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A PHASE 1/2, RANDOMIZED, OBSERVER-BLINDED, ACTIVE-CONTROLLED TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A RECOMBINANT TRIVALENT NANOPARTICLE INFLUENZA VACCINE (TRI-NIV) WITH MATRIX-M1™ ADJUVANT IN HEALTHY OLDER ADULTS ≥ 60 YEARS OF AGE

Novavax Protocol Number: tNIV-E-101

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

SAP Version and Date: Version 1.0 - 24 October 2017

Investigational Product: Hemagglutinin Nanoparticle Influenza Vaccine, Trivalent (Tri-NIV), representing A/Michigan/45/2015 (H1N1); A/HongKong/4801/2014 (H3N2); and B/Brisbane/60/2008, administered with Matrix-M1 Adjuvant

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☒ Original Statistical Analysis Plan

☐ Amended Statistical Analysis Plan

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	Adverse Event
C	Celsius
CBER	Center for Biologics Evaluation and Research
CD	Compact Disc
CHF	Chronic Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPE	Cytopathic Effect
CRO	Contract Research Organization
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EU	ELISA Unit
FDA	Food and Drug Administration
FI-RSV	Formalin Inactivated-Respiratory Syncytial Virus
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GMEU	Geometric Mean ELISA Unit
GMFR	Geometric Mean Fold-rise
GMT	Geometric Mean Titer
HAI	Hemagglutination Inhibition
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IIV	Inactivated Influenza Vaccine
IM	Intramuscular

Abbreviation or Term	Definition
IP	Investigational Product
ITT	Intent-to-treat
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Liter
M	Molar Concentration
MAE	Medically-attended Event
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µl	Microliter
µM	Micromolar
mg	Milligram
mL	Milliliter
mM	Millimolar
MMP	Methyl-α-D-mannopyranoside
MN	Microneutralization; an assay
NaCl	Sodium Chloride
ng	Nanogram
NOAEL	No-Observed-Adverse-Effect-Level
OD	Optical Density
PCA	Palivizumab-Competitive Antibody
PFS	Pre-filled Syringes
PP	Per Protocol
PPE	Per Protocol for Efficacy
PS	Polysorbate
PT	Preferred Term
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
Sf9	*Spodoptera frugiperda* — Insect Cells
SOC	System Organ Class

Abbreviation or Term	Definition
SPR	Surface Plasmon Resonance
TGS	Toxicity Grading Scale
Th2	T Helper Cell Type 2
TIV	Trivalent Influenza Vaccine
TMB	3, 3'5, 5-tetramethyl-benzidine
TMF	Trial Master File
tNIV or Tri-NIV	Nanoparticle Influenza Vaccine, Trivalent
US	United States
VED	Vaccine-enhanced Disease
Vv	Vaccinia Virus
WB	Western Blot
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 2017b]. Novavax, Inc. has developed an insect cell-derived, egg-free, influenza vaccine (Tri-NIV) based on recombinant HA nanoparticle antigens, which represent the 3 major influenza types/subtypes, recommended for inclusion in the 2017-2018 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, trivalent or quadrivalent, unadjuvanted or adjuvanted) or recombinant influenza (trivalent) vaccines are considered acceptable options [Grohskopf 2016, CDC 2017b]. 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 2017b].

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.

Several features of Tri-NIV warrant clinical investigation of its safety and immunogenicity among older adults. In ferrets, Tri-NIV administered with Matrix-M1 adjuvant elicited rapid and robust immune responses in terms of geometric mean HAI titers with responses exceeding those induced by Fluzone HD. Secondly, geometric mean 50% microneutralizing (MN) titers against a broad panel of historic H3N2 strains tested, dating to 1999 and spanning a number of clinically-significant antigenic drift events, showed 2 to 214-fold higher titers among animals given Tri-NIV with Matrix-M1 adjuvant than among animals given Fluzone HD. These data suggest that Tri-NIV may elicit antibodies to broadly-neutralizing epitopes capable of providing greater drift strain protection, even against strains such as A/HongKong/4801/2014, which are associated with impaired influenza vaccine efficacy in humans. While cross-lineage B virus antibody responses were not seen in naïve animals, the possibility of such responses should be considered, and will be evaluated, in immunologically-experienced humans.

Because Tri-NIV is produced at high yields in insect cells, it potentially presents a more cost-effective method of producing large quantities of an annual seasonal influenza vaccine when compared to the traditional egg-based manufacturing processes, and if successful, may also offer a flexible and rapidly-responsive platform for production of novel influenza

hemagglutinins from strains with pandemic potential. Initial development, however, will focus on potential superior benefits of a seasonal trivalent or quadrivalent formulation in the vulnerable older adult population.

Two Tri-NIV treatment groups evaluating either 15 or 60 µg of HA antigen per strain have been proposed to 1) allow comparison with immunogenicity and safety profile of Fluzone HD and 2) evaluate the antigen dose response to inform further clinical development of the vaccine. The Matrix-M1 adjuvant, shown to remarkably enhance immunological responses of several vaccine antigens, with an overall acceptable safety profile in over 1,400 humans exposed to date, is proposed as the adjuvant of choice.

1.1 Study Design

This is a Phase 1/2, randomized, observer-blinded, active-controlled trial. Approximately 330 eligible subjects will be enrolled and randomized into 1 of 3 treatment groups as shown in the Trial Design table (Table 1). Each group will consist of approximately 110 subjects total, stratified by age (60 to < 75 and ≥ 75 years), gender, and history of receipt of 2016 - 17 influenza vaccine. On Day 0, subjects in Groups A and B will be administered an IM injection of 15 or 60 µg HA per strain of Tri-NIV in a 0.3 or 0.8 mL volume, respectively; subjects in Group C will receive the preconfigured comparator (Fluzone HD) at the manufacturer's recommended dose and volume. On Day 21, all Group A and B subjects will be administered a rescue injection with a licensed seasonal influenza vaccine, while all Group C subjects will be administered an injection with sterile saline placebo (in a total volume of 0.5 mL) to maintain trial blind. Trial follow-up for each subject will span approximately 1 year from the Day 0 injection Schedule of Events. 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. The maximum duration of the trial will be approximately 1 year for each subject.

Enrollment will be divided into 2 stages. Stage 1 will enroll a group of approximately 60 subjects (approximately 20 subjects per treatment group) and Stage 2 will enroll the remainder of the subjects per treatment group. The only difference in the 2 stages will be a safety review in-clinic visit for Stage 1 subjects on Day 7 (+ 1 day) of the trial, whereat subjects will be asked to present their subject diaries. In Stage 2, a safety review telephone call on Day 7 (± 1 day) of the trial will replace the clinic visit. Progression from Stage 1 to Stage 2 will require favorable review of cumulative Stage 1 safety against vaccination holding rules.

Table 1: Trial Design

	Day 0 Trial Treatment Injection (non-dominant deltoid)					Day 21 Rescue Injection[2] (dominant deltoid)			
Group	Vaccine Name	HA Dose per Strain, µg (H1N1/H3N2/BV)	Total HA Dose, µg	Matrix-M1 Adjuvant Dose, µg[1]	Injection Volume, mL	Vaccine	Stage 1 Subjects[3]	Stage 2 Subjects[3]	Total Subjects per Group
A	Tri-NIV	15 / 15 / 15	45	50	0.3	Licensed seasonal influenza vaccine	20	90	110
B	Tri-NIV	60 / 60 / 60	180		0.8		20	90	110
C	Fluzone HD	60 / 60 / 60	180	None	0.5	Placebo	20	90	110
Total Trial Target Subjects							60	270	330

Note: All subjects will receive 2 vaccinations by IM injection on Day 0 and Day 21.

[1] Matrix-M1 adjuvant will be formulated with the vaccine at the time of vaccination by the unblinded pharmacist in accordance with the Trial Pharmacy Manual.

[2] All subjects who received Tri-NIV will receive a rescue injection with a licensed seasonal influenza vaccine. Subjects who received Fluzone HD on Day 0 will receive an injection with sterile saline placebo (0.5 mL) to maintain trial blind.

[3] Enrollment will be divided into 2 stages. Stage 1 will consistent of approximately 20 subjects per treatment group. Stage 2 will consist of the remainder of targeted subjects for enrollment per treatment group.

1.2 Randomization and Treatment Assignments

After the Subject is deemed by the Principal Investigator (PI) to meet the eligibility criteria and prior to the performance of any study-related assessments, a central randomization system will be used for assigning a subject ID. The subject ID will be used throughout the trial on all related documents such as source documents and electronic case report forms (eCRFs).

At the screening visit, the subject ID will be assigned. At the enrollment visit (Day 0), after the PI has confirmed that the subject meets all of the inclusion criteria and none of the exclusion criteria, subjects will be randomized at a ratio of 1:1:1 into Arms 1 through 3, respectively, using a block randomization design. Randomization will be stratified by age (60 to < 75 and ≥ 75 years), gender, and history of receipt of 2016 - 17 influenza vaccine. Stratification for both age, gender and history of 2016 - 17 influenza vaccine group will be controlled by central randomization system.

1.3 Unblinding

The pharmacy personnel and/or licensed, unblinded study coordinator will be unblinded to investigational product assignment, and will prepare and/or administer the study vaccine/placebo. The volume of the vaccine/placebo in the syringe will be verified a second time by a second unblinded staff member before administration. The unblinded study pharmacist and/or unblinded study coordinator will administer all vaccinations. These

individuals must be licensed to administer medication/vaccination and will not be involved with safety evaluations, nor will they perform subsequent assessments or engage in other protocol activities that could reveal the blind.

PIs, all investigational study staff performing assessments of the subjects, and all subjects participating in this study will be blinded to investigational product. Under special circumstances, as outlined below, unblinding of investigational product is allowed. Furthermore, all clinical, statistical, and data personnel involved in the facilitation of this study will be blinded to investigational product except under special circumstances as outlined below.

During monitoring visits, an unblinded pharmacy study monitor will check that the blind has been maintained properly. A blinded study monitor will assess the progress of the study, but not have access to the unblinded pharmacy records.

Unblinding will occur after the clinical database has been locked. In special circumstances, such as the occurrence of suspected unexpected serious adverse reactions (SUSARs) or any safety signals, the Sponsor's Medical Monitor may authorize unblinding prior to database lock. In the case of a life-threatening emergency or pregnancy, the PI or designee may authorize unblinding of an affected subject in order to ensure the safety of the subject. Unblinding procedures are described in detail in the Site Instruction Manual.

1.4 Scope of the Analysis Plan

This statistical analysis plan (SAP) provides a detailed outline of the safety and immunogenicity analyses to be performed in accordance with Study Protocol tNIV-E-101Version 3.0, dated 14 August 2017, 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 21 visits, which will include all available immunogenicity data through Day 21 and safety data (inclusive of clinical laboratory safety assessments) through Day 21. No statistical stopping rules will be established for the review of these data and no modification of the protocol is contemplated. 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 (ie, after all data through Day 365 have been collected, reviewed, and all queries resolved).

This SAP also addresses results and analyses through Study Day 365 for the final analysis of the study. The database will be locked for this analysis when all available immunogenicity, and safety data through Day 365 (inclusive of earlier visits) 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 Tri-NIV at 2 different doses, and the licensed comparator Fluzone HD (Sanofi Pasteur), in healthy older adults ≥ 60 years of age. The safety profile will include solicited short-term reactogenicity; 21-day all adverse event (AE) profile; 1-year post-dosing medically-attended adverse event (MAE), serious adverse event (SAE), and significant new medical condition (SNMC) profile; and selected pre- and post-immunization clinical laboratory parameters.
- To describe the immunogenicity of Tri-NIV at 2 different doses, and the licensed comparator Fluzone HD (Sanofi Pasteur), in healthy older adults ≥ 60 years of age, based on hemagglutination inhibition (HAI) responses to vaccine-homologous influenza A and B strains, as recommend for the 2017-18 Northern hemisphere vaccine, at Day 21 post-dosing.

2.1.2 Secondary Objectives

- To describe the immunogenicity of Tri-NIV at 2 different doses, and the licensed comparator Fluzone HD (Sanofi Pasteur), based on hemagglutination inhibition (HAI) responses to at least 2 historic and/or drifted A virus strains (one H1N1 and one H3N2).
- To describe the immunogenicity of Tri-NIV at 2 different doses, and the licensed comparator Fluzone HD (Sanofi Pasteur), based on microneutralization (MN) responses to vaccine-homologous and historic influenza A strains, and the vaccine-homologous B/Victoria lineage strain, at Day 21 post-dosing.

2.1.3 Exploratory Objectives

- To describe the immunogenicity of Tri-NIV at 2 different doses, and the licensed comparator Fluzone HD (Sanofi Pasteur), based on HAI and MN responses to a contemporary B/Yamagata lineage strain Day 21 post-dosing.
- To describe the immune response to Tri-NIV at 2 different doses, and the licensed comparator Fluzone HD (Sanofi Pasteur), as measured by competitive-binding assays using purified HA and broadly-neutralizing HA monoclonal antibodies of varying specificities on Days 0 and 21.

2.2 Study Endpoints

2.2.1 Primary Endpoints

- Number and percentage (95% confidence interval [CI]) of subjects with solicited local and systemic adverse events over the 7 days post-injection (ie, Day 0 through Day 6 post-dosing); all adverse events (including adverse changes in clinical laboratory parameters) through 21 days post-injection; and MAEs, SAEs, and SNMCs through 1 year post-Day 0 dosing.

- Antibody titers specific for the HA receptor binding domains of each of the virus strains included in Tri-NIV as measured by the HAI assay. 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 for a given treatment group.
    - Geometric mean ratio (GMR) – defined as the ratio of post-vaccination and pre-vaccination HAI GMTs within the same treatment group (designated as $GMR_{Post/Pre}$).
    - Seroconversion rate (SCR) – defined as the percentage of subjects with either a baseline HAI titer < 1:10 and a post-vaccination titer ≥ 1:40, or a baseline HAI titer ≥ 1:10 and a 4-fold increase in post-vaccination HAI titer relative to baseline.
    - Seroconversion rate difference – defined as the difference of seroconversion rates between each of the Tri-NIV vaccine groups and Fluzone HD group and its upper 95% CI.
    - Seroprotection rate (SPR) – defined as the percentage of subjects with an HAI titer ≥ 1:40.

2.2.2 Secondary Endpoints

- Antibody titers specific for the HA receptor binding domains of at least 2 historic and/or drifted A virus strains (one H1N1 and one H3N2) as measured by the HAI assay. 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 for a given treatment group.
    - Geometric mean ratio (GMR) – defined as the ratio of post-vaccination and pre-vaccination HAI GMTs within the same treatment group (designated as $GMR_{Post/Pre}$).
    - Seroconversion rate (SCR) – defined as the percentage of subjects with either a baseline HAI titer < 1:10 and a post-vaccination titer ≥ 1:40, or a baseline HAI titer ≥ 1:10 and a 4-fold increase in post-vaccination HAI titer relative to baseline.
    - Seroprotection rate (SPR) – defined as the percentage of subjects with an HAI titer ≥ 1:40.
- Neutralizing antibody titers specific for the virus strains included in Tri-NIV and the Fluzone HD comparator, as well as selected historical A strains, as measured by a microneutralization assay at Day 0 pre-dosing and Day 21 post-dosing. In view of the time-consuming nature of neutralization assays, these may be performed on an informative subset of subjects who are selected for this purpose at randomization. Derived/calculated endpoints based on these data will include:
    - Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed neutralizing titer for a given treatment group.

- Geometric mean ratio (GMR) – defined as the ratio of post-vaccination and pre-vaccination neutralizing GMTs within the same treatment group (designated as $GMR_{Post/Pre}$).
- Seroconversion rate (SCR) – defined as the percentage of subjects with either a baseline neutralizing titer < 1:10 and a post-vaccination titer ≥ 1:40, or a baseline titer ≥ 1:10 and a 4-fold increase in post-vaccination titer relative to baseline.

2.2.3 Exploratory Endpoints

- HAI and neutralizing antibody titers specific for a contemporary B/Yamagata virus strain. Derived/calculated endpoints based on these data will be as described above.
- Levels of antibodies competitive with broadly-neutralizing monoclonal antibodies to HA of varying specificities, as measured by competitive-binding in a biosensor assay.

3 ANALYSIS POPULATIONS

3.1 Safety Population

The Safety Population includes all study subjects that provide consent, are randomized, and receive a dose of test article on Day 0. 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.

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 on Day 0 according to protocol, have HAI serology results for Day 0 and Day 21, 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

Subjects with major protocol deviations may be excluded from the PP analysis set. Protocol deviations that meet the threshold of "major" will be determined prior to unblinding, at the Sponsor's discretion. The Sponsor or designee will be responsible for producing a final

deviation file prior to database lock. 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: Protocol Deviations

Self-reported PDs	Programmatically-determined PDs
Excluded Concomitant Medication or Procedure	Missed Visit
Inclusion / Exclusion Criteria	Out of Window Visit
Informed Consent	Trial Procedure Not Done
Vaccination Error	Randomization Error
	Diary Compliance

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 (Stage 1 subjects only), 21, 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)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, 21, 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 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. Note: Stage 1 subjects have additional procedures on Day 7.
- 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.
- Diary Compliance will be determined as follows: If a subject's Diary submission status in eCRF is checked as "returned to the clinic" for all 7 days post vaccination, this subject is flagged as compliant. Otherwise not. Diary Compliance does not apply to subjects who didn't receive trial treatment injection. For this trial it will be Day 0 dose only. The presence

or absence of temperature and symptom data will be apparent in the data listings, but will not be used to determine Diary Compliance deviations.

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 21.
- Receipt of immunosuppressive medication from Day 0 until the Day 21 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 who have completed the study through Day 21 and through Day 364 will be presented by treatment group for all subjects in the Safety Population. The number of subjects who discontinue the study prior to Day 364 and the reason for discontinuation (eg, withdrawal of consent, lost to follow-up, death, etc.) will be presented. Study completion status through Day 21 will be determined based on completion of the Day 21 visit, and study completion status through Day 364 will be determined based on the End of Study (EOS) electronic case report form (eCRF).

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.

A listing of all subjects in the Safety Population with one or more protocol deviations recorded through Day 21 and through Day 364, will be provided and will include: treatment group, study day associated with the deviation (as provided on the protocol deviation log if available), protocol deviation category (as described below), and a description of the deviation as recorded by the site. All deviations from protocol procedures, evaluations, and visits will be documented throughout the course of the study.

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 2016 - 17 influenza vaccine will be summarized by each treatment group for all subjects in the Safety Population and ITT Population. Descriptive statistics (number of subjects [N], mean, median, minimum and maximum values) will be presented for weight (kg) and height (cm) measurements recorded at Study Day 0. No statistical testing will be performed on these data.

Age (years) at the Day 0 vaccination will be calculated as the closest lower integer result of (date of Study Day 0 vaccination – date of birth) / 365.25, and will be presented as a continuous variable, using descriptive statistics. Gender will be summarized as a categorical variable (eg, "Male", "Female"). Ethnicity will be summarized as number and percentage of subjects according to predefined categories (ie, Hispanic or Latino, not Hispanic or Latino) listed in the CRF. Race will also be summarized as number and percentage of subjects according to predefined categories (ie, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White).

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, and for all subjects in the Safety Population. Within each SOC and PT, the number and percentage of subjects with at least one abnormality in that SOC or PT will be presented, respectively. Multiple abnormalities within a given SOC or PT for a subject will be counted once within that respective SOC or PT.

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. The number of subjects vaccinated at Day 0 will be presented by treatment group and for all subjects. The number of subjects vaccinated by location (right or left deltoid) will be presented in subject data listings.

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; per the protocol, concomitant medication includes prescription and non-prescription drugs or other treatments, and any vaccine other than study vaccines. 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 analysis of primary immunogenicity endpoints will be conducted by using PP and ITT population, with PP population as the primary analysis. No missing data will be imputed.

Antibody titers specific for the HA receptor binding domains of each of the virus strains included in Tri-NIV, H1N1, H3N2, and Bv , will be analyzed.

- Geometric mean titers (GMT) of Antibody titers specific for the HA receptor binding domains of each of the virus strains and their 95% CIs will be summarized by treatment at baseline (pre-vaccination on Day 0) and post vaccination on Day 21. GMT will be calculated as the antilog of the mean of the log-transformed HAI titers for a given treatment group. Lognormal distribution is assumed for antibody titer to construct confidence interval.

- Between-group geometric mean ratio ($GMR_{new/ref}$) and its 95% CI for each of the Tri-NIV groups against active comparator group Fluzone HD will be conducted using two-sample t distribution. A sample SAS code is given below:

```
proc ttest data=fludata alpha=0.05;
by Visit;
class grp;
var log(HAI_D21);run;
```

- 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_Long alpha=0.05;
by Visit Group;
PAIRED log(HAI_D21)*log(HAI_D0);run;
```

- Seroconversion rate (SCR) is defined as the percentage of subjects with either a baseline HAI titer < 1:10 and a post-vaccination titer ≥ 1:40, or a baseline HAI titer ≥ 1:10 and a 4-fold increase in post-vaccination HAI titer relative to baseline. The 95% confidence interval will be constructed by Clopper-Pearson method with the following sample SAS code:

```
proc freq data=fludata ;
by treatment;
tables seroconvind/ nocum norow binomial;
exact binomial;
run;
```

- Seroconversion rate difference is defined as the difference of seroconversion rates between each of the Tri-NIV vaccine groups and Fluzone HD group. The Chi-Square p-value for testing the equality of SCRs between two groups will be derived with continuity adjustment. The Newcombe method will be used to construct its 95% confidence interval with the following sample SAS code:

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

- Seroprotection rate (SPR) is defined as the percentage of subjects with an HAI titer ≥ 1:40 by treatment group. The 95% confidence interval will be constructed similarly by Clopper-Pearson method.

- Seroprotection rate difference is defined as the difference of SPRs between each of the Tri-NIV groups and Fluzone HD group. The 95% CI will be constructed similarly to that for SCR difference.

7.2 Analyses of Secondary Objectives of Immunogenicity

Antibody titers specific for the HA receptor binding domains of at least 2 historic A virus strains (one H1N1 and one H3N2) as measured by the HAI assay will be summarized as follows using the same statistical approaches as the primary immunogenicity endpoints:

- Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed HAI titers for a given treatment group.

- Geometric mean ratio (GMR) – defined as the ratio of post-vaccination and pre-vaccination HAI GMTs within the same treatment group (designated as GMRPost/Pre).

- Seroconversion rate (SCR) – defined as the percentage of subjects with either a baseline HAI titer < 1:10 and a post-vaccination titer ≥ 1:40, or a baseline HAI titer ≥ 1:10 and a 4-fold increase in post-vaccination HAI titer relative to baseline.

- Seroprotection rate (SPR) – defined as the percentage of subjects with an HAI titer ≥ 1:40.

7.3 Analyses of Exploratory Objectives of Immunogenicity

The following exploratory antibody titers will be summarized using the same statistical approaches as the primary immunogenicity endpoints.

- HAI and neutralizing antibody titers specific for a contemporary B/Yamagata virus strain.

- Levels of antibodies competitive with broadly-neutralizing monoclonal antibodies to HA of varying specificities, as measured by competitive-binding in a biosensor assay.

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 will be assessed in the Safety population including all subjects who receive any test article, and will be summarized overall and by treatment group based on solicited local and systemic adverse events, 21-day all AE profile (including adverse changes in clinical laboratory parameters) by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severe, related (possibly, probably, or definitely), and one-year MAEs, SAEs and SNMCs profiles. The number and percentage (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.

Solicited adverse events occurring in the first 7 days after each dose of test article will be presumed to be related; and severity will be graded by specific definitions included in the protocol and subject diary. Unsolicited adverse event summaries by relationship to test article will be categorized as “not related” (including “unrelated” or “unlikely”) or “related” (including “possible”, “probable”, and “definite”). 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.

Solicited adverse events will not be coded, and will be summarized by solicited term only. All unsolicited adverse events will be coded using MedDRA version 20.0.

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, pain, bruising, redness, and swelling) and systemic events (ie, oral temperature [for assessment of fever], chills, muscle pain, joint pain, diarrhea, nausea, vomiting, headache, and fatigue) 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 (did not occur), 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 (see protocol, Appendix 4). 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 Solicted 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

Solicited AEs will be tabulated and analyzed by the verbatim terms specified in the diary, and not MedDRA coded. Analysis will use exact diary wording (ie, "muscle pain" rather than changing it to "myalgia"). Only solicited adverse events which record a start date within the 7-day window of the Day 0 to Day 6 post-vaccination period will be included in the tabular summary and listing of solicited events. Solicited AEs will be presented by treatment group for all subjects.

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 Solicted 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

Solicited AEs, collected from the subject diary, which continue after the collection period(s) (ie, post-vaccination Day 6) will be captured by verbatim term, on an AE electronic case report form (eCRF) page and flagged in the listing of solicited AEs.

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).
- A summary of all 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.

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 - 21).
- A summary by severity (mild, moderate, or severe), MedDRA SOC, PT, and treatment group (Days 0 - 21).
- A summary by relationship (possibly, probably, definitely, or unlikely/unrelated) to test article, MedDRA SOC, PT, and treatment group (Days 0 - 21).

- A summary of severe related (possibly, probably, definitely) AEs, MedDRA SOC, PT, and treatment group (Days 0 - 21).

The 'twenty-one (21) days post-vaccination' dataset is intended to capture short and moderate term unsolicited AEs occurring in the approximate 3 weeks after the investigational product (or comparator) exposure and not attributable to the rescue treatment." The dataset will contain the following unsolicited AEs:

- In subjects who receive the rescue dose on Day 21, all unsolicited AEs with start dates on Days 0 to 20.
- In subjects who receive the rescue dose prior to Day 21, all unsolicited AEs with start dates on Days 0 to the day of rescue dose -1.
- In subjects who receive the rescue dose on Days 22 or 23, all unsolicited AEs with start dates on Days 0 to the day of rescue dose -1.
- In subjects who receive the rescue dose after Day 23, or who do not receive the rescue dose, all unsolicited AEs with start dates on Days 0 to 22.

In addition to the above summaries, the final analysis will also include the following summaries of unsolicited AEs:

- An overall summary of unsolicited AEs (Days 0 - 364).
- A summary by severity (normal, mild, moderate, or severe), MedDRA SOC, PT, treatment group (Days 0 - 364).
- A summary by relationship (possibly, probably, definitely, or unlikely/unrelated) to test article, MedDRA SOC, PT, treatment group (Days 0 - 364).
- A summary of severe related AEs, SAEs, MAEs, and SNMCs, by MedDRA SOC, PT, and treatment group will be prepared for Days 0 – 364, if any such events are reported after Day 21.

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.

MAEs are adverse events which result in an unscheduled visit to a healthcare provider due to symptomatic illness or injury. These may include office visits, clinic visits, home consultations, or emergency room evaluations for non-life-threatening events that do not result in hospitalization (life-threatening events or hospitalizations are SAEs, see Section 8.2 of the protocol).

SNMCs are adverse events that are new (that is, not present at baseline), clinically significant (meaning that they imply an important change in the subject's long-term health status), and

typically chronic (requiring an ongoing change in the subject's medical management). This category is not meant to include minor or transient diagnoses or age-related changes. For example, while new diagnoses of presbyopia or tinea versicolor are chronic conditions, they are not SNMCs because no significant change in health status is implied. Similarly, adverse events which are isolated, treatable events that resolve and do not require chronic therapy are also not SNMCs (examples could include an uncomplicated acute urinary tract infection or a simple fracture resolved with conservative treatment and with no residual disability). In contrast, new diagnoses of rheumatoid arthritis or coronary artery disease are SNMCs because they imply a long-term change in health status and require ongoing medical management.

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 an SNMC, and the investigator should record sufficient data in the source document 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 study 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 21 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).

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in in-patient hospitalization. Events which could have led to the above outcomes had they occurred with greater severity are not SAEs, but should be reported as AEs, MAEs, or SNMCs, as appropriate.

The eCRF will provide a field for designating an AE as 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 21 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, pulse, respiratory rate) at each visit will be presented by treatment group for all subjects in the Safety Population.

9 SAMPLE SIZE CONSIDERATIONS

The sample size is chosen as adequate for an initial description of safety and immunogenicity to direct future development and dosing. No hypothesis tests are specified and the sample size is not intended to support any statistical contrast of Tri-NIV with Fluzone HD. For safety endpoints, the probability of observing at least one adverse event among 110 subjects for each of the two Tri-NIV groups or 220 for the two Tri-NIV groups combined, are > 90% if the true rate of such events is 2.1% and 1.1%, respectively. With 110 for each of the two Tri-NIV group or 220 for the two Tri-NIV groups combined, observing no adverse events of interest (eg, vaccine-related SAE) would represent an upper bound of the one-sided 95% CI on the percentage of such events of 2.7% and 1.4%, respectively.

Tri-NIV is expected to be comparable (statistically non-inferior) to the currently licensed Fluzone HD in terms of SCR. If the underlying SRRs is 70% for both the Tri-NIV and active control groups for a given strain, with 100 subjects in each group, the trial has a 46% power to detect -0.10 non-inferiority (NI) margin. If the underlying SRR is 50%, the power will be 41%.

10 PRELIMINARY UNBLINDED AND FINAL ANALYSES

An unblinded analysis will be conducted upon completion of all Day 21 visits, which will include all available immunogenicity data through Day 21 at the time of the analysis and safety data (inclusive of clinical laboratory safety assessments) through Day 21. An unblinded review will be conducted of all available immunogenicity and safety data (including clinical assessments and concomitant medications) upon completion of all Day 21 visits. For the review, treatment codes will only be unblinded after all subjects have completed the Day 21 visit, the data are monitored, all applicable queries are resolved, and the database locked. The data and analyses provided in the review will be considered final for the material contained therein, and will not change.

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 385).

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

Immunogenicity and safety analyses from the unblinded review 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. The database will be locked and the final study report prepared, when all of the above data have been entered, reviewed, and all queries related to the data have been addressed.

The final CSR will present the balance of all immunogenicity and safety data through Day 364 (the scheduled end of study). The database will be locked and the final study report prepared, when all of the above data have been entered, reviewed and all queries related to the data have been addressed.

Full descriptions of the planned analyses are included in the SAP. Any decisions to deviate from the planned analyses will be described in detail in the final study report.

11 COMPUTER METHODS

Statistical analyses will be performed using SAS® version 9.3 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 statistical analyses will be 2-tailed and assessed at the 5% significance level.

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).

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, median, standard deviation (SD), minimum, and maximum values will be presented.

For all analyses, a p-value of < 0.05 will be considered statistically significant. 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, GMR analyses. The LLoQ values will be provided by corresponding lab or CRO as part of the data transfer.

All descriptive statistical analyses will be performed using SAS statistical software Version 9.3 or higher in a Windows environment, unless otherwise noted. Medical history and AEs will be coded using the MedDRA Version 20.0.

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

Immunogenicty endpoints will not be adjusted for pre-vaccination titer.

12.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment will be applied.

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

NA

15 REFERENCES

CDC (2017b). What you should know and do this Flu season if you are 65 years and older Retrieved June 27 2017 from https://www.cdc.gov/flu/about/disease/65over.htm.

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

Appendix 1 – TNIV-E-101 TRIAL PROCEDURES SCHEDULE

Trial Day:	**0**	**3**	**7 (Stage 1 ONLY)** [8]	**7 (Stage 2 ONLY)**[8]	**21**	**56**	**90**	**182**	**273**	**364**
Window (days):		**± 1**	**+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					
Trial Treatment Injection	X									
Rescue Injection with a licensed seasonal influenza vaccine [6]					X					
Adverse Event Review [4]	X	X [3]	X	X[3]	X	X	X	X	X	X
Concomitant Medications Review [4]	X	X	X	X	X	X	X	X	X	X
Subject Diary Review		X [3]	X [5]	X [3]	X [5]					

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 21; 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 at the Day 7 visit (Stage 1 subjects ONLY) or Day 21 visit (Stage 2 subjects ONLY).

[6] On Day 21, all Group A and B subjects will be administered a rescue injection with a licensed influenza vaccine, and all Group C subjects will be administered an injection of saline placebo to maintain trial blind. *Subjects should be free of acute illness (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature ≥ 38.0°C) in order to receive the second vaccination. Subjects presenting with an acute illness on Day 21 may return to the study site within the next 7 days to receive their 2nd vaccination. If a subject has experienced any AEs/SAE between study Days 0 and 21, then Day 21 vaccination may be administered or delayed for up to 7 days based on the Investigator's discretion.*

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

[8] All Stage 1 subjects will be required to complete a Day 7 in-clinic visit to present their subject diaries, whereas Stage 2 subjects will be required to complete a safety telephone call.