each strain in-clinic mixed with 50 µg of Matrix-M1); formulation B (60 µg HA of each strain co-formulated with 50 µg of Matrix-M1); and formulation C (60 µg HA of each strain co-formulated with 75 µg of Matrix-M1), induced comparable HAI antibody responses (using both egg-propagated or wild-type VLP agglutinins as reagents) against all evaluated homologous and drifted H3N2 strains. In addition, all three formulations outperformed Fluzone HD on HAI antibody responses to all evaluated homologous and drifted H3N2 strains using the wild-type VLP HAI assays, which assessed the binding of vaccine-induced antibodies to HA sequences reflective of circulating viruses not subjected to egg adaptation. The short-term reactogenicity and overall safety profiles (through 182 days of follow-up) of the three formulations were also comparable. Formulation C (60 µg HA of each strain co-formulated with 75 µg of Matrix-M1) induced substantially higher median counts of homologous and drifted strain-specific polyfunctional CD4+ T cells at Day 7 following immunization. Finally, formulation C elicited significantly higher mean hemagglutination inhibition (HAI) titers than unadjuvanted Quad-NIV (formulation E containing only 60 µg HA of each strain) for 5 of 6 tested viral hemagglutinins. The totality of safety and immunogenicity data to date indicate that formulation C of Quad-NIV is the best candidate to advance in further clinical development.

The Phase 2 data warrant confirmation of the non-inferiority of immunogenicity of 240 µg Quad-NIV containing antigens (60 µg HA of each strain) representing the 4 influenza strains

recommended for inclusion in the 2019-2020 Northern hemisphere seasonal influenza vaccine [VRBPAC 2019, WHO 2019], co-formulated with 75 µg Matrix-M1 adjuvant, as compared to a US-licensed quadrivalent seasonal influenza vaccine comparator, Fluzone Quadrivalent, to generate data to support licensure of Quad-NIV for the prevention of influenza disease in adults ≥ 65 years of age.

1.1 Study Design

This is a Phase 3, randomized, observer-blinded, active-controlled trial to evaluate the immunogenicity and safety of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant against a licensed comparator in clinically stable adults ≥ 65 years of age to be conducted in the United States. Approximately 2650 eligible subjects will be enrolled and randomized at a 1:1 ratio into 1 of 2 treatment groups, as shown in Table 1 below. The active group (Group A) and the comparator group (Group B) will each consist of approximately 1325 subjects. Both groups will be stratified by site, age (65 to < 75 and ≥ 75 years), and history of prior year receipt of the 2018-19 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 Quad-NIV will be 0.5 mL. 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.

Table 1: Trial Design for qNIV-E-301

	Day 0 Trial Treatment Injection					
Treatment Group	**Vaccine**	**HA Dose per Strain, µg (H1N1/H3N2/B_V/B_Y)**	**Matrix-M1 Adjuvant Dose**	**Injection Volume**	**Treatment Arm**	**Subjects Per Group**
A	Quad-NIV	60, 60, 60, 60	75 µg	0.5 mL	Non-dominant	1325
B	2019-20 Fluzone Quadrivalent[1]					1325
					Total Trial Subjects	2650

Abbreviations: B_V = B Victoria lineage; B_Y = B Yamagata lineage; HA = Hemagglutinin
Note: All subjects will receive a single vaccination by IM injection on Day 0. If the non-dominant arm is not available for injection, then the dominant arm will be used.
[1] Fluzone Quadrivalent will be administered at the manufacturer's recommended dose and volume.

1.2 Randomization and Treatment Assignments

Subject randomization will be conducted using an Interactive Web Randomization System (IWRS). Stratification will be by site, age, and history of receipt of the 2018-19 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 two 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.

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.

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-301Version 4.0, dated 31 October 2019, 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 primary endpoints (HAI antibody responses assayed with egg-propagated virus) testing of associated Day 28 serum samples for all 4 vaccine homologous influenza strains (ie, 2 influenza A and 2 influenza B strains) and safety data through Day 28. Data concerning secondary and exploratory endpoints will be included in the unblinded review of Days 0 and 28 as they become available.

Day 364 final analysis will be conducted when all immunogenicity and safety data through Day 364 have been entered, reviewed, and all queries related to the data have been addressed. Immunogenicity data required prior to the Day 364 analysis will include the mandated time-points (Days 0 and 28) for the primary and secondary endpoints, with the latter including the four vaccine-homologous A and B strain(s) and at least one antigenically-drifted influenza strain for HAI antibody titers assayed with both egg-propagated virus and wild-type VLP reagents. Immunogenicity data required prior to the Day 364 analysis will also include HAI antibody response at additional time-point Day 182 tested with a subset of subjects pursuant to secondary endpoints. Testing of additional antigenically-drifted influenza strain responses by HAI, and also Microneutralization (MN) and cellular response testing pursuant to the exploratory objectives may be completed later and included in addenda to the study report.

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To demonstrate the non-inferior immunogenicity of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, relative to a US-licensed comparator, Fluzone Quadrivalent, in clinically stable adults ≥ 65 years of age, in terms of hemagglutination inhibition (HAI) (assayed with egg-propagated virus) antibody responses to all Quad-NIV homologous influenza strains (ie, 2 influenza A and 2 influenza B strains) at Day 28 post-vaccination.
- To describe the safety profile of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, and the comparator in clinically stable 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), including immunologically-mediated adverse events of special interest (AESIs).

2.1.2 Secondary Objectives

- To describe the immunogenicity of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, and of a US-licensed comparator, Fluzone Quadrivalent, in clinically stable adults ≥ 65 years of age, in terms of HAI (assayed with both egg-propagated virus and wild-type VLP reagents) antibody responses to all Quad-NIV homologous influenza strains (2 influenza A and 2 influenza B strains) and at least 1 antigenically drifted A or B strain in terms of geometric mean titers (GMTs), geometric mean ratio (GMR), seroconversion rate (SCR), seroprotection rate (SPR), and the baseline adjusted ratio of GMTs between treatment arms at Day 28. An additional time-point at Day 182 may be tested by HAI for these outcomes in a subset of subjects in each treatment group.

2.1.3 Exploratory Objectives

- To evaluate the superior immunogenicity of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, relative to Fluzone Quadrivalent, in clinically stable adults ≥ 65 years of age, in terms of HAI (assayed with both egg-propagated virus and wild-type VLP reagents) antibody responses against all 4 vaccine homologous influenza strains (ie, 2 influenza A and 2 influenza B strains) and 1 - 2 antigenically-drifted A and/or B strains at Days 0 and 28 post-vaccination.
- To describe the immunogenicity of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, and of a US-licensed comparator, Fluzone Quadrivalent, in clinically stable adults ≥ 65 years of age, in terms of microneutralization (MN) responses to vaccine-homologous and/or antigenically-drifted influenza strains at Days 0 and 28 post-vaccination, in terms of GMTs, GMR, SCR, and the baseline adjusted ratio of GMTs between treatment arms at Days 28 post-vaccination. *Note: Due to the time-consuming nature of MN testing, this exploratory objective may be completed in a subset of participants in each study treatment group and/or a subset of strains 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. Similarly, an additional time-point at Day 182 may also be tested.

- To describe the quality and amplitude of cell-mediated immune (CMI) responses in healthy adults ≥ 65 years of age to vaccination with 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, as measured by functional T cell responses based on intracellular cytokine analysis. Additional markers of CMI (eg, memory B cells and/or other T cell subsets) may be evaluated depending on availability/recovery of cell volume. Due to the laborious nature of the cellular assays, they will be performed on subjects from a limited number of participating sites and results may be reported as an addendum to the main clinical study report.

2.2 Study Endpoints

2.2.1 Primary Endpoints

- Comparative HAI antibody responses (assayed with egg-propagated virus) on Day 28, summarized in terms of the ratio of geometric mean titers (GMTs) AND seroconversion rate (SCR) difference, between subjects receiving Quad-NIV or Fluzone Quadrivalent for all 4 vaccine homologous influenza strains (ie, 2 influenza A and 2 influenza B strains).

  Non-inferiority for each homologous strain will be demonstrated if:

  - The lower bound of the two-sided 95% CI on the ratio of the GMTs ($GMT_{QuadNIV}/GMT_{Fluzone}$) is ≥ 0.67,

  AND

  - The lower bound of the two-sided 95% CI on the difference between the SCRs ($SCR_{QuadNIV}$-$SCR_{Fluzone}$) is ≥ -10%.

- 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 through 28 days post-injection (ie, Day 0 through Day 27, inclusive); and MAEs, SAEs, and SNMCs – including AESIs – through 1 year post-injection.

2.2.2 Secondary Endpoints

- HAI antibody titers (assayed with both egg-propagated virus and wild-type VLP reagents) at Days 0 and 28 specific for vaccine-homologous A and B strain(s), and antigenically-drifted influenza strains. An additional time-point at Day 182 may also be tested with a subset of subjects. Derived/calculated endpoints based on these data will include:

  - GMT – defined as the antilog of the mean of the log-transformed HAI titers, on Days 0 and 28.

  - Geometric mean ratio (GMR) – defined as the ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs ($GMR_{Post/Pre}$) on Day 28.

- 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 ≥ 4-fold higher on Day 28.
- Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 on Day 28.
- Ratio of GMTs between treatment arms at Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).

2.2.3 Exploratory Endpoints

- Comparative HAI antibody responses (assayed with both egg-propagated virus and wild-type VLP reagents) on Day 28, summarized in terms of the ratio of geometric mean titers (GMTs) AND seroconversion rate (SCR) difference, between subjects receiving Quad-NIV or Fluzone Quadrivalent for all 4 vaccine homologous influenza strains (ie, 2 influenza A and 2 influenza B strains) and 1 - 2 antigenically-drifted A and/or B strains.

  Superior immunogenicity for each strain will be demonstrated if:

  - The lower bound of the two-sided 95% CI on the ratio of the GMTs ($GMT_{QuadNIV}/GMT_{Fluzone}$) is greater than 1.5,

  AND

  - The lower bound of the two-sided 95% CI on the difference between the seroconversion rates ($SCR_{QuadNIV}$-$SCR_{Fluzone}$) is greater than 10%.
- Microneutralization (MN) responses: Neutralizing antibody titers specific to vaccine-homologous A and B strain(s) and/or antigenically-drifted influenza strains, at Days 0 and 28 post-vaccination, as measured by a microneutralization assay. An additional time-point at Day 182 may also be tested. 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).
- Counts and/or proportions of Days 0, 7, 28, and 182 peripheral blood effector memory T cell populations that secrete one or more of IL-2, CD40L, IFN-γ, and TNF-α cytokines

following *in vitro* restimulation with HA in subjects selected for cellular immune response monitoring. Counts and/or proportions of additional markers of CMI, as appropriate.

3 ANALYSIS POPULATIONS

The following subject populations will be used in all analyses:

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 Per-Protocol Population

The Per-Protocol (PP) Population includes all subjects in the Safety Population that receive 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.

3.3 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 ≤ 5% of the subjects for each of the 2 treatment groups.

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. Examples of 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

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

- Missed Visit information in protocol deviations derived from the eCRF will be subordinate to those programmatically-determined missed visits and will not be used for the formal CSR. Missed Visit status will not be triggered by the "Subject Diary Review" procedure. Missed Visit applies to planned in-clinic visits at Days 0, 7, 28, and 182. 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 scheduled 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, 3, 7, 28, 90, 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", "Serology", "PBMC for CMI" and "Trial Treatment Injection") listed in Appendix 1 "Trial Procedure 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 programmatically by seeking possible erroneous scenarios including mis-stratification based on erroneous age or 2018-19 influenza vaccine history, possible multiple randomization, randomization without treatment, or treatment without randomization.

Additionally, all protocol deviations identified by site personnel prior to a monitoring visit or by the Site Monitor (Clinical Research Associate (CRA)) during on-site or remote visits and/or during site management activities will be documented in the 'Protocol Deviation' section of EDC by the Site personnel responsible at the site. Deviations entered into EDC by the site will be reviewed by the Site Monitor responsible for the site. The PD listing suitable for import for SAS will provide the category of protocol deviation and the corresponding description of each protocol deviation, with a flag to indicate if a deviation was considered major and resulted in the exclusion of the subject from the PP analysis set.

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" deviations:

- 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 or to provide out of protocol-specified window, a sample for serologic analysis on Day 0 and on Day 28.
- Receipt of immunosuppressive medication from Day 0 until the Day 28 visit.
- Receipt of any non-protocol influenza vaccine between 6 months prior to Day 0 and through the Day 28 visit.
- Other deviations deemed likely by the Sponsor to degrade the immune response to the test article, including especially (but not limited to):
    - receipt of non-study vaccines in the 28 days preceding and 14 days following study test article, or
    - receipt of any immune globulin preparation in the 3 months before or 28 days following study 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, PP Population, and ITT 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 Deviations 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 2018-19 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 the 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 22.0. 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), and 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 based on WHODD GLOBAL B3-Mar2019. 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

7.1.1 Analyses of Primary Immunogenicity Objectives

The Per-Protocol (PP) population (ie, randomized subjects who received the assigned dose of the test article according to the protocol, have HAI serology results at Day 0 and Day 28, and have no major protocol deviations) will be the primary population for immunogenicity analysis. 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. No missing data will be imputed. 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).

For purposes of determining non-inferiority (and exploratory superiority) in immunogenicity of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, relative to a US-licensed comparator, Fluzone Quadrivalent, for all Quad-NIV homologous influenza strains (2 influenza A and 2 influenza B strains) at 28 days post-vaccination, derived/calculated endpoints will include:

- Two-sided 95% CIs for the ratio of Day 28 post-vaccination GMTs between Quad-NIV and Fluzone Quadrivalent will be constructed using log normal distribution. The $\log_{10}$ values will be used to construct a CI using the analysis of covariance (ANCOVA) with treatment group and baseline at Day 0 (adjusted for intergroup variation in baseline [pre-vaccination] titers) as the covariates under two-sided type I error rate of 0.05. No type I error rate adjustments will be made. The mean difference and the corresponding CI limits will then be exponentiated to obtain the ratio of GMT and the corresponding CI.
  - 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;
```

- Two-sided 95% CIs for the difference of the SCRs between Quad-NIV and Fluzone Quadrivalent will be based on the Newcombe hybrid score (METHOD = SCORE riskdiff-option for PROC FREQ in SAS).
  - 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;
```

7.2 Analysis of Secondary and Exploratory Immunogenicity Objectives

Immunogenicity of 240 µg Quad-NIV co-formulated with 75 µg Matrix-M1 adjuvant, relative to a US-licensed comparator, Fluzone Quadrivalent, based on HAIs (assayed with both egg-propagated virus and wild-type VLP reagents) for all vaccine-homologous influenza A and

B strains, and at least 1 antigenically-drifted A or B strain at Day 28 post-vaccination, will be measured in terms of:

- Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed HAI titers, on Days 0 and 28.
- Geometric mean ratio (GMR) – defined as the ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs ($GMR_{Post/Pre}$) on Day 28.
  - 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 Treatment Visit;
      PAIRED log(HAI_D28)*log(HAI_D0);
run;
```

- 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 ≥ 4-fold higher on Day 28.
  - 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;
```

- Seroprotection rate (SPR) – defined as the proportion of subjects with a reciprocal HAI titer ≥ 40 on Day 28.
  - 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 Day 28 post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers).

An additional time-point at Day 182 may also be tested.

Microneutralization (MN) responses at Days 0 and 28 post-vaccination 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).

An additional time-point at Day 182 may also be tested.

The methods for the calculation of GMT, GMR, SCR, and ratios of GMTs for Microneutralization (MN) responses are the same as those for HAI responses.

Analysis of exploratory CMI response endpoints will be performed on a subset of approximately 140 subjects from several pre-designated clinical sites (approximately 70 subjects per treatment arm) and results may be reported as an addendum to the main clinical study report.

The analysis for CMI response may include:

- Counts of Peripheral Blood T Cells characterized based on various cell surface markers at Day 0, 7, 28, and 182.
- Counts and proportion of specific CD4 T cells expressing two and three cytokines in response to influenza hemagglutinin stimulation at Day 0, 7, 28, and 182.
  - The boxplots for counts of two and/or three cytokines may be generated based on $\log_{10}$ scale values.
- GMR - ratio of geometric mean of specific CD4 T cells expressing two/three cytokines between Treatment A (Quad-NIV) and Treatment B (Fluzone) at Day 7, 28, and 182.
  - The $\log_{10}$ values will be used to construct a 90% CI using the analysis of covariance (ANCOVA) with treatment group and baseline at Day 0 as the covariates under two-sided type I error rate of 0.10.
  - LLOQ is defined as 1. If counts is zero, it will be set to half that limit to take $\log_{10}$ scale (ie, $\log_{10}(1/2) = -0.3$).
- Geometric mean ratio of specific CD4 T cells expressing two/three cytokines between Day 7/28/182 and Day 0.
  - LLOQ is defined as 1. If counts is zero, it will be set to half that limit to take $\log_{10}$ scale (ie, $\log_{10}(1/2) = -0.3$).
  - The bar graphs with corresponding CIs may be generated.
- Reverse cumulative distribution displays of double- or triple-staining cell counts for homologous influenza strains (ie, 2 influenza A and 2 influenza B strains) at Day 7/28/182 post-vaccination may be displayed separately by the treatment group.

8 SAFETY ANALYSES

8.1 Analyses of Primary Objectives of Safety

Safety analyses 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 - 6, 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.

8.1.1 Solicited Adverse Events

Solicited AEs for this study are pre-specified in Section 8.1.1 and Table 3 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], and 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.

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 4. 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) as shown in Table 5, 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 adverse event that occurs outside the 7-day diary solicitation period. The number (percentage) of subjects with unsolicited AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) coded by system organ class (SOC) and preferred term (PT). All unsolicited AEs will be assessed for severity (Section 8.4 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 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*).

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, and 182 will be presented by treatment group for all subjects in the Safety Population.

9 SAMPLE SIZE CONSIDERATIONS

This study has a single comparison between Quad-NIV and Fluzone Quadrivalent at Day 28 post-vaccination for the primary immunogenicity objective. No adjustment of the Type I error rate for multiple comparisons is warranted since the simultaneous successes of all 8 comparisons planned for the 4 strains contained in the vaccines and the two endpoints (GMT and SCR) are required for the demonstration of the primary non-inferiority objective of the study.

Non-inferiority is defined as the lower bound of the 2-sided 95% CI on the ratio of GMTs (Quad-NIV vs Fluzone) ≥ 0.67 (ie, unadjusted 1-sided p-value < 0.025 against the null hypothesis of H0: Ratio of GMT < 0.67) and the lower bound of the two-sided 95% CI on the

difference of the SCRs (Quad-NIV - Fluzone) ≥ -10% (ie, unadjusted 1-sided p-value < 0.025 against the null hypothesis of H0: Difference of SCRs < -10%).

For the calculation of sample size estimation, we used assumptions of true differences, ie, the ratio of GMTs (Quad-NIV vs Fluzone Quadrivalent) is 1.0 for all 4 homologous strains, and the difference of the SCRs is -2% for each of the 4 homologous strains, based on the average performance in the previous trial (qNIV-E-201). To achieve an overall 90% power (ie, ~ 97.5% power for each of the 4 strains) to demonstrate a non-inferiority margin for SCR difference of -10%, the SCR of reference group (Fluzone Quadrivalent) is assumed to be 0.5 and the SCR of treatment group (Quad-NIV) is assumed to be 0.48 under the null hypothesis of inferiority (H0: Difference of SCRs < -10%). The significance level of the testing is 0.025. Sample size was estimated to be 1195 in each group by assuming equal size in each group. The sample size accounted for a 10% attrition rate for the per-protocol population such that the primary analysis population for all immunogenicity endpoints will be 1325 in each group.

In a previous trial (qNIV-E-201), the observed vaccine-homologous strain-specific standard deviations of $\log_{10}$ HAI titers ranged from approximately 0.3 (B/Colorado/06/2017 and B/Phuket/3073/2013) to approximately 0.4 (A/Singapore/INFIMH-16-0019/2016 and A/Michigan/45/2015). The calculated power for each strain, unadjusted for multiple comparisons, is close to 100% to detect a 1.5-fold difference in GMTs. For 4 strains, this study is designed to exclude a GMT ratio of < 0.67 with 100% power. Therefore, for demonstrating non-inferiority for 4 strains with the true ratio of GMTs of 1.0 and the true SCR differences of -2%, this study provides ≥ 90% overall power.

For safety endpoints, the probability of observing at least 1 adverse event among 1325 subjects for Quad-NIV is > 90% if the true rate of such events is 0.18%. With 1325 subjects for Quad-NIV, 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 0.2%.

10 PRELIMINARY UNBLINDED AND FINAL ANALYSES

An unblinded analysis will be conducted upon completion of all Day 28 visits, which will include all primary endpoints (HAI antibody responses assayed with egg-propagated virus) testing of associated Day 28 serum samples for all 4 vaccine homologous influenza strains (ie, 2 influenza A and 2 influenza B strains) and safety data through Day 28. Data concerning secondary and exploratory endpoints will be included in the unblinded review of Days 0 and 28 as they become available. 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.

In order to execute Day 28 unblinded data 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 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 364).

Day 364 final analysis will be conducted when all immunogenicity and safety data through Day 364 have been entered, reviewed, and all queries related to the data have been addressed. Immunogenicity data required prior to the Day 364 analysis will include the mandated time-points (Days 0 and 28) for the primary and secondary endpoints, with the latter including the four vaccine-homologous A and B strain(s) and at least one antigenically-drifted influenza strains for HAI antibody titers assayed with both egg-propagated virus and wild-type VLP reagents. Immunogenicity data required prior to the Day 364 analysis will also include HAI antibody response at additional time-point Day 182 tested with a subset of subjects pursuant to secondary endpoints. Testing of additional antigenically-drifted influenza strain responses by HAI, and also Microneutralization (MN) and cellular response testing pursuant to the exploratory objectives may be completed later and included in addenda to the study report.

Immunogenicity and safety analyses from the Day 28 unblinded analysis may be presented in an abbreviated Unblinded clinical study report (CSR) drafted by the Sponsor that may be submitted to regulatory authorities as needed.

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.

Any decisions to deviate from the planned analyses stated in the 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 14, version 14.0.15 released on May 23, 2019.

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, p-value of < 0.05 will be considered statistically significant.

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. 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 MedDRA Version 22.0.

Each parameter will be reported with the below defined decimal numbers in Table 6.

Table 6: Decimal Numbers for Parameters

Parameter	Number of Decimal
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, and 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 6.4 – 6.5 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 REFERENCES

CDC. (2017). Seasonal Influenza Vaccine Effectiveness, 2005-2017. Retrieved 19 April 2018 from https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html.

.

Doyle JD, Chung JR, Kim SS, et al. Interim Estimates of 2018-2019 Seasonal Influenza Vaccine Effectiveness - United States, February 2019. MMWR Morb Mortal Wkly Rep (2019); 68(6): 135-9.

Shinde V, Fries L, Wu Y, et al. Improved Titers Against Influenza Drift Variants with a Nanoparticle Vaccine. N Engl J Med (2018); 378(24): 2346-8.

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.

VRBPAC. (2019). Summary Minutes: 152nd Vaccines and Related Biological Products Advisory Committee. Retrieved 27 March 2019. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM633766.pdf.

WHO. (2018). Recommended Composition of Influenza Virus Vaccines for Use in the 2018-2019 Northern Hemisphere Influenza Season. Retrieved 29 March 2018, from https://www.who.int/influenza/vaccines/virus/recommendations/2018_19_north/en/.

WHO. (2019). Recommended Composition of Influenza Virus Vaccines for Use in the 2019-2020 Northern Hemisphere Influenza Season. Retrieved 27 March 2019, from https://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/.

APPENDIX 1 – QNIV-E-301 TRIAL PROCEDURES SCHEDULE

Trial Day:	**0**	**3**	**7**	**28**	**90**	**182**	**364**
Window (days):		**± 1**	**± 1**	**± 4**	**± 7**	**± 7**	**± 14**
Trial Procedures							
Trial Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical/Medication History	X						
Physical Exam	X		X [4]	X [4]		X [4]	
Vital Signs	X [1]		X	X		X	
Serology	X			X		X	
PMBC for CMI	X[5]		X[5]	X[5]		X[5]	
Trial Treatment Injection	X						
Adverse Event Review [2]	X	X	X	X	X	X	X
Concomitant Medications Review [2]	X	X	X	X	X	X	X
Subject Diary Review				X [3]			
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] 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.

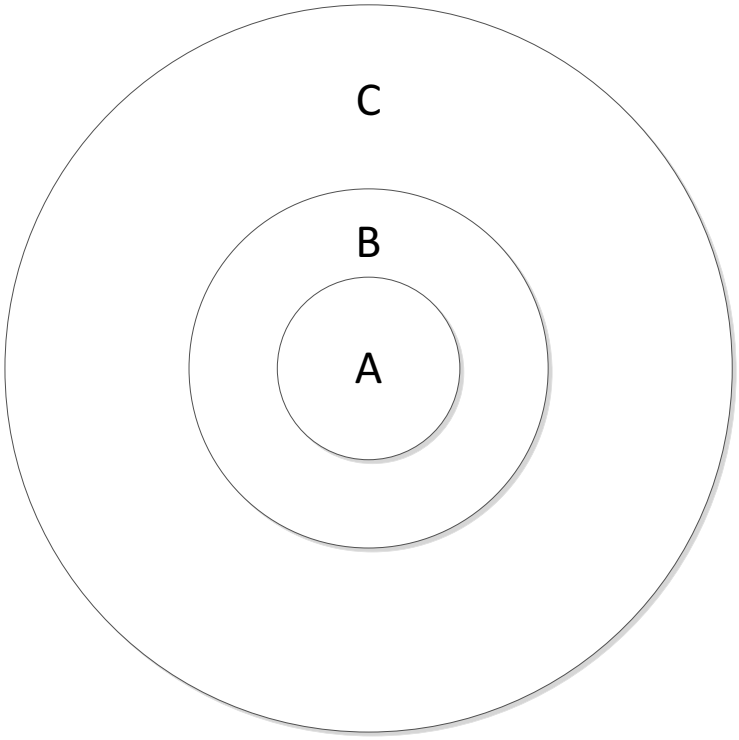
[3] The subject diary will be reviewed by the investigator and collected at the Day 28 visit.

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

[5] To be collected from a subset of approximately 140 subjects from several pre-designated clinical sites.

APPENDIX 2 – QNIV-E-301 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