Human Immune Responses to an Adjuvanted H5 Vaccine:
Durability and Impact of the Seasonal Influenza Vaccine on H5 Induced B Cell Responses

Protocol Number: HIPCVAX-010 supplement

Sponsored by:

National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH)

Principal Investigator:

Nadine Rouphael, MD

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Statement of Compliance

The trial will be carried out in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);

Compliance with these standards provides public assurance that the rights, safety and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

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Protocol Summary

Title: Human Immune Responses to an Adjuvanted H5 Vaccine: Durability and Impact of the Seasonal Influenza Vaccine on H5 Induced B Cell Responses

Population: Up to 50 subjects who previously participated in HIPCVAX-010 Systems Biology of Influenza A (H5N1) Virus Monovalent Vaccine with and without AS03 Adjuvant, and who are in good health and meet the eligibility criteria

Clinical Site: The Hope Clinic of the Emory Vaccine Center, Emory University

Study Duration: Approximately 18 months

Subject Duration: Approximately 12 months

Description of Agent: One dose delivered intramuscularly of the FDA-approved 2018-2019 seasonal influenza vaccine

Objective:

- To assess the durability and impact of the seasonal influenza vaccine on H5 induced B cell responses

Study Outcome Measures:

Primary:

- Number of participants with a four-fold increase in stem-specific antibody titers against H5N1 at day 29 after vaccination with the seasonal influenza vaccine.

Secondary:

- Number of solicited and unsolicited adverse events grade 2 and above at days 8 and 29, respectively, after vaccination with the seasonal influenza vaccine.
- Number of serious adverse events after vaccination with the seasonal influenza vaccine for the duration of the study.

Tertiary:

- Rate of seroprotection to H5N1 at days 100, 180, and 365 after vaccination with the seasonal influenza vaccine.
- Change in memory B cell responses at days 100, 180, and 365 after vaccination with the seasonal influenza vaccine.
- Rate of seroconversion to the 4 seasonal vaccine strains at days 29, 100, 180, and 365 after vaccination with the seasonal influenza vaccine.
- Baseline H5-specific B cell responses induced by the AS03 adjuvanted vs. un-adjuvanted H5N1 vaccination up to 4-5 years post-vaccination.

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1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

Antibody responses to seasonal influenza vaccines wane over time and are also narrow in terms of the number of epitopes targeted. In addition, the responding B cells do not significantly gain additional somatic hypermutations over the course of the response. The current seasonal influenza vaccines used in the US in healthy young adults are un-adjuvanted and the B cell response to such vaccines are dominated by those originating from the pre-existing memory B cells. In 2015, we completed a study where we analyzed human B cell responses to a pandemic H5N1 vaccine either alone or when combined with the GlaxoSmithKline (GSK) adjuvant AS03 (HIPCVAX010, NCT 01910519). Fifty subjects received, in 2:1 randomization, two 3.75 µg doses (21 days apart) of the H5N1 vaccine (derived from A/Indonesia/5/05) formulated with or without the AS03 adjuvant with sample collection out to 100 days post-vaccination. Analysis of these samples showed that the AS03 adjuvant substantially enhanced both the primary and secondary plasmablast response, inducing both H5 HA stem, and head-specific antibodies. The H5 HA stem antibodies showed a high level of somatic hypermutation (SHM) compared to the head-specific antibodies which showed very little SHM. These data indicate that the AS03 adjuvant enhanced both naïve and memory B cell responses, with the first wave inducing H5 HA stem reactive antibodies coming from pre-existing memory B cell pool, and the second wave head-specific antibodies from naïve B cell pool. Interestingly, the H5 HA stem antibodies induced by the adjuvanted vaccine were broadly cross-reactive to not only group 1 but also group 2 influenza strains. In contrast, the head-specific antibodies were highly specific to the immunizing H5 strain. This cohort is now 4-5 years post-AS03 adjuvanted H5N1 vaccination. For the proposed study we plan to bring these volunteers back into the clinic to collect samples from 4-5 years post-H5N1 vaccination (depending on when initially vaccinated). Using this valuable cohort, we aim to address important questions that are highly relevant to the development of a universal influenza vaccine.

1.2 Rationale

The longevity of the human immune response, particularly the durability of the primary (H5 head) versus the secondary (H5 stem) antibody responses to the adjuvanted AS03 H5N1 vaccine 4 to 5 years post-vaccination, and the characteristics of the H5 vaccine-

induced HA head and stem specific antibody responses upon receipt of the seasonal influenza vaccine are unknown. Here we attempt to assess the durability of antibody responses to the H5N1 vaccine and impact of an FDA-approved seasonal influenza vaccine, recommended for individuals greater than 6 months of age, on H5-induced B cell responses in subjects who were previously administered the pandemic H5N1 vaccine either alone or combined with the GSK adjuvant AS03.

1.3 Potential Risks and Benefits

The study utilizes an FDA-approved 2018-2019 seasonal influenza vaccine, Fluarix Quadrivalent. See package insert for full risks and benefits of the vaccine.[1]

1.3.1 Potential Risks

The potential risks to subjects are those associated with intramuscular administration of the seasonal influenza vaccine, possible reactions to the vaccine, and having blood drawn.

The potential risks of receiving the seasonal influenza vaccine, Fluarix Quadrivalent, include but are not limited to local pain (36%), muscle aches (16%), headache (16%), fatigue (16%), arthralgia (8%), gastrointestinal symptoms (7%), shivering (4%), local swelling (2%), local redness (2%), and fever (2%).[1]

Serious adverse events occurring within 21 days of vaccination were reported in 0.5% of subjects who received Fluarix Quadrivalent.[1] Across 4 clinical trials in adults (N=10,923), there was one case of anaphylaxis within one day following administration of Fluarix.[1]

Associated with the 1976 flu vaccine, a few patients experienced temporary paralysis, a condition known as Guillain-Barré Syndrome. However, this syndrome has not been seen with the more modern influenza vaccine preparations. Most persons who develop Guillain-Barré Syndrome recover completely, although the recovery period may be as little as a few weeks or as long as a few years. About 30% of those with Guillain-Barré Syndrome still have residual weakness after 3 years and about 3% may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack. Intensive surveillance of Guillain-Barré Syndrome after administration of inactivated influenza vaccines since 1976 has shown a slight increase in risk over background cases (more than one additional case of Guillain-Barré Syndrome per million persons) following vaccination, typically with onset within 6 weeks after vaccination.[2] Interestingly, although vaccination rates have increased in the last 10 years, the numbers of reported cases of vaccine-associated Guillain-Barré Syndrome have declined.[3] Randomized, controlled clinical trials of the inactivated seasonal influenza vaccine in patients with asthma

indicate that there is no significant increase in asthma exacerbations immediately after vaccination.

Blood sample collection involves transient discomfort and may cause fainting, which is managed by having the subject lie down prior, if needed. The blood draw site may bruise, and this can be ameliorated by holding pressure to this site following the blood draw. The sites of blood draw are potential sites of infection, but this risk is made very unlikely by the use of sterile technique.

There may be other unknown side effects.

1.3.2 Known Potential Benefits

Administration of the seasonal influenza vaccine can offer protection to subjects against influenza A subtype viruses and type B viruses contained in the vaccine.[1] CDC recommends annual influenza vaccination for all individuals greater than 6 months of age. The benefit for the study is predominately scientific, allowing for a better understanding of the longevity of the immune response to the AS03 adjuvanted H5N1 vaccine, as well as the immune response to the seasonal influenza vaccine following receipt of the AS03 adjuvanted H5N1 vaccine. Findings from this study may assist researchers in developing a universal influenza vaccine.

2 OBJECTIVES

2.1 Study Objectives

- To assess the durability and impact of the seasonal influenza vaccine on H5 induced B cell responses

2.2 Study Outcome Measures

Primary:

- Number of participants with a four-fold increase in stem-specific antibody titers against H5N1 at day 29 after vaccination with the seasonal influenza vaccine.

Secondary:

- Number of solicited and unsolicited adverse events grade 2 and above at days 8 and 29, respectively, after vaccination with the seasonal influenza vaccine.
- Number of serious adverse events after vaccination with the seasonal influenza vaccine for the duration of the study.

Tertiary:

- Rate of seroprotection to H5N1 at days 100, 180, and 365 after vaccination with the seasonal influenza vaccine.
- Change in memory B cell responses at days 100, 180, and 365 after vaccination with the seasonal influenza vaccine.
- Rate of seroconversion to the 4 seasonal vaccine strains at days 29, 100, 180, and 365 after vaccination with the seasonal influenza vaccine.
- Baseline H5-specific B cell responses induced by the AS03 adjuvanted vs. un-adjuvanted H5N1 vaccination up to 4-5 years post-vaccination.

3 STUDY DESIGN

This will be an exploratory study with up to 50 subjects total, who previously participated in the HIPCVAX-010 Systems Biology of Influenza A (H5N1) Virus Monovalent Vaccine with and without AS03 Adjuvant study, are in good health, and meet all eligibility criteria. Each subject will make a total of seven visits to the Hope Clinic.

4 STUDY POPULATION

4.1 Selection of the Study Population

The target sample size will be up to 50 subjects who will receive the 2018-2019 Fluarix Quadrivalent seasonal influenza vaccine. Subjects will be screened for eligibility according to the inclusion/exclusion criteria by history. Informed consent will be obtained for study participation.

4.2 Inclusion/Exclusion Criteria

Subjects eligible to participate shall meet all of the following **inclusion criteria:**

1. Participated in HIPCVAX-010 Systems Biology of Influenza A (H5N1) Virus Monovalent Vaccine with and without AS03 Adjuvant study

2. Capable of informed consent and provision of written informed consent before any study procedures.

3. Capable of attending all study visits according to the study schedule.

4. Are in good health, as determined by medical history and targeted physical exam related to this history.

5. Female subjects of childbearing* age must have a negative urine pregnancy test before study vaccination, and must use at least one form of contraception** to avoid pregnancy for 28 days before and 28 days after Fluarix Quadrivalent administration.

** Not sterilized via tubal ligation, bilateral oophorectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation test at least 90 days after the procedure, and still menstruating or <1 year of the last menses if menopausal.*
***Includes, but is not limited to, non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for 180 days or more prior to the subject receiving the first study vaccination, barrier methods such as condoms or diaphragms, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill).*

Subjects eligible to participate shall not meet any of the following **exclusion criteria**:

1. Have an acute illness, including any fever (≥ 100.4 F [≥ 38.0C], regardless of the route) within 72 hours before vaccination.[a]

2. Have any acute or chronic medical condition that, in the opinion of the principal investigator, would make vaccination unsafe or interfere with the evaluation of immune response to study vaccination.[b]
3. Alcohol or drug abuse and psychiatric conditions that, in the opinion of the investigator, would preclude compliance with the trial or interpretation of safety or endpoint data.
4. Have a suppressed immune system as a result of illness, immunosuppressive medication, chemotherapy, or radiation therapy within 3 years prior to study vaccination.[c]
5. Are pregnant or breastfeeding or plan to within one month of vaccination.
6. Have taken oral or parenteral corticosteroids of any dose within 28 days before study vaccination.[a]
7. Have a known history of autoimmune disease.
8. Have a history of Guillain-Barre Syndrome.
9. Have a history of bleeding disorders.
10. Have known hypersensitivity or allergy to any component of the vaccine, including egg and latex allergies, or history of anaphylaxis with influenza vaccine or vaccine component.
11. Have received blood or blood products 3 months prior to study entry or expected to receive through 6 months after study entry.
12. Have received any live virus vaccines within 4 weeks prior to study entry or expected receipt within 4 weeks after study entry.[a]
13. Have received any inactivated vaccine within 2 weeks or expected receipt within 2 weeks after study entry.[a]
14. Have received any experimental agents within 6 weeks prior to study or plan to through study duration.
15. Have received the 2018-2019 influenza seasonal vaccine.
16. Documented influenza infection during the 2018-2019 influenza season.
17. Social, occupational, or any other condition that in the opinion of the investigator might interfere with compliance with the study and vaccine evaluation.

[a]An individual who initially is excluded from study participation based on one or more of the time-limited exclusion criteria (e.g., acute illness, receipt or expected receipt of live or inactivated vaccines) may be reconsidered for enrollment once the condition has resolved as long as the subject continues to meet all other entry criteria. Subjects receiving > 20 mg/day of prednisone or its equivalent daily or on alternate days for more than 2 weeks may enter the study after therapy has been discontinued for more than 3 months.

[b]Chronic medical problems including (but not limited to) insulin dependent diabetes, severe heart disease, severe lung disease, severe liver disease, severe kidney disease, auto immune diseases, severe gastrointestinal diseases and uncontrolled hypertension.

[c]Impaired immune function or chronic infections including (but not limited to) HIV, hepatitis B or C; organ transplant; cancer; current and/or expected receipt of chemotherapy, radiation therapy or any other immunosuppressive therapy (i.e. more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more in the past 3 months[a]), congenital immunodeficiency, anatomical or functional asplenia.

5 STUDY PROCEDURES/EVALUATIONS

5.1 Study Procedures

Medical history will be obtained by interview of study subjects on Day 1 (Visit 1) prior to the study vaccination. Subjects will be asked about a known history of significant medical disorders, cancer, immunodeficiency, allergies, psychiatric illness, substance use, and autoimmune diseases.

Medications history will include a review of all current medications and any medications taken in the last 28 days before study vaccination and those to be taken for 28 days after vaccinations. Medications included in this history will only include prescription medication and prohibited treatments listed in the above Inclusion/Exclusion Criteria section.

On Day 1 (Visit 1) and before the study vaccination, a targeted physical examination may be performed by the investigator, who is licensed to make medical diagnoses. At Visits 2-7, a targeted physical examination may be performed based on interim health history.

Vital signs (oral temperature, pulse rate, and blood pressure) will only be measured on Day 1 (Visit 1) and if needed at other visits.

Height and weight will be measured on Day 1 (Visit 1) before study vaccination.

Blood will be collected for baseline study labs on Day 1 (Visit 1) before study vaccination. At Visits 2-7, blood will be collected for immunogenicity analysis.

Subjects will be observed in the clinic for at least 20 minutes after study vaccination on Day 1 (Visit 1).

5.1.1 Laboratory Evaluations/Assays

Urine pregnancy tests will be performed on the same day as and prior to study vaccination (Day 1). Results must be negative and known prior to study vaccination.

5.1.2 Special Assays or Procedures

The immunologic assays will be performed at Dr. Ahmed’s Laboratory on the Emory University main campus.

5.1.3 Specimen Collection, Preparation, Handling and Analyses

Blood will be collected at each of the seven study visits as per the Study Schedule in Appendix A.

6 STUDY SCHEDULE

6.1 Screening/Enrollment/Baseline, Visit 01 Day 01

Study subjects will be given a description of the study and have an opportunity to have their questions and concerns addressed by the study principal investigator or designee.

Subjects will be given the informed consent form to read and discuss with study staff, and if they wish to enroll will sign the document before any study vaccination, procedures, or lab draws are performed.

A medical history, targeted physical exam and vital signs, as outlined in the Study Procedures section, will be conducted in order to assess compliance with study inclusion and exclusion criteria.

A list of prescribed medications taken by subjects in the past 28 days and those to be taken for 28 days after vaccinations will be documented on the appropriate study form.

A urine pregnancy test will be conducted for female subjects, and a negative result will be required and documented on the appropriate study form prior to any study interventions.

Vital signs, including pulse rate, blood pressure, oral temperature, and height and weight will be measured and documented on the appropriate study form.

Blood will be collected for baseline study labs prior to vaccination as outlined in the Study Procedures section.

Subjects will be given a 7-day memory aid, ruler, and thermometer to record local and systemic reactogenicity.

A single dose of the FDA-approved 2018-2019 seasonal influenza vaccine (Fluarix Quadrivalent) will be administered. Subjects will be asked to remain at the clinic for 20 minutes to monitor for any reactions or adverse events. Any reactions or adverse events grade 2 and above will be documented on the appropriate study form.

Subjects will be informed to contact the study team should they experience any concerning reactions to the vaccine, and they will be asked to visit the clinic for evaluation should the principal investigator or designee deem the reaction in need of evaluation.

6.2 Follow-up and Final Visits

6.2.1 Visit 02 Day 08, Visit 03 Day 15 and Visit 04 Day 29

Interim medical history, and targeted physical exam and vital signs, if necessary, will be conducted.

Medications taken during the interim from the previous visit and any grade 2 and above adverse events or serious adverse events will be documented on the appropriate study form.

Blood will be collected for immunogenicity analysis.

A review of the memory aid will be done at Visit 02.

6.2.2. Visit 05 Day 100, Visit 06 Day 180 and Visit 07 Day 365

Interim medical history, and targeted physical exam and vital signs, if necessary, will be conducted.

Any serious adverse events will be documented on the appropriate study form.

Blood will be collected for immunogenicity analysis.

6.3 Early Termination Visit (if needed)

The following will be performed at any early termination visit, if necessary, for subjects who withdraw or who are withdrawn from the study:

Interim medical history, and targeted physical exam and vital signs, if necessary, will be conducted.

A review of the memory aid will be conducted (if visit occurs within 7 days of vaccination).

Medications taken during the interim from the previous visit will be documented on the appropriate study form (if prior to D29).

Any grade 2 and above adverse events (prior to D29) or serious adverse events will be documented on the appropriate study form.

Blood will be collected for immunogenicity analysis.

7 STATISTICAL CONSIDERATIONS

The goal of this study is to assess the longevity of the human immune response to the AS03 H5N1 vaccine and evaluate the immune response to the 2018-2019 seasonal influenza vaccine, Fluarix Quadrivalent, in individuals with previous receipt of the adjuvanted or unadjuvanted AS03 H5N1 vaccine. This is an exploratory study designed to assess the durability and impact of the seasonal influenza vaccine on H5 induced B cell responses.

Since this is an exploratory study, our aim is to study a convenient sample of up to 50 subjects, who previously participated in the HIPCVAX-010 Systems Biology of Influenza A (H5N1) Virus Monovalent Vaccine with and without AS03 Adjuvant study, receiving the seasonal influenza vaccine.

The biostatistician will perform descriptive statistics to assess the longevity of the H5 induced B cell responses and the impact that receipt of the seasonal influenza vaccine has on these immune responses.

8 QUALITY CONTROL AND QUALITY ASSURANCE

The study will undergo internal quality control and quality assurance per the Hope Clinic standard operating procedures.

9 ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1 Ethical Standard

The site principal investigator will ensure that this trial is conducted in full conformity with the principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable.

9.2 Institutional Review Board

Prior to enrollment of subjects into this trial, the approved protocol and informed consent form will be reviewed and approved by the Emory IRB. The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this study.

9.3 Informed Consent Process

The site principal investigator and designee will choose subjects in accordance with the eligibility criteria detailed in Section 4. Before any study procedures are performed, subjects must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continuing throughout the individual's study participation. Before any study procedures are performed, subjects will receive a comprehensive explanation of the proposed study procedures and study interventions/products, including the nature and risks of the trial, alternate therapies, any known adverse effects, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their serum samples. Subjects will be allowed sufficient time to consider participation in the study, after having the nature and risks of the trial explained to them, and have the opportunity to discuss the trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Informed consent forms describing in detail the study interventions/products, study procedures, risks and possible benefits are given to subjects. The informed consent form must not include any exculpatory statements. Informed consent forms will be IRB-approved and subjects will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site principal investigator (or designee) will explain the research study to subjects and answer any questions that may arise. Subjects must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the trial, including administering study product.

Study personnel may employ IRB-approved recruitment efforts prior to obtaining the subject's consent; however, before any study procedures are performed to determine protocol eligibility an informed consent form must be signed. Subjects will be given a copy of all informed consent forms that they sign.

By signing the informed consent form, subjects agree to complete all evaluations required by the trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from the trial for any reason.

The rights and welfare of subjects will be protected by emphasizing to subjects that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

9.4 Exclusion of Women, Minorities, and Children (Special Populations)

This trial will be inclusive of all adults who participated in the HIPCVAX-010 Systems Biology of Influenza A (H5N1) Virus Monovalent Vaccine with and without AS03 Adjuvant study and who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background.

9.5 Subject Confidentiality

Subjects will have the same patient identification number that was assigned to them in the HIPCVAX-010 study, followed by the letter, "S," and will not be identified by name. Subject confidentiality is strictly held in trust by principal investigator and the Hope Clinic personnel directly involved in the study. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects. The study protocol, documentation, data, and all other information generated will be held in strict confidence.

9.6 Future Use of Stored Specimens

Subjects will be asked for permission to keep any remaining samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. The samples will not be sold or used directly for production of any commercial product. Human genetic tests may be performed on samples for future research only. Each sample will be labeled with a unique tracking number to protect subject's confidentiality. There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subject's samples will NOT be kept in their health records.

Subjects may be given the option to decide if they want their samples to be used for future research or have their samples destroyed at the end of the study. The subject's decision can be changed at any time prior to the end of the study by notifying the study doctors or nurses in writing. However, if the subject originally consents to future use and

subsequently changes his/her decision, any data from a previously collected sample may still be used for this research.

10 LITERATURE REFERENCES

1. FLUARIX QUADRIVALENT [package insert]. GlaxoSmithKline, Inc., Research Triangle Park, NC; 2018.

2. Lasky T, Tarracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, Clark S, Haber P, Stolley PD, Schonberger LB and Chen RT. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N. Engl. J. Med.;339:1797-1802 (1998).

3. Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E and Chen RT. Guillain-Barre syndrome following influenza vaccination. JAMA; 292:2478-2481 (2004).

4. National Cancer Institute. National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0. (2017). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

SUPPLEMENTS/APPENDICES

Appendix A: Study Schedule

Study Visit Number	V01	V02	V03	V04	V05	V06	V07
Study Day +/- Window (days)	**D1**	**D8+1**	**D15 +/-2**	**D29 +/-3**	**D100 +/-14**	**D180 +/-14**	**D365 +/-30**
Obtain Informed Consent[#]	X*						
Review Eligibility Criteria	X*						
Medical History[+]	X*	X	X	X	X	X	X
Concomitant Medications	X*[%]	X	X	X			
Vital Signs (Oral Temperature, Pulse Rate, and BP)	X*[&$]	(X[$])	(X[$])	(X[$])	(X[$])	(X[$])	(X[$])
Height and Weight	X*						
Targeted Physical Examination	X*	(X)	(X)	(X)	(X)	(X)	(X)
Urine Pregnancy Test	X*[@]						
Study Vaccination	X						
20-minute Evaluation Period After Study Vaccination	X						
Venous Blood Collection for Study Assays	X	X	X	X	X	X	X
Memory Aid review		X					
Adverse events Grade 2 and above	X	X	X	X			
Serious adverse events	X	X	X	X	X	X	X

[#]Prior to study procedures

*Prior to study vaccination.

[%]All current medications and medications taken within 28 days prior to day 1 of the study.

[&]Vital signs assessed on Day 1 (Visit 1) before the study vaccination will be considered as baseline.

[$]Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

() Targeted physical examination and vital signs if indicated based on review of complete or interim medical history.

[@]Must be performed on all female subjects of childbearing potential within 24 hours prior to each study vaccination and results must be negative and known prior to each study vaccination.

[+]Complete medical history by interview of subjects to be obtained on Day 1 (Visit 01) prior to the first study vaccination and interim medical history by interview of subjects to be obtained at follow-up visits after study vaccination.

Appendix B: Adverse Events Grading[4]

	INJECTION SITE REACTIONS			
	Grade			
	0	1	2	3
Swelling	None	Mild induration/swelling 2.5-5cm; does not interfere with activity	Moderate induration/swelling 5.1-10cm; limiting instrumental activities of daily living	Severe induration/swelling >10 cm; limiting self-care activities of daily living
Redness	None	Mild erythema 2.5-5cm; does not interfere with activity	Moderate erythema 5.1-10cm; limiting instrumental activities of daily living	Severe erythema >10cm; limiting self-care activities of daily living
Pain	None	Mild pain; does not interfere with activity	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living

	GENERAL ADVERSE REACTIONS			
	Grade			
	0	1	2	3
Fatigue	None	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental activities of daily living	Fatigue not relieved by rest, limiting self-care activities of daily living
Body ache (myalgia)	None	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living
Chills	None	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics
Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Diarrhea	None	Increase of <4 stools per day over baseline	Increase of 4 - 6 stools per day over baseline; limiting instrumental activities of daily living	Increase of >6 stools per day over baseline; hospitalization indicated; limiting self-care activities of daily living
Headache	None	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living
Joint pain (arthralgia)	None	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living
Fever*	None	100.4 - 102.2 degrees F	102.3 - 104.0 degrees F	>104.0 degrees F

* Oral temperature; no recent hot or cold beverages or smoking