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

Investigational Materials:	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
Protocol Number:	tNIV-E-101
Sponsor:	Novavax, Inc. (Novavax) 20 Firstfield Road Gaithersburg, MD 20878 USA
Responsible Clinical Operations Manager:	[redacted] Clinical Operations Novavax, Inc. Gaithersburg, MD 20878 Office: [redacted] Email: [redacted]
Version & Date:	Version 5.0 – 13 November 2017
Prior Version(s):	Version 4.0 – 18 October 2017 Version 3.0 – 24 August 2017 Version 2.0 – 21 July 2017 Version 1.0 – 14 July 2017

PROTOCOL APPROVAL PAGE

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

Investigational Material(s):	Hemagglutinin Nanoparticle Influenza Vaccine, Trivalent (Tri-NIV), representing A/Michigan/45/2015 (H1N1); A/HongKong/4801/2014 (H3N2); and B/Brisbane/60/2008; administered with Matrix-M1 Adjuvant
Protocol:	tNIV-E-101
Date of Issue:	13 November 2017

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

Novavax, Inc.

[redacted] Clinical Development
Novavax, Inc.

Date

[redacted] Clinical Operations
Novavax, Inc.

Date

Clinical Trial Site

Print Name – Principal Investigator

Date

Signature

PROTOCOL CHANGE HISTORY

Protocol Version 5.0, 13 November 2017 (revised from 4.0, 18 October 2017)

The following is a summary of changes made to this version.

Location of Change	Change/Modification in Version 5.0
Section 7.2.1	The description of the hemagglutination inhibition (HAI) assay has been updated to include the following text: *Based on new findings in a recent investigation concerning egg passage-induced point mutations in contemporary A(H3N2) strains [Zost 2017], testing (for at least H3N2 strains) will also be performed in a qualified assay using hemagglutinating antigens produced by recombinant methods capable of generating HA with and without specific egg-induced mutations*.
Section 12	The following reference has been added: *Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. PNAS 2017. www.pnas.org/cg/doi/10.1073/pnas.1712377114.*

Protocol Version 4.0, 18 October 2017 (revised from 3.0, 24 August 2017)

The following is a summary of changes made to this version.

Location of Change	Change/Modification in Version 4.0
Section 2.2, 3.2.2, Synopsis	The secondary objective and endpoint have been updated to indicate that hemagglutination inhibition (HAI) and microneutralization responses will not only be assessed against historic A strains, but may also assess a drifted A strain.
Section 3.2.1, Synopsis	The 21 days post vaccination all adverse event (AE) profile period has been further defined by the addition of the following: Note: The 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose

Location of Change	Change/Modification in Version 4.0
	before or after day 21, or no rescue dose, are detailed in the statistical analysis plan. Primary endpoint "Seroconversion rate difference – defined as the difference of seroconversion rates between each of the Tri-NIV vaccine groups and Fluzone HD group and its two-sided 95% CI" has been deleted to avoid redundancy.
Section 8.1	It has been clarified that the 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose before or after day 21, or no rescue dose, are detailed in the statistical analysis plan.
Section 8.1.1	In the event of a Grade 3 solicited adverse event reported by telephone during the solicitation period, it has been clarified that investigator should enter the AEs in the subject diary, instead of in the adverse event electronic case report form, as was originally written.
Table 4	The list of adverse events of special interest has been updated to include 2 additional AEs, ie, Eaton-Lambert syndrome and rosacea.
Section 6.6	Table of protocol deviations has been updated to include "diary compliance" under programmatically-determined protocol deviations and "others" under self-reported protocol deviations. These will be any protocol deviations that do not belong under any pre-specified category.
Section 10.4.1.2, Synopsis	Text has been corrected to indicate that within-group geometric mean ratio ($GMR_{post/pre}$) will be conducted using paired t-test, and not analysis of covariance.
Section 10.5, Synopsis	The following text has been deleted because non-inferiority assessment is not an objective of this trial: 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%.
General	Minor changes have been made to improve the readability and consistency of the document.

Protocol Version 3.0, 24 August 2017 (revised from 2.0, 21 July 2017)

The following is a summary of changes made to this version.

Location of Change	Change/Modification in Version 3.0
Section 3.1, 3.1.1, Table 1, Synopsis	To ensure safety of trial participants, enrollment has been 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 that have been specified in a new Section 3.1.1.1.
Section 3.1.1.1, Synopsis	Section has been added to specify vaccination holding rules, which are: 1) The occurrence of at least 1 serious adverse event among any Stage 1 subject assessed by the sponsor as definitely related to the trial treatment. 2) The occurrence of any severe (grade 3) solicited (local or systemic) adverse event term in > 10% of all Stage 1 subjects.
Section 3.1.1.2, Synopsis	Section has been added to indicate that subjects will continue to be evaluated for safety even after Stage 1 enrollment.
Section 3.5	It has been specified that subject trial treatment may be unblinded also in the event a vaccination holding rule is met.
Section 6.1.4, Synopsis	All Stage 1 subjects will be required to complete an in-clinic visit on Day 7 (+1 day) of the trial and present their subject diaries. Stage 2 subjects will be required to complete a safety telephone call on Day 7 (± 1 day). These subjects will present their subject diaries on their Day 21 visit.
Section 10.4.1.2, Synopsis	It has been specified that the within-group geometric mean ratio (GMRpost/pre) will be conducted using the analysis of covariance (ANCOVA) adjusted by the baseline value based on log-transformed values, when evaluating neutralizing antibody titers.
Appendix 1, Synopsis	The distinction between an onsite visit for Stage 1 subjects and a safety telephone call for Stage 2 subjects has been specified in the table.
General	Minor changes have been made to improve the readability and consistency of the document.

Protocol Version 2.0, 21 July 2017 (revised from 1.0, 14 July 2017)

The following is a summary of changes made to this version.

Location of Change	Change/Modification in Version 2.0
Section 1.6	Minor modifications have been made to text describing RSV-E-205 data.
Synopsis, Section 6.1.5, Appendix 1	Criteria specifying whether subjects can receive Day 21 injection have been added. Specifically, 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 adverse event/serious adverse event 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.
Section 1.4, 4.1	The size of the HA nanoparticle has been specified to approximately 20 to 40 nm.
Section 4.2.2	The manufacturing process of Tri-NIV has been updated to indicate that an additional purification step is required for the B/strain nanoparticle (ie, Capto Blue Chromatography) and that nanoparticles from both strains are nanofiltered prior to being loaded onto the lentil lectin column.
General	Minor changes have been made to improve the readability and consistency of the document.

TABLE OF CONTENTS

LIST OF TABLES

GLOSSARY OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cells
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CD	Compact Disc
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
cm	Centimeter
CMO	Chief Medical Officer
CQA	Clinical Quality Assurance
CRO	Contract Research Organization
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HAI	Hemagglutination Inhibition
HD	High Dose
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure

Abbreviation or Term	Definition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IM	Intramuscular(ly)
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Liter
LLOQ	Lower Limit of Quantitation
M	Molar Concentration
MAE	Medically-attended Event
MDCK	Madin Darby Canine Kidney (cells line)
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
MHC	Major Histocompatibility Complex
µL	Microliter
µM	Micromolar
MMP	Methyl-α-D-mannopyranoside
mg	Milligram
mL	Milliliter
mM	Millimolar
MN	Microneutralization
NA	Neuraminidase
NaCl	Sodium Chloride
ng	Nanogram
NI	Non-inferiority
NP	Nucleoprotein
NZW	New Zealand White (rabbits)
OD	Optical Density

Abbreviation or Term	Definition
PBMC	Peripheral Blood Mononuclear Cell
PD	Protocol Deviation
PP	Per Protocol
PS	Polysorbate
PT	Preferred Term
RBC	Red Blood Cell
RDE	Receptor Destroying Enzyme
RSV F	Respiratory Syncytial Virus Fusion
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
Sf	*Spodoptera frugiperda*
SNMC	Significant New Medical Condition
SOC	System Organ Class
SPR	Seroprotection Rate or Surface Plasmon Resonance
TCID	Tissue Culture Infective Dose
TGS	Toxicity Grading Scale
TMAE	Trimethylaminoethyl
TMF	Trial Master File
tNIV or Tri-NIV	Nanoparticle Influenza Vaccine, Trivalent
US	United States
WBC	White Blood Cell
WHO	World Health Organization
w/v	Weight to Volume

CLINICAL PROTOCOL SYNOPSIS

NAME OF COMPANY Novavax, Inc.	**INDIVIDUAL TRIAL TABLE SYNOPSIS**	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF ACTIVE INGREDIENT Nanoparticle Influenza Vaccine, Trivalent: A/Michigan/45/2015 (H1N1); A/HongKong/4801/2014 (H3N2); and B/Brisbane/60/2008; Matrix-M1™ Adjuvant		
Protocol Number: tNIV-E-101		
Protocol Title: 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		
Sponsor: Novavax, Inc., 20 Firstfield Road, Gaithersburg, MD 20878		
Investigational Material: 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		
Reference Materials: Fluzone® High-Dose (HD), a United States (US)-licensed, egg-derived and formaldehyde-inactivated, seasonal trivalent influenza vaccine manufactured for the 2017-2018 Northern Hemisphere season		
Regimen and Dosing: All subjects will receive an intramuscular (IM) injection on Day 0 of the assigned test article. Injections will contain either 15 µg hemagglutinin (HA) antigen from each of 3 strains (Tri-NIV) with 50 µg Matrix-M1 adjuvant (Group A); 60 µg HA antigen from each of 3 strains (Tri-NIV) with 50 µg Matrix-M1 adjuvant (Group B); or the recommended dose of Fluzone HD (Group C). All Group A and B subjects will be administered a rescue injection on Day 21 with a licensed seasonal influenza vaccine while all Group C subjects will be administered a sterile saline placebo injection on Day 21 to maintain the trial blind.		
Phase of Development: Phase 1/2		
Trial Rationale: The influenza virus poses a formidable risk of infection to older adults. Based on estimates by the Centers for Disease Control and Prevention (CDC), in the US alone, up to 85% of all influenza-related deaths and 70% of all influenza-related hospitalizations occur in people 65 years of age or older [CDC 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 1400 humans exposed to date, is proposed as the adjuvant of choice.

Trial Objectives:

***Primary*:**

- 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.

Secondary:

- 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 and/or drifted influenza A strains, and the vaccine-homologous B/Victoria lineage strain, at Day 21 post-dosing.

Exploratory:

- 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.

Trial Endpoints:

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. Note: The 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose before or after day 21, or no rescue dose, are detailed in the statistical analysis plan.
- 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 at Day 0 pre-dosing and Day 21 post-dosing. 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 Day 21 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.

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 at Day 0 pre-dosing and Day 21 post-dosing. 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 Day 21 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.

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.

Trial 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 below. 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 as defined in Safety Monitoring of Enrollment and Vaccinations Section below.

Safety Monitoring of Enrollment and Vaccinations:

This will be a first-in-human trial with Tri-NIV formulated with Matrix-M1 adjuvant. Thus, vaccination holding rules will be used to govern progression from the Stage 1 group to full enrollment in Stage 2. Solicited and unsolicited AEs reported from all Stage 1 subjects within 7 days of Day 0 vaccination will be evaluated against vaccination holding rules (See Vaccination Holding Rules below). These AE data will be summarized by the sponsor statistician, reviewed, and provided to an independent medical monitor in aggregate form (without unblinding or subdivision by treatment group). If vaccination holding rules are not met, the independent medical monitor will notify the sponsor Chief Medical Officer (CMO) to proceed with enrollment of subjects. If vaccination holding rules are met, the independent medical monitor will notify the sponsor CMO who will pause enrollment pending further review and request unblinding of the data. The independent medical monitor and the sponsor will review the unblinded data and develop a report and recommendation to either: a) resume enrollment, b) amend the protocol and resume enrollment, or c) terminate the protocol. The report, the recommendation, and the amended protocol and ICF (if relevant), will be provided to the IRB and CBER, and enrollment will not recommence until IRB approval is obtained.

Vaccination Holding Rules:

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

1) The occurrence of at least 1 serious adverse event among any Stage 1 subject assessed by the sponsor as definitely related to the trial treatment.

2) The occurrence of any severe (grade 3) solicited (local or systemic) adverse event term in > 10% of all Stage 1 subjects.

If vaccination holding rules are met at any review point, the independent medical monitor will:

1) Review a summary of all individual data of the relevant subject(s), including the unblinded treatment assignment, and summary safety data relative to all treatment groups; and

2) If there exists any imbalance that is higher in one of the two Tri-NIV treatment groups compared to the Fluzone HD group, review a detailed accounting from the investigator(s) as to the exact nature of the clinical symptoms or physical findings in the subject(s) triggering the holding rule, including any potential causation and evidence of

resolution with or without treatment.

Ongoing Evaluation:

In addition to the above vaccination holding rules after Stage 1, solicited adverse events enrollment and vaccination will be suspended pending discussion with CBER and the IRB in the event of:

1) Any tabulation of solicited adverse events (to be repeated approximately weekly during active enrollment) which demonstrates the occurrence of any severe (grade 3) solicited (local or systemic) adverse event term in > 10% of all subjects (note that unmonitored data will perforce be used for this tabulation), or
2) The occurrence of at least 1 serious adverse event in any subject assessed by the sponsor as definitely related to the trial treatment.

Trial Design

Group	Day 0 Trial Treatment Injection (non-dominant deltoid)					Day 21 Rescue Injection[2] (dominant deltoid)	Stage 1 Subjects [3]	Stage 2 Subjects [3]	Subjects per Group
	Vaccine Name	HA Dose per Strain, µg (H1N1/H3N2/Bv)	Total HA Dose, µg	Matrix-M1 Adjuvant Dose, µg[1]	Injection Volume, mL				
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 on Day 21. Subjects who receive 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 consist of approximately 20 subjects per treatment group. Stage 2 will consist of the remainder of targeted subjects for enrollment per treatment group.

Trial Visit Procedures:

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

Day 0 – Screening Visit

Healthy male and female volunteers, ≥ 60 years of age, who have provided written informed consent to participate in the trial and who are able to comply with trial requirements, will have the following procedures performed: review of inclusion and exclusion criteria; medical history, including influenza vaccination history during the previous 3 years (with emphasis on 2016 - 17 vaccine) and history of adverse reactions to prior influenza vaccines and allergies; medication history; physical examination of HEENT (head, eyes, ears, nose, and throat), abdomen, extremities, and at least inguinal, cervical, and axillary nodes, gross motor function, and skin; vital signs (heart rate, blood pressure, respiratory rate, and oral temperature), height, and weight; and assessment of concomitant medications. Note that further procedures may be performed at the investigator's discretion in order to adequately screen subjects against eligibility criteria. Potential subjects who meet all inclusion criteria and none of the exclusion criteria (see Eligibility Criteria) may be enrolled.

Day 0 – Trial Treatment Injection Visit

All subjects who have eligibility confirmed will be randomized to 1 of 3 treatment groups and will have blood drawn for baseline immunogenicity testing (eg, HAI/MN titers; 20 mL) and clinical laboratory safety parameters assessments (ie, serum chemistry and hematology; 10 mL). Subjects will then receive a single IM injection of Tri-NIV or Fluzone HD in their non-dominant deltoid, according to treatment assignment. Note: if only the dominant deltoid is available for injection, it is acceptable to administer the trial treatment in the dominant deltoid.

Subjects will be monitored in the clinic for 30 to 60 minutes following injection with the trial treatment for the occurrence of any AEs and for the evaluation of post-vaccination vital signs.

Starting on vaccination day (Day 0) and for 6 days thereafter (Day 0 through Day 6 inclusive), subjects will maintain diaries for daily recording of their body temperature and any adverse event spontaneously offered. In addition, the following local injection site and systemic reactions will be solicited by diary: injection site (local) events – pain, bruising, redness, and swelling; general systemic events – oral temperature, chills, muscle pain, joint pain, diarrhea, nausea, vomiting, headache, and fatigue; and facial/respiratory systemic events – cough, difficulty breathing, difficulty swallowing, hoarseness, chest tightness, sore throat, wheezing, eye redness, and facial swelling. Subjects will also be asked to record any concomitant medications, physician visits, or hospitalizations associated with these solicited adverse events.

Follow-up Telephone Contact/In-clinic Visits

Safety follow-up visits will be performed by scripted telephone contact on Day 3 to query for any grade 3 solicited or unsolicited event and/or SAE experienced since the last visit or telephone contact, and any concomitant medications taken for these events. *Subjects who report a grade 3 event and/or SAE may be asked to return to the clinic for an unscheduled visit at the investigator's discretion.* Subjects in Stage 1 of the trial will complete a Day 7 (+1 day) in-clinic visit to return their diaries, provide vital signs, report any AEs they experienced since their last visit, and schedule their next Day 21 (± 2 days) in-clinic visit. Subjects will Stage 2 will complete a Day 7 (±1 day) telephone call with the trial staff and will return their diaries on their next Day 21 (± 2 days) in-clinic visit. On their Day 21 visit, all subjects will be queried for any AEs, MAEs, SNMCs, and SAEs occurring since the last trial visit, and any concomitant medications taken. In addition, the following procedures will be performed on Day 21 for all subjects: vital sign collection and collection of blood samples for immunogenicity testing (eg, HAI/MN titers; 20 mL) and clinical laboratory safety assessments of hematology and serum chemistry parameters (10 mL). A rescue injection with a licensed seasonal influenza vaccine will be administered to all subjects that received Tri-NIV on Day 0, according to the manufacturer's instruction, whereas all subjects who received Fluzone HD on Day 0 will be given an injection of sterile saline placebo to maintain trial blind. Administration should be performed on the dominant deltoid. *Note: if only the non-dominant deltoid is available for injection, it is acceptable to administer the trial treatment in the non-dominant deltoid. 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.* Subjects will be monitored in the clinic for 30 to 60 minutes following injection with the trial treatment for the occurrence of any AEs and for the evaluation of post-vaccination vital signs.

Additional safety follow-up will include an in-clinic visit on Day 56 (± 2 days), a telephone contact visit on Day 90 (± 7 days) and Day 273 (± 7 days), and an in-clinic visit on Day 182 (± 7 days) and Day 364 (± 14 days) to query for any MAEs, SNMCs, and SAEs occurring since the last trial visit or telephone contact, and any concomitant medications taken for these events.

Schedule of Events:

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]

Schedule of Events (Continued):

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										
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.

Eligibility Criteria:

Inclusion:

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

1) Healthy adult male or female, ≥ 60 years of age,
2) Willing and able to give informed consent prior to trial enrollment, and
3) Able to attend trial visits, comply with trial requirements, and provide reliable and complete reports of adverse events.

Exclusion:

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

1) Any ongoing, symptomatic acute or chronic illness requiring medical or surgical care.
   - Asymptomatic chronic conditions or findings (eg, mild hypertension, dyslipidemia) that are not associated with evidence of end-organ damage are not exclusionary provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time-course of this trial) in the opinion of the investigator.
   - Acute or chronic illnesses or conditions which may be reasonably predicted to become symptomatic if treatment were withdrawn or interrupted are exclusionary, even if stable.
   - Acute or chronic illnesses reasonably expected to be associated with increased risks in the event of influenza infection (eg, cardio-pulmonary diseases, diabetes mellitus, renal or hepatic dysfunction, hemoglobinopathies) are exclusionary, even if stable.
   - Note that illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (see exclusion criteria 2, 5, 8, 9).
2) Participation in research involving investigational product (drug / biologic / device) within 45 days before planned date of first injection.
3) History of a serious reaction to prior influenza vaccination, or known allergy to constituents of influenza vaccines - including egg proteins - or polysorbate 80.
4) History of Guillain-Barré Syndrome (GBS) within 6 weeks following a previous influenza vaccine.
5) Receipt of any vaccine in the 4 weeks preceding the trial vaccination and any influenza vaccine within 6 months preceding the trial vaccination.
6) Any known or suspected immunosuppressive illness, congenital or acquired, based on medical history and/or physical examination.
7) Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the trial vaccine. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
8) Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the trial vaccine or during the trial.
9) Acute disease at the time of enrollment (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature > 38.0°C, on the planned day of vaccine administration).
10) Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled or could interfere with evaluation of the vaccine or interpretation of trial results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).
11) Known disturbance of coagulation.
12) Suspicion or recent history (within 1 year of planned vaccination) of alcohol or other substance abuse.

Statistical Methods:

General

All analysis populations will be defined and full descriptions of each population will be provided. Demographic parameters and other baseline characteristics (age, sex, race, ethnicity, as well as influenza vaccine exposure within the 2016-17 influenza season) will be summarized by treatment group for all subjects in the safety population, as well as the number and description of protocol deviations.

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

Analyses Concerning Safety Objective

Safety analysis will be descriptive and based on the safety population, defined as all subjects who received a dose of trial treatment. Safety will be summarized overall and by individual treatment arms based on solicited short-term reactogenicity post-injection on Day 0, 21-day all AE profile by MedDRA preferred term, and 1-year MAE, SAE, and SNMC profiles post-injection on Day 0. Note: The 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose before or after day 21, or no rescue dose, are detailed in the statistical analysis plan. All AEs, MAEs, SAEs, and SNMCs will be tabulated by severity, related (possibly, probably, or definitely vs. non-related per investigator assessment), and severe and related. The number and percentage (with 95% CI) of subjects in each treatment group with a given term will be summarized. Clinical laboratory data will be summarized by means and 95% confidence interval, minima and maxima, at Day 0 and Day 21 in each treatment group, as well as means and 95% confidence interval of change from baseline at Day 21. Changes from baseline will also be summarized at Day 21 for each treatment group in terms of the proportion of subjects with no change in toxicity grade versus proportions with one, two, or three grade changes. A listing and narratives of SAEs will also be produced.

Analyses Concerning Immunogenicity Objectives

The immunogenicity analysis will be based on the per-protocol (PP) population. A separate intent-to-treat (ITT) population analysis will not be produced unless > 10% of at least 1 treatment group is excluded from the PP population. HAI antibody titers specific for each of the vaccine-homologous, historical and/or drifted, and cross-lineage virus strains tested will be summarized by treatment group based on the following parameters (with 95% CIs):

1) Geometric mean titer (GMT) at baseline (screening) and post-vaccination on Day 21. Samples with no detectable HAI activity at the lowest dilution (1:10) will be assigned a value of 5 for calculation.
2) GMR – the ratio of the post-vaccination GMT on Day 21 to the baseline (Day 0) value.
3) 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 on Day 21 in post-vaccination HAI titer relative to baseline.
4) Seroprotection rate (SPR) – defined as the percentage of subjects with an HAI titer ≥ 1:40 at a given time point.

Neutralizing antibody titers specific for each of the virus strains will be summarized by treatment group for each virus stain tested based on the following parameters (with 95% CIs):

1) GMT at baseline (screening) and post-vaccination on Day 21. Samples with no detectable neutralizing activity at the lowest dilution (1:10) will be assigned a value of 5 for calculation.
2) GMR – the ratio of the post-vaccination GMT on Day 21 to the baseline (Day 0) value.

3) 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 on Day 21 in post-vaccination titer relative to baseline.

Percentages of subjects with immune response will be calculated along the corresponding two-sided exact (Clopper-Pearson) binomial CIs. GMTs will be summarized by treatment group and visit day along with the corresponding two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. Two-sided 95% CIs for the difference in proportions of participants demonstrating SCR and SPR between a Tri-NIV group and the Fluzone HD group will be based on the Newcombe hybrid score (METHOD = SCORE riskdiff-option for PROC FREQ in SAS). The within-group geometric mean ratio (GMRpost/pre) will be conducted using paired t-test based on log transformed value. Then, the mean difference and the corresponding 95% CI limits will be exponentiated to obtain the GMT ratio and the corresponding CI.

Reverse cumulative distribution displays of HAI and MN titers for each virus strain will be produced in which Day 0 and Day 21 distributions will be displayed separately by treatment group. Titers reported below the lowest 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).

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.

1 INTRODUCTION

1.1 Influenza Virus

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

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

1.2 Influenza Disease Burden in Older Adults

Older adults are at the greatest risk of hospitalization and death due to influenza infection [CDC 2017 -b]. A retrospective study of 3 managed-care organizations during 1996 to 1997 through 1999 to 2000 estimated that the incidence rate of hospitalization during influenza season among people ≥ 65 years of age with underlying high-risk conditions was 55.6 pneumonia and influenza-associated hospitalizations per 10,000 persons, compared with 18.7 per 10,000 among lower-risk people of the same age group. Older adults between the ages of 50 to 64 with underlying conditions were also at increased risk for hospitalization during influenza seasons (12.3 per 10,000), compared with healthy older adults (1.8 per 10,000) [Mullooly 2007]. Between the years 1976 to 2007, approximately 21,098 older adults (≥ 65 years) were estimated to have died annually due to an influenza-related cause, corresponding to 90% of estimated annual average influenza-related mortality across all age groups [CDC 2010]. Data from modeling analyses of population-based surveillance covering 2010 to 2011 through 2012 to 2013 influenza seasons suggests that 71 to 85% of all influenza-related deaths occurred in adults ≥ 65 years of age [Reed 2015, Grohskopf 2016].

1.3 Licensed Vaccines Against Influenza Virus for Older Adults

Vaccination is the cornerstone of influenza control, particularly for high-risk individuals older than 65 years, immunocompromised patients, and young children; and offers the most cost-effective approach to reduce the morbidity, mortality, and economic burden associated with influenza infection [Paules 2017]. To date, 6 quadrivalent inactivated or recombinant influenza vaccines, consisting of 2 A virus strains (A/H3N2 and A/H1N1) and strains of both B lineages, are licensed for sale in the U.S. [FDA 2017, CDC 2017a]. Nine (9) trivalent inactivated or recombinant influenza vaccines are also approved in the US, including 1 vaccine available in 3 trivalent formulations (high-dose, standard trivalent, and intradermal). Live attenuated vaccines have been excluded from the preceding counts as they are not approved for persons over 49 years of age.

Of all currently-licensed vaccines, 2 are specifically approved for use in older adults, and include a high-dose (ie, Fluzone® High-Dose initially approved in the US in 2009) and an adjuvanted (ie, FLUAD™ initially approved in the US in 2015) trivalent inactivated influenza vaccine [CDC 2017a]. Although Fluzone High-Dose (Fluzone HD) has reported an increased relative vaccine efficacy of approximately 24% in the older adult population compared with standard dose Fluzone [DiazGranados 2014, Monto 2017], efficacy rates reported in older adults have remained quite variable season-to-season since the approval of Fluzone HD in 2009 ranging anywhere from -5.8% to 45% from 2009 to 2016 [Griffin 2011, Treanor 2012, Ohmit 2014, Reed 2014, McLean 2015, Flannery 2016, Zimmerman 2016, CDC 2017]. This variability is likely, in part, due to antigenic drift or mismatch between circulating and vaccine influenza strains leading to reduced effectiveness of seasonal influenza vaccines. For example, Fluzone HD was ~36% more effective in reducing mortality in 2012-13 compared with ~2.5% in 2013-14 due to the increase in the circulation of A(H3N2) strains known to be associated with higher mortality in the elderly [Shay 2017]. There are currently no randomized studies comparing FLUAD with Fluzone HD [CDC 2017b]. Thus, there remains a significant need for influenza vaccines with improved efficacy, and, in particular, the capacity to buffer the consequences of antigenic drift occurring between strain selection and circulation of the virus. This is particularly true in the older adult population, which remains vulnerable to serious complications, including death, resulting from influenza infection. Accordingly, a vaccine with both strong homologous hemagglutination inhibiting (HAI) and broadly neutralizing antibody responses, which might address drifted strains, could be of added value and could help meet the unmet medical need in older adults. Generally, for all influenza vaccines, a hemagglutination inhibition (HAI) titer $\geq$ 1: 40 has been associated with protection from influenza illness [Hobson 1972].

1.4 Nanoparticle Influenza Vaccine, Trivalent (Tri-NIV)

Novavax's Tri-NIV is based on purified, recombinant, full-length HA that self-assembles into distinct nanoparticle structures of approximately 20 to 40 nm. A baculovirus/*Spodoptera frugiperda* (Sf9) insect cell system is used to clone and express recombinant influenza HAs from influenza strains recommended for the 2017 - 18 Northern Hemisphere influenza season: A/Michigan/45/2015 (H1N1); A/HongKong/4801/2014 (H3N2); and B/Brisbane/60/2008 [WHO 2017]. Sf9 insect cells produce recombinant, uncleaved, glycosylated HAs that

assemble into homo-oligomers as trimers. When purified, HA trimers form higher order structures composed of 2 to 9 or more trimers per nanoparticle.

1.5 Matrix-M1 Adjuvant

Adjuvants are compounds which, when combined with a specific vaccine antigen, serve to increase the immune response to the vaccine. In general, adjuvants work by engaging one or more components of the innate immune system, a system that provides a rapid response to infection or tissue damage based on recognition of molecular structures common to large groups of microbial pathogens [Coffman 2010]. Thus, adjuvants may both quantitatively increase the antibody response and also qualitatively broaden its specificity. In addition, some adjuvants may modulate the cellular immune response.

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

1.6 Nonclinical Investigations

1.6.1 Matrix-M1-adjuvanted Tri-NIV

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

Additionally, a good laboratory practices (GLP)-compliant repeat-dose toxicology study was conducted in New Zealand White (NZW) rabbits investigating the safety and immunogenicity of a total dose of 60 µg Tri-NIV (30 µg each of A/Switzerland/9715293/2013 and

B/Brisbane/60/2008 [in addition to A/Anhui/1/2013 neuraminidase and RSV F protein, which are not present in the current candidate]). Tri-NIV was administered to animals on Days 1 and 15, alone or with Matrix-M1 adjuvant. Results showed no adverse effects on mortality, physical examinations, cageside observations, dermal Draize observations, body weights, body weight changes, food consumption, body temperatures, ophthalmology, clinical chemistry, hematology, gross pathology, or histopathology, with robust influenza-specific responses observed among actively-immunized animals, when compared to placebo. A complete description of the non-clinical development and datasets for Tri-NIV may be found in the Investigators' Brochure.

1.6.2 Other Matrix-M1-adjuvanted Vaccines

The totality of the GLP-compliant toxicology data obtained in animal studies to evaluate Matrix-M1 alone, or when co-administered with multiple different antigens (including egg-derived influenza antigens, recombinant-produced influenza hemagglutinin and neuraminidase, recombinant HSV-2 proteins, *Plasmodium falciparum* circumsporozoite protein sequences, RSV F antigen, and Ebolavirus glycoprotein) has failed to demonstrate overt systemic or organ-specific toxicities; and treatments overall, were generally well-tolerated. Transient and inconsistent reductions in body weight and red cell mass parameters, as well as temperature elevations, were noted in adjuvanted vaccine recipients in some studies, but these findings either resolved completely or tended to resolution following the recovery period. Local injection site inflammation and regional lymph node hyperplasia consistent with active immunization were present in acute necropsies, but again showed resolution at recovery time-points. Vaccines adjuvanted with Matrix-M1 demonstrated immune responses to vaccine antigens, substantiating active treatment and responsiveness to the test articles. A summary of the non-clinical experience with Matrix-M1 is available in the Matrix-M Adjuvant Safety Data Supplement (Version 3.0).

1.7 Clinical Investigations

1.7.1 Matrix-M1-adjuvanted Vaccines

Matrix-M adjuvant, in 1 of 2 formulations (ie, Matrix-M1 and Matrix-M2), has been administered with a variety of vaccine antigens to 1,433 human subjects in a total of 14 clinical trials in the US, Europe, and Australia; 9 are completed and 5 are ongoing, and may or may not have unblinded data available. A total of 896 subjects have received vaccines containing the Matrix-M1 adjuvant (proposed for use in this trial) and 537 subjects have received vaccines containing Matrix-M2 adjuvant. Among all 14 studies, no reported serious adverse events (SAE) have been classified as related to exposure to the Matrix-M adjuvant.

Please refer to the Matrix-M Adjuvant Safety Data Supplement (Version 3.0) for detailed summaries of the clinical experience with Matrix-M1-adjuvanted vaccines.

1.8 Trial Rationale

The influenza virus poses a formidable risk of infection to older adults. Based on estimates by the Centers for Disease Control and Prevention (CDC), in the US alone, up to 85% of all

influenza-related deaths and 70% of all influenza-related hospitalizations occur in people 65 years of age or older [CDC 2017b]. Novavax, Inc. has developed an insect cell-derived, egg-free, influenza vaccine (Tri-NIV) based on recombinant hemagglutinin (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, the trivalent nanoparticle candidate administered with Matrix-M1 adjuvant elicited rapid and robust immune responses in terms of geometric mean hemagglutinin inhibition (HAI) titers, with responses exceeding those induced by Fluzone HD. Secondly, geometric mean 50% microneutralizing (MN) titers against a broad panel of historic H3N2 strains tested, dating to 1999 and spanning a number of clinically-signficant antigenic drift events, showed 2 to 214-fold higher titers among animals given Tri-NIV with Matrix-M1 adjuvant than among animals given Fluzone HD. These data suggest that Tri-NIV may elicit antibodies to broadly-neutralizing epitopes capable of providing greater drift strain protection, even against strains such as A/HongKong/4801/2014, which are associated with impaired influenza vaccine efficacy in humans. 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 in Tri-NIV 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 1400 humans exposed to date, is proposed as the adjuvant of choice.

1.9 Expected Risks from Tri-NIV with Matrix-M1 Adjuvant

This proposed trial will be the first human exposure to Tri-NIV with Matrix-M1 adjuvant. Expected risks of vaccination with Tri-NIV in combination with Matrix-M1 adjuvant can be extrapolated from older adult studies of Novavax's respiratory syncytial virus fusion protein (RSV F) nanoparticle vaccine, which is manufactured using the same baculovirus/Sf9 insect cell system technology used to produce Tri-NIV.

The first of these studies was a Phase 3 trial of a high dose of an unadjuvanted RSV F nanoparticle antigen (135 µg) given to a total of 5,921 older adult subjects, conducted from 07 November 2015 to 23 November 2016. An additional 5,935 older adult subjects received placebo. The safety profile of active vaccinees was not remarkably different from that of placebo subjects. Similar proportions of active and placebo subjects reported an adverse event (AE) relating to short-term reactogenicity of trial treatment (ie, 25 and 22%, respectively). About 1 to 2% of subjects from each group described these events as severe, which included injection site pain, bruising, redness, and swelling, as well as severe headache, fatigue, muscle pain, diarrhea, joint pain, chills, nausea, vomiting, and fever. Only 2 (out of 5,921 total) active subjects reported severe fever (ie, oral temperature of > 38.9°C). Similar proportions of active and placebo subjects also reported unsolicited adverse events (ie, 58 and 57%, respectively). Among these, 6 and 7% of placebo and active subjects, respectively, experienced an AE considered related to trial treatment. Commonly-reported (> 5 subjects per group) related AEs included upper respiratory tract infection, bronchitis, sinusitis, arthralgia, pain in extremity, myalgia, blood pressure systolic increased, blood pressure increased, blood pressure diastolic increased, cough, rhinorrhea, oropharyngeal pain, nasal congestion, sneezing, sinus congestion, diarrhea, nausea, headache, dizziness, fatigue, pyrexia, chills, pain, injection site bruising, injection site pruritus, injection site pain, injection site erythema, hypertension, rash, and pruritus.

While most AEs were mild to moderate in nature, about 0.4% placebo and 0.7% active subjects reported a severe AE considered related to the treatment. Severe and related AEs reported by more than 1 trial subject included increase in blood pressure (13 active subjects and 8 placebo), including systolic (13 active subjects and 9 placebo) and diastolic (3 active subjects and 3 placebo); and headache (2 active subjects and 0 placebo). About 9% of subjects in each group reported a serious adverse event (SAE). SAEs considered by the investigator to be related to treatment included acute myocardial infarction (1 active subject), cardiac failure congestive (1 active subject), transient ischemic attack (1 active subject), and large intestine stenosis and

diverticulitis (1 placebo subject). Novavax accepted the trial investigator's assessment of these SAEs with caution, given that all SAEs could readily be explained by the subject's medical history and/or natural disease progression in the general older adult population. No differences were noted in active or placebo subjects' tendency to seek medical care.

The second trial is an ongoing Phase 2 older adult trial of low and high doses of the RSV F nanoparticle antigen (ie, 35, 65, 95, 120, and 135 µg), given with or without 50 µg Matrix-M1 adjuvant or an aluminum adjuvant, either as a 1-dose or 2-dose regimen on Days 0 and 21, with the goal of identifying a vaccine formulation and regimen that would maximize the immunogenicity of the antigen. A total of 149 subjects received the RSV F antigen with Matrix-M1 adjuvant; 99 subjects received RSV F antigen with aluminum; 25 subjects received placebo; and 26 subjects received 135 µg of unadjuvanted RSV F antigen.

Safety data from an interim unblinding at 3 months into the trial revealed that all formulations of the RSV F nanoparticle antigen, with or without Matrix-M1 adjuvant or the aluminum adjuvant, were well-tolerated among subjects. More subjects reported an AE among Matrix-M1-adjuvanted vaccinees (65 to 100%), than among aluminum-adjuvanted vaccinees (50 to 76%), unadjuvanted vaccinees (77%), or placebo recipients (56%). As was expected, short-term reactogenicty among 2-dose Matrix-M1-adjuvanted vaccinees was increased when compared to reactogenicity among 1-dose Matrix-M1-adjuvanted vaccinees (70 to 80% vs. 40 to 60% of vaccines, respectively), and was consistently higher than subjects that received the unadjuvanted RSV F antigen (27%) and those that received placebo (36%). The proportions of subjects with severe solicited AEs among 2-dose Matrix-M1-adjuvanted vaccinees was higher (0 to 13% of subjects [ie, 6 subjects]), when compared to 1-dose Matrix-M1-adjuvanted vaccinees (0 to 4% [ie, 1 subject]), and placebo recipients (0%). An antigen-dose response in terms of severe solicited AEs was present among Matrix-M1-adjuvanted vaccinees, where subjects that received 65 or 135 µg RSV F antigen appeared to experience more severe AEs than subjects that received 35 µg, regardless of whether they received 1 or 2 doses of trial treatment. Notably, all the described short-term reactogenicity events were transient.

The reported incidence of unsolicited AEs was similar across treatment groups, ie, 46 to 68% of aluminum-adjuvanted vaccinees, 46 to 88% of Matrix-M1-adjuvanted vaccinees, 65% unadjuvanted vaccinees, compared to 48% placebo. AEs considered related to treatment were reported by 8 to 40% of Matrix-M1-adjuvanted vaccinees, 8 to 36% of aluminum-adjuvanted vaccinees, 27% unadjuvanted vaccinees, and 12% placebo subjects. Related AEs reported by >1 Matrix-M1-adjuvanted vaccinee included upper respiratory tract infection, injection site pain, fatigue, injection site reaction, injection site erythema, muscle spasms, blood urea increased, and oropharyngeal pain.

Severe and treatment-related unsolicited AEs were reported in only 3 subjects (none received Matrix-M1), and included pyrexia, lower respiratory tract infection, and skin lesion, and no antigen-dose or Matrix-M1 adjuvant relationship was noted. A total of 8 subjects reported SAEs. These included 4 aluminum-adjuvanted vaccinees and 4 Matrix-M1-adjuvanted vaccinees. None of these SAEs were considered by the investigator as related to the treatment. No relationship between the incidence of significant new medical conditions (SNMCs) or

medically-attended adverse events (MAEs), and receipt of the RSV F antigen with or without Matrix-M1 adjuvant was noted.

1.10 Risks Associated with Fluzone HD

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

A variety of events have been reported in the post-marketing experience with Fluzone and Fluzone HD, but a causal relationship has not been established. Information regarding the post-marketing safety data for Fluzone products is available in the Package Insert, which will be supplied to Investigators. Of note, Fluzone HD is produced in eggs, in common with the majority of inactivated vaccines. Therefore, subjects with known history of severe allergic reaction to any influenza vaccine, or allergy to egg proteins, should not receive Fluzone HD. Additionally, subjects with a history of Guillain-Barré syndrome within 6 weeks of any influenza vaccine should not receive Fluzone HD or be enrolled in this trial (see trial exclusion criteria in Section 5.2).

2 TRIAL OBJECTIVES

2.1 Primary Objectives

- To describe the safety and tolerability of 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.

2.2 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 and/or drifted influenza A strains, and the vaccine-homologous B/Victoria lineage strain, at Day 21 post-dosing.

2.3 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.

3 TRIAL OVERVIEW

3.1 Design

This is a Phase 1/2, randomized, observer-blinded, active-controlled clinical trial. Approximately 330 eligible subjects will be enrolled and randomized into 1 of 3 treatment groups, as shown in 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. 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 as defined in Section 3.1.1.1.

3.1.1 Safety Monitoring of Enrollment and Vaccinations

This will be a first-in-human trial with Tri-NIV formulated with Matrix-M1 adjuvant. Thus, vaccination holding rules will be used to govern progression from the Stage 1 group to full enrollment in Stage 2. Solicited and unsolicited AEs reported from all Stage 1 subjects within 7 days of Day 0 vaccination will be evaluated against vaccination holding rules (3.1.1.1). These AE data will be summarized by the sponsor statistician, reviewed, and provided to an independent medical monitor in aggregate form (without unblinding or subdivision by treatment group). If vaccination holding rules are not met, the independent medical monitor will notify the sponsor Chief Medical Officer (CMO) to proceed with enrollment of subjects. If vaccination holding rules are met, the independent medical monitor will notify the sponsor CMO who will pause enrollment pending further review and request unblinding of the data. The independent medical monitor and the sponsor will review the unblinded data and develop a report and recommendation to either: a) resume enrollment, b) amend the protocol and resume enrollment, or c) terminate the protocol. The report, the recommendation, and the amended protocol and

ICF (if relevant), will be provided to the IRB and CBER, and enrollment will not recommence until IRB approval is obtained.

3.1.1.1 Vaccination Holding Rules

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

1) The occurrence of at least 1 serious adverse event among any Stage 1 subject assessed by the sponsor as definitely related to the trial treatment.

2) The occurrence of any severe (grade 3) solicited (local or systemic) adverse event term in > 10% of all Stage 1 subjects.

If vaccination holding rules are met at any review point, the independent medical monitor will:

1) Review a summary of all individual data of the relevant subject(s), including the unblinded treatment assignment, and summary safety data relative to all treatment groups; and

2) If there exists any imbalance that is higher in one of the two Tri-NIV treatment groups compared to the Fluzone HD group, review a detailed accounting from the investigator(s) as to the exact nature of the clinical symptoms or physical findings in the subject(s) triggering the holding rule, including any potential causation and evidence of resolution with or without treatment.

3.1.1.2 Ongoing Evaluation

In addition to the above vaccination holding rules after Stage 1, enrollment and vaccination will be suspended pending discussion with CBER and the IRB in the event of:

1) Any tabulation of solicited adverse events (to be repeated approximately weekly during active enrollment) which demonstrates the occurrence of any severe (grade 3) solicited (local or systemic) adverse event term in > 10% of all subjects (note that unmonitored data will perforce be used for this tabulation), or

2) The occurrence of at least 1 serious adverse event in any subject assessed by the sponsor as definitely related to the trial treatment.

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.

3.2 Trial Endpoints

3.2.1 Primary Endpoints

- Number and percentage (95% confidence intervals [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. Note: The 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose before or after day 21, or no rescue dose, are detailed in the statistical analysis plan.
- 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 at Day 0 pre-dosing and Day 21 post-dosing . 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.

3.2.2 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 at Day 0 pre-dosing and Day 21 post-dosing. 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 virus 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.

3.2.3 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.

3.3 Randomization and Blinding Procedure

Subject randomization will be conducted using an Interactive Web Randomization System (IWRS). Stratification will be by age (60 to < 75 and ≥ 75 years), gender, and history of receipt of 2016 - 17 influenza vaccine. Proportions of subjects in the various strata will not be pre-specified; rather, the goal will be to achieve an approximately equal distribution of subjects with these characteristics across the various treatment groups.

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

3.4 Maintaining the Blinded Randomization Scheme

Randomization procedures will be performed by IWRS, with treatment assignments known only to the responsible unblinded vaccine administrators at the trial center. Subjects and the main trial team clinical staff will remain blinded for the duration of the trial unless emergency unblinding is necessary. Refer to Section 3.5 for information regarding the process for emergency unblinding.

All treatment assignments, vaccine storage and accountability, and/or dosing-related matters will be monitored by a designated “unblinded monitor”. Any deviations will be discussed, documented, and resolved by the unblinded monitor and the unblinded site personnel. Reports provided by the unblinded monitor will be reviewed by designated unblinded personnel at either

Novavax or the clinical research organization (CRO), not involved with the main trial team. No reports from the unblinded monitor will be released to the Trial Master File (TMF) until database lock for Day 364 and official declaration of unblinding is given by Novavax.

3.5 Procedure for Unblinding Individual Subjects During the Trial

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

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

If unblinding of an individual subject is deemed necessary, the unblinded staff member shall obtain subject dose details from the IWRS. The date and time of breaking the blind as well as the reason must be recorded and placed in the Pharmacy Binder by unblinded staff. The individual subject dose details should be revealed only in case of an emergency where further treatment of the subject is dependent on knowing the investigational product he/she has received. The investigator should not otherwise divulge the subject's treatment assignment to site staff, and should provide the information only to those individuals involved in the direct care of the subject. The date and reasons for breaking the blind must be submitted to the Medical Monitor within 24 hours.

3.6 Trial Duration

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

4 TRIAL TEST ARTICLES

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

4.1 Overview of Product and Manufacturing Process for Clinical Trial Material

Tri-NIV is based on purified, recombinant full-length HA that self-assembles into distinct nanoparticle structures of approximately 20 to 40 nm. The baculovirus/Sf9 insect cell system was used to clone and express recombinant influenza HAs from the influenza strains recommended for the 2017-18 Northern Hemisphere influenza season: A/Michigan/45/2015 (H1N1); A/HongKong/4801/2014 (H3N2); and B/Brisbane/60/2008 [WHO 2017]. In Sf9 insect cells, recombinant, uncleaved HAs are produced that are glycosylated and assemble into homo-oligomers as trimers. Purified, HA trimers form higher order structures composed of 2 to 9 or more trimers per nanoparticle.

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

4.2 Manufacture of Bulk Antigen

4.2.1 Recombinant Baculovirus

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

4.2.2 Production and Purification of Tri-NIV

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

selectively binds the glycosylated protein. After washing, the HA protein is eluted from the column with buffer containing methyl-α-D-mannopyranoside (MMP) and polysorbate 80 (PS80). Eluted fractions are processed by tangential flow filtration, to concentrate the HA product and exchange it into the final formulation buffer. The product is then diluted to a final formulation containing sodium phosphate and PS80, and then filtered (0.22 μm) to produce bulk drug substance that is clear and colorless, and contains no preservatives. Each HA bulk drug substance is stored at ≤ -60°C until the 3 strains are mixed and diluted to the target concentration with buffer, and filled as drug product. The final composition of the drug product formulation is 25 mM sodium phosphate, 150 mM sodium chloride, 100 mM arginine hydrochloride, 5% w/v trehalose, and 0.03% w/v PS80, pH 7.5.

4.2.3 Manufacture of Matrix-M1 Adjuvant

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

4.3 Description of Clinical Trial Dosage Formulation

The HA protein content in each purified bulk drug substance is measured and the 3 HA drug substances are mixed and diluted to the target concentration specified in the protocol in 25 mM sodium phosphate, 150 mM sodium chloride, 100 mM arginine hydrochloride, 5% w/v trehalose, and 0.03% w/v PS80, pH 7.5. The formulated drug product for Tri-NIV is then filled into 2R single-use glass vials.

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

A simple in-clinic mixing strategy will be developed which allows administration of the target doses by the addition of Matrix-M1 in integral multiples of 0.1 mL to the Tri-NIV antigen, followed by mixing, then withdrawal and injection of 0.3 or 0.8 mL volumes intramuscularly into subjects. The Pharmacy Manual will provide detailed mixing instructions for the unblinded pharmacist.

4.4 Placebo

Sterile saline will be used as placebo for subjects in Group C for their Day 21 injection (supplied in a single-dose vial at a concentration of 9 mg/mL in a 2 mL volume by VWR International).

4.5 Fluzone HD – Active Comparator

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

4.6 Investigational Product Packaging, Storage, and Handling

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

4.7 Compliance and Drug Accountability

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

5 SELECTION OF TRIAL SUBJECTS

5.1 Inclusion Criteria

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

1) Healthy adult male or female, ≥ 60 years of age,

2) Willing and able to give informed consent prior to trial enrollment, and

3) Able to attend trial visits, comply with trial requirements, and provide reliable and complete reports of adverse events.

5.2 Exclusion Criteria

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

1) Any ongoing, symptomatic acute or chronic illness requiring medical or surgical care.
   - Asymptomatic chronic conditions or findings (eg, mild hypertension, dyslipidemia) that are not associated with evidence of end-organ damage are not exclusionary provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time-course of this trial) in the opinion of the investigator.
   - Acute or chronic illnesses or conditions which may be reasonably predicted to become symptomatic if treatment were withdrawn or interrupted are exclusionary, even if stable.
   - Acute or chronic illnesses reasonably expected to be associated with increased risks in the event of influenza infection (eg, cardio-pulmonary diseases, diabetes mellitus, renal or hepatic dysfunction, hemoglobinopathies) are exclusionary, even if stable.
   - Note that illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (see exclusion criteria 2, 5, 8, 9).
2) Participation in research involving investigational product (drug / biologic / device) within 45 days before planned date of first injection.
3) History of a serious reaction to prior influenza vaccination, or known allergy to constituents of influenza vaccines - including egg proteins - or polysorbate 80.
4) History of Guillain-Barré Syndrome (GBS) within 6 weeks following a previous influenza vaccine.
5) Receipt of any vaccine in the 4 weeks preceding the trial vaccination and any influenza vaccine within 6 months preceding the trial vaccination.
6) Any known or suspected immunosuppressive illness, congenital or acquired, based on medical history and/or physical examination.
7) Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the trial vaccine. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose

≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

8) Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the trial vaccine or during the trial.

9) Acute disease at the time of enrollment (defined as the presence of a moderate or severe illness with or without fever, or an oral temperature > 38.0°C, on the planned day of vaccine administration).

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

11) Known disturbance of coagulation.

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

6 TRIAL ASSESSMENTS AND PROCEDURES

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

6.1 Trial Visit Procedures

6.1.1 Day 0 – Screening Visit

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

- Written informed consent will be obtained in conformance with Section 11.3 of this protocol.
- Inclusion and exclusion criteria review consistent with Section 5.
- Review of medical history, including influenza vaccination history in the previous 3 years (with emphasis on 2016 - 17 vaccine) and history of adverse reactions to prior influenza vaccines and allergies.
- Medication history, including concomitant medications and vaccines within the last year.
- Physical examination including the head, eyes, ears, nose, and throat (HEENT), abdomen, extremities, and at least inguinal, cervical, and axillary nodes, gross motor function, and skin; vital signs (heart rate, blood pressure, respiratory rate, and oral temperature), height, and weight.

Note that further procedures may be performed at the investigator's discretion in order to adequately screen subjects against eligibility criteria and/or to confirm medical history. Potential subjects who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled.

6.1.2 Day 0 – Injection 1 Visit

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

- Blood draw for baseline immunogenicity testing (20 mL, see Section 7.2) and clinical safety assessments (10 mL).
- Randomization to a treatment group.
- Alcohol swab cleansing of the injection site followed by IM injection into the non-dominant deltoid of the assigned trial treatment. *Note that if only the dominant deltoid is available for the injection, it is acceptable to inject the assigned trial treatment into the dominant deltoid.*
- Monitoring for any AEs for 30 - 60 minutes) following vaccination.
- Post-injection vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature) at 30 - 60 minutes following vaccination.
- Distribution of the subject diary, thermometer, and a measuring tool to facilitate documentation of any AEs (solicited and unsolicited), concomitant medications, physicians visits, or hospitalizations, occurring from the time of discharge from the trial clinic on Day 0 through Day 6 (inclusive). Subjects will also be instructed to call the trial clinic for any

grade 3 (severe) solicited or unsolicited health events, and/or health status changes of concern to the subject.

- Schedule the Days 3 telephone contact, Day 7 follow-up visit (Stage 1 ONLY) or Day 7 telephone contact (Stage 2 ONLY), and Day 21 in-clinic visit before subjects may be dismissed from the clinic.

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

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

6.1.4 Day 7 (+1 day) – Safety Follow-up Visit for (Stage 1 Subjects ONLY)

All Stage 1 subjects will return to the clinic on approximately Day 7 for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Review and collection of subject diary.
- Interval history to query for any unsolicited AEs, including MAEs, SNMCs, or SAEs, occurring since the last trial visit, and any concomitant medications taken. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- Schedule the Day 21 visit.

6.1.5 Day 7 (± 1 day) – Safety Telephone Contact (Stage 2 Subjects ONLY)

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

6.1.6 Day 21 (± 2 days) – Injection 2 Visit

All subjects will return to the clinic on approximately Day 21 for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Review and collection of subject diary (Stage 2 subjects ONLY).
- Interval history to query for any unsolicited AEs, including MAEs, SNMCs, or SAEs, occurring since the last trial visit, and any concomitant medications taken. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- Blood draw for immunogenicity assessments (20 mL) and clinical safety assessments (10 mL).

- Alcohol swab cleansing of the injection site followed by IM injection into the dominant deltoid of a licensed seasonal influenza vaccine (using the manufacturer's instructions) for Group A and B subjects only, and of saline placebo for Group C subjects only. *Note that if only the non-dominant deltoid is available for the injection, it is acceptable to inject the assigned trial treatment into the non-dominant deltoid. 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.*
- Monitoring for any AEs for 30 - 60 minutes following vaccination.
- Post-injection vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature) at 30 - 60 minutes following vaccination.
- Schedule the Day 56 visit.

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

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

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

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

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

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

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

- Vital sign collection (heart rate, blood pressure, respiratory rate, and oral temperature).
- Interval history to query for any MAEs, SNMCs, or SAEs occurring since the last telephone contact, and any concomitant medications taken for these events. A directed physical examination may be performed at the investigator's discretion to evaluate any AEs.
- Schedule the Day 273 telephone contact and the end of the trial visit (Day 364) in-clinic visit.

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

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

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

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

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

6.2 Unscheduled Visits

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

6.3 Concomitant Therapy

Subjects may receive all concomitant medications and procedures deemed necessary to provide adequate healthcare during the trial, with the exception of those specified in the exclusion criteria. Routine medical standards of care are permitted, including vaccines needed for emergent indications (eg, tetanus booster in response to a penetrating injury). Routine (ie, non-emergent) vaccinations are permitted for all subjects after completion of the Day 21 trial visit.

Concomitant medications, procedures, and hospitalizations will be recorded throughout the trial including the period from the day informed consent is obtained through the end of trial follow-up. All new or changed concomitant medications taken through Day 21 will be recorded; thereafter, only concomitant medications taken for MAEs, SNMCs, or SAEs will be recorded. The investigator will document the reason for use of the concomitant medication.

6.4 Declining Trial Treatments or Procedures

Subjects have the right to decline trial treatment or other trial procedures for any reason at any time during the trial. This trial contemplates 2 injections containing either Tri-NIV with Matrix-M1 adjuvant, Fluzone HD, or saline placebo. Refusal of the investigational test article on Day 0 constitutes trial withdrawal without exposure, and no further follow-up is required. If a subject declines trial procedures subsequent to receipt of the investigational product, it should be recorded as a protocol deviation and the reason should be clearly documented in the source

document. The subject will be asked to complete all other trial procedures as applicable. If the subject does not wish to remain in the trial, the subject can choose to withdraw consent and discontinue at any time as outlined in Section 6.5.

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

6.5 Premature Discontinuation from Trial

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

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

In the event of early termination, investigators will make every reasonable effort to perform trial completion procedures. Trial completion procedures will include a query for any MAEs, SNMCs, or SAEs occurring since the last trial visit, and any concomitant medications taken to treat these events, as well as a blood draw for serology testing (20 mL) and clinical safety laboratory testing (10 mL) if prior to the Day 21 trial visit. Subjects that terminate from the trial early will not be replaced.

6.6 Protocol Deviations

A protocol deviation (PD) will be defined as a failure to comply with the requirements set forth in the protocol. While the majority of PDs will be self-reported by the clinical sites in the electronic case report form (eCRF), in certain instances PDs may also be determined programmatically through the course of the trial. Examples of both types of PDs are provided in Table 2.

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

Table 2: Protocol Deviations

Self-reported PDs	Programmatically-determined PDs
Other[1]	Diary Compliance

[1] PDs that do not belong under any pre-specified category will be categorized as "Other" using an open-text field.

6.7 Trial Termination

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

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

7 TRIAL LABORATORY REQUIREMENTS

Appendix 3 specifies the maximum amount of blood (up to 60 mL) to be drawn for safety laboratory assessments and immunogenicity laboratory assessments to be completed throughout the trial.

7.1 Clinical Laboratory Testing

The following laboratory tests will be performed by a qualified central laboratory designated by Novavax on blood samples collected from subjects on Days 0 and 21.

- Serum chemistry – alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), creatinine, and blood urea nitrogen (BUN).

  Hematology – complete blood count (CBC) with hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, and white blood cell (WBC) count with differential.

7.2 Serological Assessments of Immunogenicity

Immunogenicity assessments will be made on subject sera collected on Days 0 and 21. The primary measure of immunogenicity for the trial is HAI titers specific for the HA receptor binding domains of each of the virus strains included in Tri-NIV. The secondary and /exploratory variables of immunogenicity include HAI titers specific for the HA receptor binding domains of at least 2 historic A virus strains (one H1N1 and one H3N2), and a representative of the B/Yamagata lineage; and neutralizing antibody titers specific for the virus strains included in Tri-NIV and the Fluzone HD comparator, as well as selected historical strains and a B/Yamagata strain. In addition, exploratory measures of immunogenicity also include antibodies competitive with broadly-neutralizing monoclonal antibodies to HA of varying specificities, as measured by competitive-binding in a biosensor assay.

7.2.1 Hemagglutination Inhibition (HAI) Assay (Q^2 Solutions and Other HAI Laboratories)

Hemagglutination inhibition testing will be conducted by Q^2 Solutions using thawed frozen subject serum samples in a standardized and validated method with virus antigens produced in embryonated chicken eggs. Sera will be first treated to remove non-specific inhibitors of hemagglutination and then plated onto a microtiter well, starting with an initial dilution of 1:10 and followed by a series of 2-fold dilutions. The appropriate virus antigen and indicator erythrocyte suspension will be added to designated wells in 2 steps, with mixing and incubation at each step. The titration end-point will be taken as the highest dilution that demonstrates complete inhibition (100%) of hemagglutination. The serum HAI titer will be the geometric mean of triplicate test results. Based on new findings in a recent investigation concerning egg passage-induced point mutations in contemporary A(H3N2) strains [Zost 2017], testing (for at least H3N2 strains) will also be performed in a qualified assay using hemagglutinating antigens produced by recombinant methods capable of generating HA with and without specific egg-induced mutations.

7.2.2 Microneutralization Assay (Novavax)

The influenza virus microneutralization assay will be based on the WHO manual for the laboratory diagnosis and virological surveillance of influenza, with minor modifications [WHO 2011]. Briefly, subject test sera will be treated with receptor-destroying enzyme (RDE) and heat-inactivated at 56°C for 30 minutes. Sera will be prepared in 2-fold serial dilutions (starting from 1:10) in duplicates, in 96-well plates. Positive and negative virus controls and anti-influenza serum standards will also be included. An approximate tissue culture infective dose of 100 $TCID_{50}$ will be added and incubated for 60 minutes at 37°C ± 2°C in 5.0% ± 1% CO_2. After incubation, 100 µL of trypsinized MDCK cells at a concentration of 1.5 x 10^5/mL will be added to each well and incubated for 18 to 22 hours at 37°C ± 2°C in 5.0% ± 1% CO_2. On Day 2, plates will be fixed, blocked, and incubated with anti-influenza A nucleoprotein (NP) monoclonal antibody pool (1:1 of MAB8257 and MAB8258, Millipore Billerica, MA), followed by washing and incubation with a peroxidase-conjugated goat anti-mouse IgG (Kirkegaard and Perry Laboratories, Gaithersburg, MD). Finally, plates will be washed and incubated with 3,3',5,5'-tetramethylbenzidine substrate (Sigma) and the optical density (OD) will be read after adding the stop solution. A 4-parameter fit (SoftMax Pro software) will use the following equation to determine the OD value at which 50% of the MDCK cells are infected:

X = [(average OD of virus control wells) – (average OD of cell control wells)] / 2

All values ≤ X will be deemed positive for neutralization activity.

7.2.3 Biosensor Competitive-binding Assay (Novavax)

A surface plasmon resonance (SPR) assay to evaluate subject serum antibodies competitive with known broadly-neutralizing monoclonal antibodies is under development by Novavax, Inc. Biosensor surfaces will be loaded with the different HA nanoparticles Subject serum samples (diluted to sub-saturating antibody concentrations) for Day 0 and 21 will be reacted with the immobilized HA to capture anti-HA antibody. Broadly-neutralizing monoclonal antibodies (mAb) will then be reacted with the immobilized HA:anti-HA antibody sensors. The presence of broadly-neutralizing antibodies in subject sera will be determined by quantitating the amount of mAb competition.

7.3 Retention and Use of Archived Specimens

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

8 TRIAL ASSESSMENT OF SAFETY

8.1 Adverse Events

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

Data concerning all classes of adverse events will be collected at scheduled visits from the time informed consent is obtained through 21 days post-injection. Note: The 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose before or after day 21, or no rescue dose, are detailed in the statistical analysis plan.. After these specified days, data concerning MAEs, SNMCs, and SAEs will be collected (see Sections 8.1.5 and 8.2 for details of these AEs), as well as additional information regarding outcomes/resolutions of AEs reported prior that had no stop date recorded. In addition to the scheduled visits, subjects will be instructed to notify the investigator and/or return to the clinic if any severe AE (solicited or otherwise) or event fulfilling the definition of an SAE occurs at any time following vaccination. If at a scheduled or unscheduled visit, symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected. Adverse events will be recorded as observed by the investigator, designated personnel, or as provided by the subject on the diary card or during the in-person visit. Full details of the AE (ie, nature, date of onset, and recovery, as well as an assessment of severity, relationship to trial treatment [unsolicited events only], seriousness, treatment, and outcome) will be recorded in the source documentation and captured in the eCRF, and will generally require the investigator(s) causality assessment, except as discussed below.

8.1.1 Solicited Adverse Events/Subject Diary

Subjects will be provided with a diary for the documentation of any AEs, daily recording of their body temperature and certain common post-vaccination symptoms, and concomitant medications and procedures starting on vaccination day and for six days following the Day 0 vaccination (ie, from Day 0 through Day 6, inclusive). A series of local injection site and systemic reactions that are reasonably likely to occur in vaccine programs (Table 3) will be solicited daily in the diary and standardized severity grades offered to the subject. Subjects will report injection site events occurring on the deltoid where the test article was administered. A standard tool for the measurement of visible local reactions will be provided (see example provided in Appendix 4) as will a digital oral thermometer. Subjects will also be asked to record any physician visits or hospitalizations, and any unsolicited AEs experienced during Day 0

through Day 6. In addition to reporting Grade 3 solicited adverse events in the diary card, subjects should be encouraged to contact the investigator by telephone if these occur. The investigator may request an *ad hoc* clinic visit at his/her judgment, and should enter any Grade 3 solicited adverse events reported by telephone in the solicited AE subject diary promptly, even if the balance of diary data is not yet available.

Table 3: Listing of Diary Solicited Events

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

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

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

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

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

8.1.2 Unsolicited Adverse Events

Any AEs reported spontaneously by subjects will be categorized as unsolicited events and Medical Dictionary for Regulatory Activities (MedDRA) coded by system organ class (SOC)

and preferred term (PT). Solicited events with an onset after the solicitation period will also be classified as unsolicited AEs. Unsolicited events that occur within 7 days following vaccination should also be recorded in the subject diary. If any Grade 3 unsolicited event is reported during this period, subjects should be encouraged to contact the investigator by telephone. The investigator may request an *ad hoc* clinic visit at his/her judgment, and should enter any Grade 3 unsolicited adverse event reported by telephone in the unsolicited AE eCRF promptly, even if the balance of diary data is not yet available. All unsolicited AEs will be assessed for severity (as defined in Section 8.1.2) and for causality (as discussed in Section 8.5), and will be documented in the source documents and captured in the eCRF.

8.1.3 Vital Sign Abnormalities as Adverse Events

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

8.1.4 Clinical Laboratory Findings as AEs

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

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

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

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

8.1.5 Medically-attended Events and Significant New Medical Conditions

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

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

Significant new medical conditions (SNMCs) are adverse events that are new (that is, not present at baseline), clinically significant (meaning that they imply an important change in the subject's long-term health status), and typically chronic (requiring an ongoing change in the subject's medical management). This category is not meant to include minor or transient diagnoses or age-related changes. For example, while new diagnoses of presbyopia or tinea versicolor are chronic conditions, they are not SNMCs because no significant change in health status is implied. Similarly, adverse events which are isolated, treatable events that resolve and do not require chronic therapy are also not SNMCs (examples could include an uncomplicated acute urinary tract infection or a simple fracture resolved with conservative treatment and with no residual disability). In contrast, new diagnoses of rheumatoid arthritis or coronary artery disease are SNMCs because they imply a long-term change in health status and require ongoing medical management. Additionally, because it has been hypothesized that immunizations with or without adjuvant may be associated with autoimmunity, regulatory authorities have requested that Novavax instruct investigators to be especially vigilant regarding the adverse events of special interest (AESI) listed in Table 4. Note that this regulatory request is not specific to Novavax's Tri-NIV or Matrix-M1 adjuvant; and there is no current evidence to suggest that the trial drugs in this protocol are, or are not, associated with these illnesses. The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESIs.

Table 4: Adverse Events of Special Interest

Categories	Diagnoses (as MedDRA® Preferred Terms)
Neuroinflammatory Disorders:	Acute disseminated encephalomyelitis (including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (eg, Bell's palsy), Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis (including Eaton-Lambert syndrome), multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis
Musculoskeletal and Connective Tissue Disorders:	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome
Vasculidities:	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and anti-neutrophil cytoplasmic antibody [ANCA] positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis)
Gastrointestinal Disorders:	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis
Hepatic Disorders:	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis
Renal Disorders:	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulo-nephritis, membranoproliferative glomerulonephritis, and mesangio-proliferative glomerulonephritis
Cardiac Disorders:	Autoimmune myocarditis/cardiomyopathy
Skin Disorders:	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome, rosacea
Hematologic Disorders:	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome

Table 4: Adverse Events of Special Interest

Categories	Diagnoses (as MedDRA® Preferred Terms)
Metabolic Disorders:	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, sarcoidosis, pernicious anemia

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

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

8.2 Serious Adverse Events

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

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

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent 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 an SAE. SAEs are associated with enhanced reporting requirements (see Section 8.3).

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

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

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

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

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

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

8.4 Severity

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

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

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

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

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

Table 5: Definition of Severity Grading for Adverse Events

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

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

Severity Grade	Gastrointestinal Adverse Event			Fever
	Nausea	**Vomiting**	**Diarrhea**	
0 – Normal	No noticeable symptom	No noticeable symptom	No noticeable symptom	< 38.0
1 – Mild	No interference with activity, or 1	No interference with activity, or 1	1 to 3 unformed (loose)	38.0 to 38.4

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

Severity Grade	Gastrointestinal Adverse Event			Fever
	Nausea	**Vomiting**	**Diarrhea**	
	to 2 episodes/ 24-hour period	to 2 episodes/ 24-hour period	stools/24-hour period	
2 – Moderate	Some interference with activity, or > 2 episodes/ 24-hour period	Some interference with activity, or > 2 episodes/ 24-hour period	4 to 5 unformed (loose) stools/24-hour period	38.5 to 38.9
3 – Severe	Prevents daily activity, or requires intravenous hydration	Prevents daily activity, or requires intravenous hydration	≥ 6 loose stools/24-hour period, or requires intravenous hydration	> 38.9

8.5 Relationship (Causality)

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

Table 7: Definition of Relationship for Adverse Events

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

Table 7: Definition of Relationship for Adverse Events

Relationship	Relationship Description
	• Consistent with known actions of the test article or product class; • Cannot be reasonably explained by known characteristics of the subject's clinical state, common intercurrent illnesses, or other treatments administered to the subject. • May be confirmed by rechallenge (if applicable).

9 TRIAL DATA MANAGEMENT

9.1 Recording and Collection of Data

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

9.2 Data Quality Assurance

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

9.3 Monitoring

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

The clinical trial sites will be monitored periodically for database accuracy and completeness, adherence to the protocol, regulatory compliance, safety reporting, clinical trial material accountability, and the maintenance of comprehensive source documents. Where applicable, the database will be checked against applicable source documents to verify completeness and accuracy. When data entry has been completed by the appropriate trial staff, source documents

verified and monitored by Novavax and/or CRO representatives, and reviewed by the investigator, the investigator should sign and date the *Investigator Signature Page*.

9.4 Audit and Inspection

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

9.5 Adherence to and Changes to the Protocol

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

9.6 Retention of Records

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

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

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

PROTOCOL, ETC.) ARE TO BE RETAINED IN A SECURE PLACE AND TREATED AS CONFIDENTIAL MATERIAL.

10 TRIAL STATISTICAL CONSIDERATIONS

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

10.1 Subject Populations

The following subject populations will be used in all analyses:

- Safety Population - Includes all trial subjects that provide consent, are randomized, and receive the test article. The Safety Population will be used for all safety analyses; and will be analyzed as actually treated.
- Per-Protocol Population (PP) - Includes all subjects in the Safety Population that received the assigned dose of the test article according to protocol, have HAI serology results for Day 0 and Day 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.
- 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.

10.2 General

All analysis populations will be defined and full descriptions of each population will be provided. Demographic parameters and other baseline characteristics (age, sex, race, ethnicity, as well as influenza vaccine exposure within the 2016 influenza season) will be summarized by treatment group for all subjects in the safety population, as well as the number and description of protocol deviations.

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

10.3 Demographics and Protocol Compliance

Demographic parameters and other baseline characteristics (eg, age, sex, race, and ethnicity) will be summarized by treatment group for all subjects in the safety population, as well as the number and description of protocol deviations.

10.4 Analyses Addressing Protocol Objectives

10.4.1 Analyses of Primary Objectives

10.4.1.1 Safety

Safety analysis will be descriptive and based on the safety population, defined as all subjects who received a dose of trial treatment. Safety will be summarized overall and by individual treatment arms based on solicited short-term reactogenicity post-injection on Day 0, 21-day all AE profile by MedDRA preferred term, and 1-year MAE, SAE, and SNMC profiles post-injection on Day 0. Note: The 21 day post vaccination all adverse event profile will include all unsolicited AEs reported from test article receipt until the day preceding the rescue dose, ie, events with onset dates between days 0 to 20 for subjects who receive the rescue dose as scheduled on day 21. Rules for defining the dataset in subjects who receive the rescue dose before or after day 21, or no rescue dose, are detailed in the statistical analysis plan. All AEs, MAEs, SAEs, and SNMCs will be tabulated by severity, related (possibly, probably, or definitely vs. non-related per investigator assessment), and severe and related. The number and percentage (with 95% CI) of subjects in each treatment group with a given term will be summarized. Clinical laboratory data will be summarized by means and 95% confidence interval, minima and maxima, at Day 0 and Day 21 in each treatment group, as well as means and 95% confidence interval of change from baseline at Day 21. Changes from baseline will also be summarized at Day 21 for each treatment group in terms of the proportion of subjects with no change in toxicity grade versus proportions with one, two, or three grade changes. A listing and narratives of SAEs will also be produced.

10.4.1.2 Immunogenicity

The immunogenicity analysis will be based on the PP population. A separate ITT population analysis will not be produced unless > 10% of at least 1 treatment group is excluded from the PP population. HAI antibody titers specific for each of the vaccine-homologous, historical and/or drifted, and cross-lineage virus strains tested, will be summarized by treatment group based on the following parameters (with 95% CIs):

1) Geometric mean titer (GMT) at baseline (screening) and post-vaccination on Day 21. Samples with no detectable HAI activity at the lowest dilution (1:10) will be assigned a value of 5 for calculation.
2) GMR – the ratio of the post-vaccination GMT on Day 21 to the baseline (Day 0) value.
3) 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 on Day 21 in post-vaccination HAI titer relative to baseline.
4) Seroprotection rate (SPR) – defined as the percentage of subjects with an HAI titer ≥ 1:40 at a given time-point.

Neutralizing antibody titers specific for each of the virus strains will be summarized by treatment group for each virus stain tested based on the following parameters (with 95% CIs):

1) GMT at baseline (screening) and post-vaccination on Day 21. Samples with no detectable neutralizing activity at the lowest dilution (1:10) will be assigned a value of 5 for calculation.
2) GMR – the ratio of the post-vaccination GMT on Day 21 to the baseline (Day 0) value.
3) 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 on Day 21 in post-vaccination titer relative to baseline.

Percentages of subjects with immune response will be calculated along the corresponding two-sided exact (Clopper-Pearson) binomial CIs. GMTs will be summarized by treatment group and visit day along with the corresponding two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. Two-sided 95% CIs for the difference in proportions of participants demonstrating SCR and SPR between a Tri-NIV group and the Fluzone HD group will be based on the Newcombe hybrid score (METHOD = SCORE riskdiff-option for PROC FREQ in SAS). The within-group geometric mean ratio (GMRpost/pre) will be conducted using paired t-test based on log-transformed values. Then, the mean difference and the corresponding 95% CI limits will be exponentiated to obtain the GMT ratio and the corresponding CI.

Reverse cumulative distribution displays of HAI and MN titers for each virus strain will be produced in which Day 0 and Day 21 distributions will be displayed separately by treatment group. Titers reported below the lowest 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).

10.5 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.

10.6 Plan for Statistical Summaries and Analyses

10.6.1 Day 21 Unblinded Data Review

An unblinded review will be conducted of all available immunogenicity and safety data (inclusive of clinical laboratory safety assessments) upon completion of Day 21 visits for all subjects. 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 21 visit and the data are monitored. The determination of the readiness will be based on the blinded review of outstanding queries of critical data points.

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

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

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

10.6.2 Final Clinical Study Report

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

10.7 Computer Methods

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

11 TRIAL LEGAL AND ETHICAL REQUIREMENTS

11.1 Compliance with Regulatory Requirements

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

11.2 Institutional Review Board

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

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

11.3 Informed Consent

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

11.4 Required Site Documentation

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

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

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

11.5 Subject Confidentiality

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

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

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

11.6 Disclosure of Information

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

12 REFERENCES

CDC. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. MMWR Morb Mortal Wkly Rep 2010; 59(33): 1057-62.

CDC. (2017). Seasonal Influenza Vaccine Effectiveness, 2005-2017. Retrieved 14 July 2017 from https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.

CDC. (2017 -a). Influenza vaccine - United States, 2016-17 influenza season Retrieved June 27 2017 from https://www.cdc.gov/flu/protect/vaccine/vaccines.htm.

CDC. (2017 -b). 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.

Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. Immunity 2010; 33(4): 492-503.

DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med 2014; 371(7): 635-45.

FDA. (2017). Vaccines Licensed for Use in the United States. Retrieved July 13 2017, from https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833.

Flannery B, Chung J. (2016). Influenza vaccine effectiveness, including LAIV vs IIV in children and adolescents, US Flu VE Network, 2015-16. Retrieved 14 July 2017 from https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-05-flannery.pdf.

Griffin MR, Monto AS, Belongia EA, et al. Effectiveness of non-adjuvanted pandemic influenza A vaccines for preventing pandemic influenza acute respiratory illness visits in 4 U.S. communities. PLoS One 2011; 6(8): e23085.

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

Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg (Lond) 1972; 70(4): 767-77.

McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. J Infect Dis 2015; 211(10): 1529-40.

Monto AS. Moving Toward Improved Influenza Vaccines. J Infect Dis 2017; 215(4): 500-02.

Mullooly JP, Bridges CB, Thompson WW, et al. Influenza- and RSV-associated hospitalizations among adults. Vaccine 2007; 25(5): 846-55.

Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011-2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis 2014; 58(3): 319-27.

Paules C and Subbarao K. Influenza. Lancet 2017.

Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One 2015; 10(3): e0118369.

Reed C, Kim IK, Singleton JA, et al. Estimated influenza illnesses and hospitalizations averted by vaccination--United States, 2013-14 influenza season. MMWR Morb Mortal Wkly Rep 2014; 63(49): 1151-4.

Shay DK, Chillarige Y, Kelman J, et al. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012-2013 and 2013-2014. J Infect Dis 2017; 215(4): 510-17.

Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis 2012; 55(7): 951-9.

WHO (2011). Manual for the laboratory diagnosis and virological surveillace of influenza WHO global influenza surveillance network

WHO. (2017). Recommended composition of influenza virus vaccines for use in the 2017-2018 northern hemisphere influenza season. 2 March 2017.

Zimmerman RK, Nowalk MP, Chung J, et al. 2014-2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. Clin Infect Dis 2016; 63(12): 1564-73.

Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. PNAS 2017. www.pnas.org/cg/doi/10.1073/pnas.1712377114.

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).

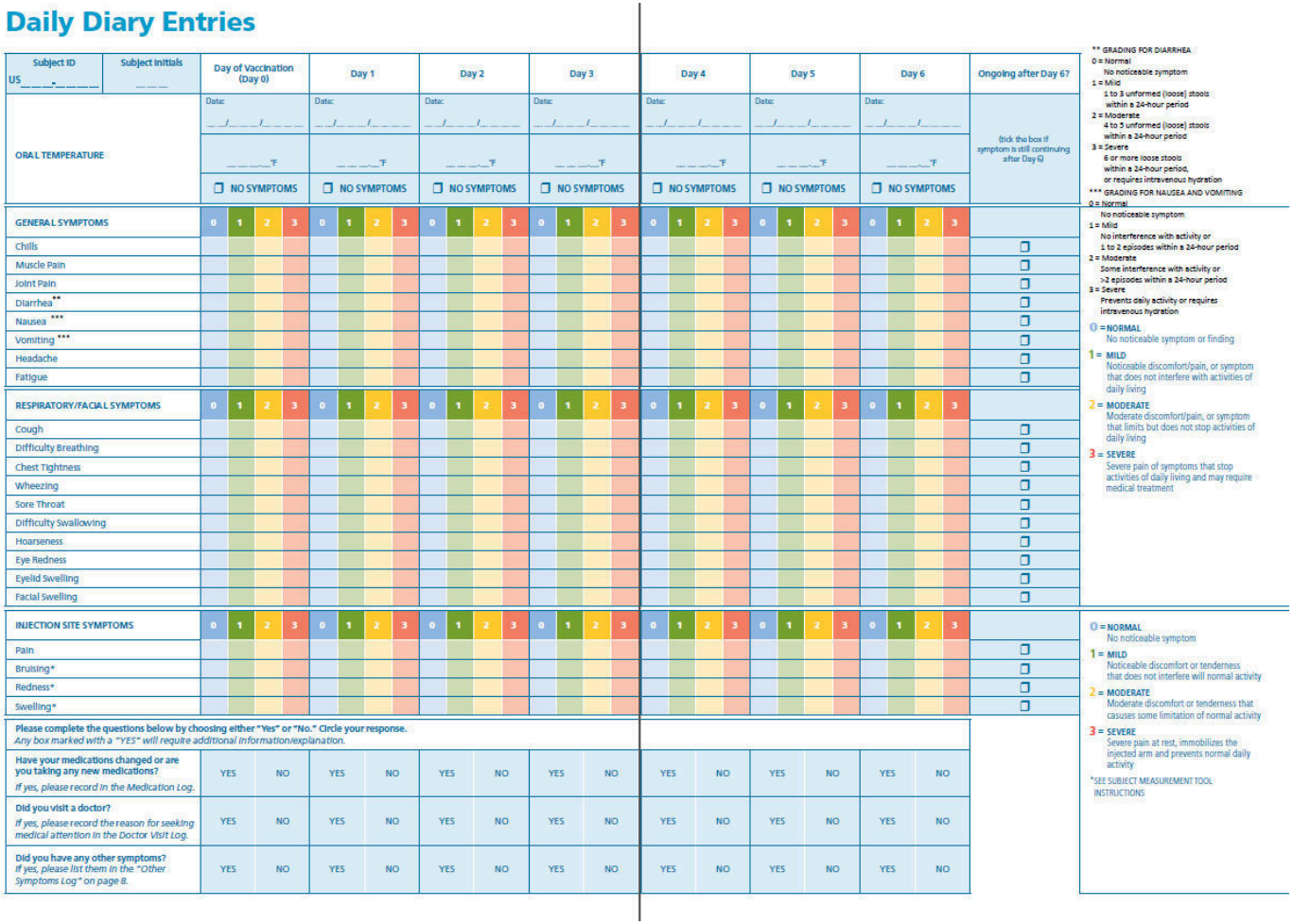
[6] On Day 21, all Group A and B subjects will be administered a rescue injection with a licensed influenza vaccine, and all Group C subjects will be administered an injection of saline placebo to maintain trial blind. *Subjects should be free of acute illness (defined as the presence of a moderate or 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.

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										

[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.

APPENDIX 2 – TNIV-E-101 SUBJECT DIARY CARD (DRAFT)



Daily Diary Entries

Subject ID US_____	Subject Initials	Day of Vaccination (Day 0)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Ongoing after Day 6?
ORAL TEMPERATURE		Date:	Date:	Date:	Date:	Date:	Date:	Date:	(tick the box if symptom is still continuing after Day 6)
		❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	
GENERAL SYMPTOMS		0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	
Chills									❒
Muscle Pain									❒
Joint Pain									❒
Diarrhea**									❒
Nausea ***									❒
Vomiting ***									❒
Headache									❒
Fatigue									❒
RESPIRATORY/FACIAL SYMPTOMS		0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	
Cough									❒
Difficulty Breathing									❒
Chest Tightness									❒
Wheezing									❒
Sore Throat									❒
Difficulty Swallowing									❒
Hoarseness									❒
Eye Redness									❒
Eyelid Swelling									❒
Facial Swelling									❒
INJECTION SITE SYMPTOMS		0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	
Pain									❒
Bruising*									❒
Redness*									❒
Swelling*									❒
Please complete the questions below by choosing either "Yes" or "No." Circle your response. *Any box marked with a "YES" will require additional information/explanation.*									
Have your medications changed or are you taking any new medications? *If yes, please record in the Medication Log.*		YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	
Did you visit a doctor? *If yes, please record the reason for seeking medical attention in the Doctor Visit Log.*		YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	
Did you have any other symptoms? *If yes, please list them in the "Other Symptoms Log" on page 8.*		YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	

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

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

0 = NORMAL
No noticeable symptom or finding

1 = MILD
Noticeable discomfort/pain, or symptom that does not interfere with activities of daily living

2 = MODERATE
Moderate discomfort/pain, or symptom that limits but does not stop activities of daily living

3 = SEVERE
Severe pain of symptoms that stop activities of daily living and may require medical treatment

0 = NORMAL
No noticeable symptom

1 = MILD
Noticeable discomfort or tenderness that does not interfere will normal activity

2 = MODERATE
Moderate discomfort or tenderness that casuses some limitation of normal activity

3 = SEVERE
Severe pain at rest, immobilizes the injected arm and prevents normal daily activity

*SEE SUBJECT MEASUREMENT TOOL INSTRUCTIONS

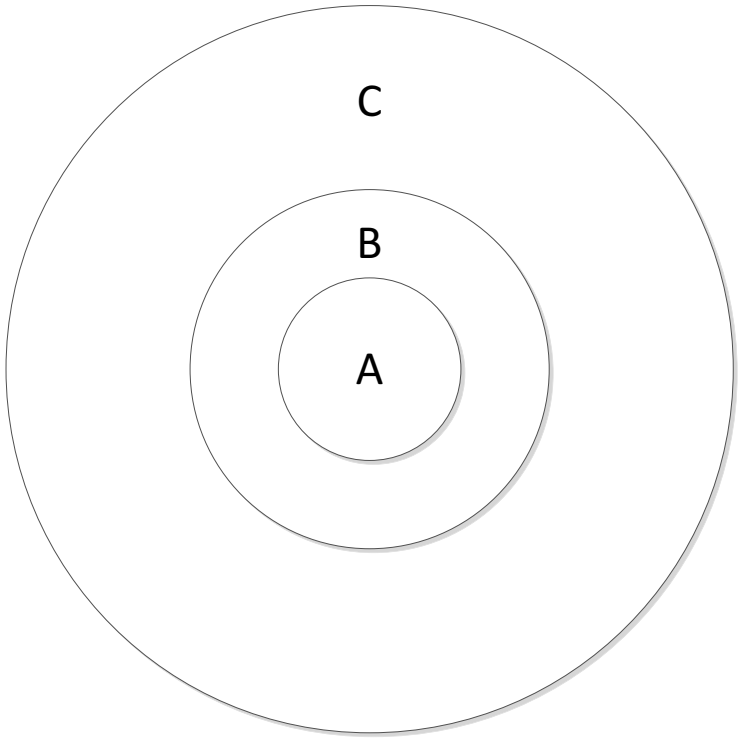
*A subject diary will be provided to all subjects to record solicited and unsolicited adverse events experienced, concomitant medications used, and any medical visits/procedures sought, within the first seven days following Day 0 vaccination. The above is a sample excerpt from such a diary. **It is provided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

APPENDIX 3 – TNIV-E-101 BLOOD DRAW SCHEDULE

Trial Visit Day	Amount of Blood Drawn for Immunogenicity Assessment (mL)	Amount of Blood Drawn for Clinical Safety Assessment (mL)
Day 0 *(pre-vaccination)*	20	10
Day 21 *(± 2 days)*	20	10
TOTAL FOR ENTIRE TRIAL (mL)	60	

APPENDIX 4 – TNIV-E-101 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