CLINICAL STUDY PROTOCOL

EXTENT AND DURABILITY OF IMMUNE RESPONSE FOLLOWING SEASONAL INFLUENZA VACCINATION IN HEALTHY VOLUNTEERS

VERSION 1.0 26APRIL 2017

ALTIMMUNE, INC.

19 Firstfield Road
Gaithersburg, MD 20878

CONFIDENTIALITY STATEMENT

INVESTIGATOR AGREEMENT

EXTENT AND DURABILITY OF IMMUNE RESPONSE FOLLOWING SEASONAL INFLUENZA VACCINATION IN HEALTHY VOLUNTEERS

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Altimmune representative listed below.

Sybil A Tasker	
Print Name	**Signature**
SVP Clinical R+D	27 APR 2017
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives, and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as an Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Investigator	
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

Protocol Number:	ALT-FLZ-401
Product:	Fluzone Intramuscular Quadrivalent vaccine
Active Ingredient(s)/INN:	Vaccine
Study Title:	Extent and Durability of Immune Response Following Seasonal Influenza Vaccination in Healthy Volunteers
Study Phase:	Phase 4
Indication Under Investigation:	Influenza
Study Objectives:	**Primary Objective** To evaluate antibody response against matched influenza strains as measured by hemagglutination inhibition (HAI) following administration of a seasonal influenza vaccine. **Secondary Objectives** To evaluate 1) antibody responses to divergent influenza strains 2) cellular immune responses and 3) mucosal antibody responses following administration of seasonal influenza vaccine (Fluzone Quadrivalent)
Study Design:	This will be an open-label, single administration dose study in adult healthy male and female subjects. After qualifying for the study, subjects will receive a single intramuscular injection of the FDA approved 2016-2017 quadrivalent influenza vaccine. Subjects will be screened within 28 days prior to enrollment into the study. After qualifying for the study subjects will visit the clinical unit on Day 1 and will have pre-dose blood samples taken for humoral (serum) and cellular (peripheral blood mononuclear cells PBMCs) immunity testing and nasopharyngeal swabs for assessment of mucosal immunity, and will then be given the vaccine. Over the next 6 months, 10-mL blood samples will be collected on Days 4, 8, 15, 29, 91 and 181 for HAI testing. Peripheral blood mononuclear cells will be collected on Day 8 to assess cellular responses. A nasopharyngeal swab will also be done on Day 29. Screening assessments will include clinical laboratory tests (hematology, chemistry, urinalysis

	[UA], drug and alcohol testing), vital signs, 12-lead electrocardiogram and physical examination. Adverse events (AEs) will be monitored throughout the study.
Study Duration:	The duration of the study for each individual subject will be up to 7 months from the start of Screening (within 28 days of dosing). Dosing will be on a single occasion with follow-up for 6 months.
Study Sites and Location:	The study will be conducted at: Optimal Research, Rockville MD
Planned Sample Size:	20 healthy subjects will be enrolled and receive a single dose of the vaccine.
Subject Eligibility Criteria:	Inclusion Criteria: 1. Men and women 18 to 50 years of age, inclusive 2. Good general health status, as determined by the Investigator 3. Adequate venous access for repeated phlebotomies 4. Screening laboratory results within institutional normal range or Grade 1 elevation if the Investigator documents clinical insignificance. Bilirubin may be Grade 2 if associated with normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and the Investigator considers the result not to be clinically significant (e.g. vigorous exercise or Gilbert's syndrome) 5. Negative drug and alcohol screen at Screening and predose on Day 1 6. For women of child bearing potential, negative pregnancy test 7. Willingness to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, surgical sterilization (hysterectomy, or bilateral tubal

ligation, salpingectomy, or oophorectomy), licensed hormonal methods, intrauterine device (IUD), or consistent use of a barrier method (e.g., condom, diaphragm) with spermicide for 28 days after the Fluzone Intramuscular Quadrivalent vaccine dose

8. Willingness to participate and comply with all aspects of the study through the entire study period, including nasal swabs and blood samples

9. Provision of written informed consent

Exclusion Criteria:

1. Pregnant, possibly pregnant, or lactating women

2. Body mass index > 35.0 kg/m^2

3. Positive results for HIV, hepatitis B virus, or hepatitis C virus at Screening

4. Asthma or other chronic lung disease that is greater than mild in severity. Specifically excluded are participants with any of the following events in the past year:

   - Daily symptoms
   - Daily use of short acting beta 2 agonists
   - Use of inhaled steroids or theophylline
   - Use of pulse systemic steroids
   - Emergency care or hospitalization related to asthma or other chronic lung disease
   - Systemic steroids for asthma exacerbation

5. History of diabetes mellitus (gestational diabetes is allowed if treatment was not required postpartum and serum glucose is currently in the normal range)

6. History of coronary artery disease, arrhythmia, or congestive heart failure

7. Clinically significant ECG abnormality

8. Poorly controlled hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 95 mmHg) at Screening or predose on Day 1

9. History of anaphylaxis or angioedema

10. Known allergy to any of the ingredients in the vaccine formulation including egg allergy

11. History of chronic rhinitis, nasal septal defect, cleft palate, nasal polyps, or other nasal abnormality that might affect vaccine administration

12. Previous nasal surgery or nasal cauterization

13. Any symptoms of upper respiratory infection or temperature > 38°C within 3 days before Day 1

14. Significant nasal congestion or rhinorrhea as assessed by the investigator.

15. Known or suspected malignancy, excluding non-melanoma skin cancers and other early stage surgically excised malignancies that the Investigator considers to be exceedingly unlikely to recur

16. Immunocompromised individuals, including those who have used corticosteroids (including intranasal steroids), alkylating drugs, antimetabolites, radiation, immune-modulating biologics, or other immunomodulating therapies within 90 days before Day 1 or those who plan use during the study period

17. Use of statin medication within 30 days before Day 1 (including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, pitavastatin)

18. Receipt of intranasal medications (including over-the-counter medications) within 30 days before Day 1

19. Receipt of any IP within 30 days before Day 1

	20. Receipt of any vaccine within 30 days before Day 1 21. Receipt of intranasal vaccine within 90 days before Day 1 22. Receipt of any influenza vaccine within 6 months before Day 1 23. Any change in medication for a chronic medical condition within 30 days before Day 1 24. Past regular use or current use of intranasal illicit drugs or any regular use of illicit drugs by any other route. 25. Use of tobacco products or electronic cigarettes within 30 days before Day 1. Any other smoking products including marijuana will be excluded. 26. Any medical, psychiatric, or social condition or any occupational or other responsibility that in the judgment of the Investigator would interfere with or serve as a contraindication to protocol adherence, assessment of safety (including immunogenicity), or a subject's ability to give informed consent
Dosage Form, Dose and Route of Administration:	• Solution dose (0.5 mL), intramuscular
Study Endpoints:	**Efficacy (immunogenicity)** Antibody and cellular immune responses following seasonal influenza vaccination **Safety** AEs
Statistical Analyses:	**Sample Size Determination** Based on practical considerations, 20 subjects will be enrolled. **Safety** For safety, the primary assessment will be adverse event rate, type of adverse event, severity.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract Research Organization
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
EoS	End-of-Study
ET	Early Termination
FDA	Food and Drug Administration
HAI	hemagglutination inhibition
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IRB	Institutional Review Board
OTC	over-the-counter
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SOP	Standard Operating Procedure

Abbreviation	Definition
UA	urinalysis
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

Influenza is a major cause of morbidity and mortality worldwide with the elderly being at highest risk of complications and death. Seasonal flu vaccines are designed to protect against infection and illness caused by the flu viruses research indicates will be most common during the flu season. "Quadrivalent" flu vaccines are formulated to protect against four flu viruses, but do not protect against infection and illness caused by other viruses that can also cause flu-like symptoms. There are many other viruses besides flu viruses that can result in flu-like illness (also known as influenza-like illness) that spread during the flu season. These non-flu viruses include rhinovirus (one cause of the "common cold") and respiratory syncytial virus, which is the most common cause of severe respiratory illness in young children, as well as a leading cause of death from respiratory illness in those aged 65 years and older.

Fluzone Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine (1). It is approved in US for use in persons 6 months of age and older.

Antibody protection is traditionally measured by hemagglutinin-inhibition (HAI), where antibodies to the virus block the function of hemagglutinin to prevent viral attachment to host cells. It is believed that HAI antibody levels closely correlate with virus neutralization assays, however, it should not be considered a marker of efficacy (2).

The Safety profile of the Quadrivalent vaccine is similar to seasonal flu vaccines made to protect against three viruses, with similar mild side effects (injection site pain, malaise, headache).

This study is being undertaken to evaluate antibody and cellular immune responses to various influenza strains following seasonal influenza vaccination. Blood samples collected at 1 week and at various intervals up to 6 months post vaccination will be analyzed for assessment of cellular and antibody responses to the vaccine. Nasopharyngeal swabs collected at baseline and 4 weeks following immunization will be used to assess mucosal antibody response to influenza.

1.1 Study Rationale

The rationale for the study is to evaluate immunological responses to Fluzone Quadrivalent vaccine.

1.2 Risks and Benefits for Study Subjects

There will be no direct benefit for study subjects from receipt of the study drug. Indirect benefits to the subjects enrolled in this study are the free medical tests received at Screening and during the study.

The safety monitoring practices employed by this protocol (i.e., AE monitoring) are standard and considered adequate to protect the subjects' safety.

The total volume of blood that will be collected from each subject during this study is about 201 mL (see Section 15.1). For this 6-month study, the volume of blood collected from healthy adults is considered to be safe.

Anticipated risks of Fluzone Quadrivalent include injection site pain, myalgia, headache and malaise.

1.3 Population, Route, Dosage, Dosage Regimen, Treatment Period

The study population will be composed of male and female subjects, 18 to 50 years of age, inclusive, with a BMI ≤35 kg/m^2. Refer to Section 4 for details regarding the study population.

All subjects will be administered a single intramuscular dose of approved Fluzone Intramuscular Quadrivalent vaccine. Refer to Section 5 for details regarding study treatment.

1.4 Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95)[5], and the following regulations and guidance:

United States (US) Food and Drug Association GCP Regulations: Code of Federal Regulations (CFR) Title 21, Parts 11, 50, 54, 56, and 312[6], as appropriate

The Health Insurance Portability and Accountability Act (HIPAA)[7]

Other applicable local regulations

1.4.1 Subject Confidentiality

The Investigator and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the Case Report Forms (CRFs) or other documents submitted to the Sponsor, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms [ICFs]) should be kept in strict confidence by the Investigator and designee.

In compliance with Federal regulations/ICH GCP guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agencies, and the Institutional Review Board (IRB) direct access to review the subject's medical and study records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

1.4.2 Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's and designee's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator or designee should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical

principles that have their origin in the Declaration of Helsinki. The consent form and any revisions should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and dated by the subject, and by the person who conducted the informed consent discussion (the Investigator or designee). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date that informed consent was given should be recorded on the CRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Additional consent is required for all subjects, in accordance with HIPAA. Subjects will consent to virology testing (including human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody) as part of their initial informed consent. This testing will be described in the ICF.

1.4.3 Regulatory Compliance

The study protocol, subject information, consent form, Product Insert, any or written instructions to be given to the subject, available safety information, subject recruitment tools and procedures (e.g., advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's or designee's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to their implementation. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment.

The Investigator or designee must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities, or key personnel. The Investigator or designee should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from the Sponsor or Contract Research Organization (CRO), in accordance with local procedures.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is:

To evaluate the antibody response as measured by HAI following administration of the approved Fluzone Intramuscular Quadrivalent vaccine.

2.2. Secondary Objectives

The secondary objectives of this study are:

To evaluate antibody responses to divergent influenza strains following seasonal influenza vaccination

To evaluate cellular immune responses following seasonal influenza vaccination

To evaluate mucosal antibody responses following seasonal influenza vaccination

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a phase 4, single center, open-label, study designed to collect blood and nasopharyngeal samples from subjects who received a single intramuscular injection of the FDA approved 2016-2017 quadrivalent influenza vaccine.

Prior to any study procedures being conducted, all subjects will be required to sign an ICF after having the study medication and requirements of the protocol fully explained. Prior to and after immunization, blood and nasopharyngeal swabs will be collected for HAI and cellular immune response and mucosal antibody response testing, respectively.

3.1.2. Treatment Groups

All subjects will receive one dose of the vaccine and there is only one treatment group.

Details for each study visit are provided in the study procedures (see Section 6) and in the Schedule of Events (see Section 15.2).

3.1.3. Study Endpoints

3.1.3.1. Immunogenicity Endpoints

Antibody and cellular immune responses following seasonal influenza vaccination

3.1.3.2 . Safety Endpoint

Adverse events

3.1.4. Duration of the Study

The duration of the study will be approximately up to 7 months.

3.1.5. Duration of Subject Participation

The duration of the study for each individual subject will be approximately up to 7 months from the start of Screening (within 28 days of dosing) through the final study visit. Dosing will be on a single occasion, followed by blood sampling up to 6 months post dose.

3.2 Selection of Dose

The dose of the vaccine to be administered (0.5 mL) is approved by FDA (see Section 15.3).

4. STUDY POPULATION

4.1. Enrollment

The Investigator will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex), date, and outcome of screening process (e.g., enrolled in the study, reason for ineligibility, refused to participate).

Investigator will be expected to maintain an enrollment log of all subjects enrolled in the study indicating their assigned study number.

Investigator will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers upon enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

4.2. Inclusion and Exclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

Inclusion Criteria

1. Men and women 18 to 50 years of age, inclusive
2. Good general health status, as determined by the Investigator
3. Adequate venous access for repeated phlebotomies
4. Screening laboratory results within institutional normal range or Grade 1 elevation if the Investigator documents clinical insignificance. Bilirubin may be Grade 2 if associated with normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and the Investigator considers the result not to be clinically significant (e.g. vigorous exercise or Gilbert's syndrome)
5. Negative drug and alcohol screen at Screening and predose on Day 1
6. For women of child bearing potential (WOCBP), negative pregnancy test
7. Willingness to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, surgical sterilization (hysterectomy, or bilateral tubal ligation, salpingectomy, or oophorectomy), licensed hormonal methods, intrauterine device (IUD), or consistent use of a barrier method (e.g., condom, diaphragm) with spermicide for 28 days after the Fluzone Intramuscular Quadrivalent vaccine dose
8. Willingness to participate and comply with all aspects of the study through the entire study period, including nasal swabs and blood and urine samples
9. Provision of written informed consent

Exclusion Criteria:

1. Pregnant, possibly pregnant, or lactating women
2. Body mass index > 35.0 kg/m^2
3. Positive results for HIV, hepatitis B virus, or hepatitis C virus at Screening
4. Asthma or other chronic lung disease that is greater than mild in severity. Specifically excluded are participants with any of the following events in the past year:
   - Daily symptoms
   - Daily use of short acting beta 2 agonists
   - Use of inhaled steroids or theophylline
   - Use of pulse systemic steroids
   - Emergency care or hospitalization related to asthma or other chronic lung disease
   - Systemic steroids for asthma exacerbation
5. History of diabetes mellitus (gestational diabetes is allowed if treatment was not required postpartum and serum glucose is currently in the normal range)
6. History of coronary artery disease, arrhythmia, or congestive heart failure
7. Clinically significant ECG abnormality
8. Poorly controlled hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 95 mmHg) at Screening or predose on Day 1
9. History of anaphylaxis or angioedema
10. Known allergy to any of the ingredients in the vaccine formulation, including egg allergy
11. History of chronic rhinitis, nasal septal defect, cleft palate, nasal polyps, or other nasal abnormality that might affect vaccine administration
12. Previous nasal surgery or nasal cauterization
13. Any symptoms of upper respiratory infection or temperature > 38°C within 3 days before Day 1
14. Significant nasal congestion or rhinorrhea as assessed by the investigator.

15. Known or suspected malignancy, excluding non-melanoma skin cancers and other early stage surgically excised malignancies that the Investigator considers to be exceedingly unlikely to recur

16. Immunocompromised individuals, including those who have used corticosteroids (including intranasal steroids), alkylating drugs, antimetabolites, radiation, immune-modulating biologics, or other immunomodulating therapies within 90 days before Day 1 or those who plan use during the study period

17. Use of statin medication within 30 days before Day 1 (including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, pitavastatin)

18. Receipt of intranasal medications (including over-the-counter medications) within 30 days before Day 1

19. Receipt of any IP within 30 days before Day 1

20. Receipt of any vaccine within 30 days before Day 1

21. Receipt of intranasal vaccine within 90 days before Day 1

22. Receipt of any influenza vaccine within 6 months before Day 1

23. Any change in medication for a chronic medical condition within 30 days before Day 1

24. Past regular use or current use of intranasal illicit drugs, or any illicit drug by any route

25. Use of tobacco products or electronic cigarettes within 30 days before Day 1, or smoking of any type, including marijuana

26. Any medical, psychiatric, or social condition or any occupational or other responsibility that in the judgment of the Investigator would interfere with or serve as a contraindication to protocol adherence, assessment of safety (including immunogenicity), or a subject's ability to give informed consent

4.3. Removal of Subjects From Therapy

4.3.1. Reasons for Withdrawal/Early Discontinuation

Any subject who discontinues from the study for any reason will have their study discontinuation recorded.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

AE or SAE

Lost to follow-up

Withdrawal of consent by subject

Physician decision

Study terminated by sponsor

Other

If a subject withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal and the reason for withdrawal.

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures (Day 181).

4.3.2. Withdrawal Procedures

Subjects who withdraw from the study will be required to undergo Check-out/Early Termination procedures (Day 181). If a subject withdraws from the study prior to Day 29, they will be required to undergo Check-out/Early Termination procedures (Day 29).

If the subject is withdrawn due to an AE, the Investigator or designee will attempt to follow the subject until the AE has been resolved or stabilized. Whenever possible, withdrawn subjects will undergo End of Study (EoS) procedures after withdrawal and Follow-up. More follow-up safety assessments than those prescribed in this protocol may be ordered at the Investigator's or designee's discretion in subjects who are withdrawn due to an AE, but non-protocol assessments will not necessarily be included in the clinical database.

4.3.3. Subject Replacement

Subjects who discontinue will not be replaced unless approved by the Sponsor.

5. TREATMENTS ADMINISTERED

5.1 Investigational Products

Fluzone Intramuscular Quadrivalent vaccine is a marketed product, although for this study it is referred to as IP.

5.2. Method of Assigning Subjects to Treatments and Blinding

This is an open-label study. There is no blinding of study treatment.

5.3. Method of Assessing Treatment Compliance

To ensure treatment compliance, each intramuscular dose of vaccine will be administered delivered by a clinic staff member. The time and date the medication is given will be recorded in the CRF.

5.4. Labeling and Packaging

Fluzone Intramuscular Quadrivalent vaccine will be obtained from commercial sources. All prefilled single dose syringes will be labeled with the contents identified.

5.4.1. Preparation

No preparation of the study drug is required by a pharmacist.

The study drug will be administered in accordance with the protocol. Study drug will be administered only to subjects participating in the clinical study. It is a violation of the regulations to use unapproved study products for purposes other than stated in the protocol.

The site will complete the required documentation as provided by the Sponsor or its representatives to document dispensing of the product. All information will be recorded immediately on a drug dispensing form each time the study drug is dispensed to a subject.

5.4.2. Storage Conditions

Fluzone Intramuscular Quadrivalent vaccine is to be stored at 2°C to 8°C (35°F to 46°F) in a secure, limited access storage area.

In the event that storage conditions exceed the permissible temperatures, the Sponsor should be contacted within 24 hours of becoming aware of the incident.

5.4.3. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the site. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the IP. The record must be kept current and should contain the dates and quantities of drug received, subject's (identification number and/or initials or supply number as applicable), for whom the IP was dispensed, the date and quantity of

IP dispensed and remaining, if from individual subject drug units as well as the initials of the dispenser.

At EoS, or as directed, all unused, partially used, or empty containers, will be returned to a designee as instructed by Sponsor. IP will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of IP must be documented and the documentation included in the shipment. At EoS, a final IP reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by Sponsor and Sponsor has received copies of the site's drug handling and disposition Standard Operating Procedures (SOPs).

All IP inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.4.4. Retention Samples

No retention samples are required.

5.5. Concomitant Medications

Medications used within 30 days prior to Screening will be recorded. Receipt of any vaccine or the influenza vaccine within approximately 1 and 6 months, respectively, of enrollment in this study is exclusionary.

Use of any prescription or OTC medications (systemic or topical), vitamins, or dietary/herbal supplements will be permitted except those specified in Exclusion criteria or those deemed by the Investigator that could possibly interfere with the study.

Any immunosuppressive medication or vaccines (other than study drug administered) taken by subjects during the course of the study will be recorded and coded using the World Health Organization (WHO) dictionary. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator or designee and Sponsor whether to continue or discontinue the subject.

5.6. Lifestyle Guidelines

All subjects must agree not to donate blood, plasma, platelets, or any other blood components from Screening through 6 months post dose.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 15.2.

The Screening phase will take place on Day -28 through Day -1.

The following activities and/or assessments will be performed:

Day -28 through Day -1

- Informed consent
- Medical/surgical history, demographics, and eligibility criteria
- Physical examination including height, weight, and BMI
- Urine drug screen (opiates, benzodiazepines, amphetamines, cocaine, barbiturates, phencyclidine), and alcohol breath test
- Virology blood test including HIV antibody, HBsAg, HCV antibody
- Urine pregnancy test for WOCBP
- Clinical laboratory tests for serum chemistry, hematology, and UA
- Vital signs recorded after at least 5 min in the supine position consisting of pulse, diastolic blood pressure (DBP), systolic blood pressure (SBP), and oral temperature
- 12-Lead ECG
- Record prior/concomitant medications
- AE monitoring

6.2 Randomization

Not applicable.

6.3 Treatment Period

6.3.1 Day 1

Subjects will check in to the clinic approximately 30 minutes to 1 hour before study procedures for pre-dose assessments. The following procedures will be performed:

- All subjects will be questioned to affirm that the inclusion and exclusion criteria/restrictions have not been violated since Screening (Section 4).
- All WOCBP will undergo a urine pregnancy test; negative results must be obtained for eligibility
- Vital signs (temperature, DBP, SBP, pulse) recorded after at least 5 minutes in the supine position. If the Investigator considers that any of the vital signs measurements are clinically significant, these parameters may be repeated at least 5 minutes later. If any of them remain clinically significant the subject will be discontinued from the study.
- Urine drug screen and alcohol breath test
- Physical examination
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI testing)

- Collect 50-mL blood sample for generation of PBMCs for cellular responses to the vaccine (cytotoxicity, cytokine, chemokine release).
- Collect a nasopharyngeal swab and process per standard methods
- Administer the influenza vaccine (0.5 mL in deltoid muscle)

The following activities and/or assessments will be performed on each of the study days.

Day 4 ±1

- Record concomitant medications
- AE monitoring
- Limited physical examination, if needed
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI)

Day 8 ±1

- Record concomitant medications
- AE monitoring
- Limited physical examination, if needed
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI)
- Collect 50-mL blood sample for generation of PBMCs for cellular responses to the vaccine

Day 15 ±1

- Record concomitant medications
- AE monitoring
- Limited physical examination, if needed
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI)

Day 29 ±1

- Record concomitant medications
- AE monitoring
- Limited physical examination, if needed
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI)
- Collect a nasopharyngeal swab and process per standard methods

Day 91 ±10

- Record concomitant medications
- AE monitoring
- Limited physical examination, if needed
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI)

Day 181 ±10

- Record concomitant medications
- AE monitoring
- Limited physical examination, if needed
- Collect 10-mL blood sample for immunogenicity testing (e.g., HAI)

6.4 End-of-Study

Subjects will be discharged from the study after the study procedures have been completed on Day 181. If subjects discontinue from the study before Day 181 the procedures specified for Day 29 visit (Section 6.3.1) should be performed.

6.5 Follow-up

None.

6.6 Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which that was given approval/favorable opinion by the IRB.

A deviation to any protocol procedure, or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. The Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or investigational treatment, and had one administration of IP, data should be collected for safety purposes.

The Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

None.

8. IMMUNOGENICITY ASSESSMENTS

Immunogenicity testing:

A 10-mL blood sample using serum separator Vacutainer tube will be obtained and serum will be prepared using standard laboratory procedures, stored at -80°C until shipment to the designated laboratory.

PBMC:

Fifty (50) mL of blood collected prior to vaccination (Day 1) and a week post-vaccination (Day 8) will be used to isolate and viable freeze PBMC. In brief, PBMCs, are isolated using Ficoll-Hypaque® gradient-density technique and centrifugation steps are adjusted to obtain optimal yield and viability with site equipment. Cell counting will be performed by automatic cell counter. Vials containing approximately 10x10^6 cells will be cryopreserved with standard cryo-freezing procedure with 10% dimethyl sulfoxide. A Strata-cooler will be used to ensure 1^0C decrease per minute; Stratacooler containing viable frozen vials will be placed at -80^0C. Viable frozen samples will be kept at -80°C until shipment to the designated laboratory. Cryopreserved PBMC will be thawed for evaluation of cellular response in designated laboratory.

All shipments of serum and PBMC for analysis will occur per sponsor instructions.

Nasopharyngeal swabs:

The procedure for collection of the nasopharyngeal swabs is as follows:

1. Subject should be seated on exam table. Investigator will insert the swab into one nostril straight back (not upwards) and continue along the floor of the nasal passage and move it posteriorly (as tolerated) alongside the nasal septum until the point where the cavity narrows.
2. The subject will then take the swab and perform the following steps for each nostril:
    a. Subject will move the swab further up the nasal cavity as far as comfort/tolerability will dictate, under the close supervision of the Investigator. Do not force swab, if obstruction is encountered before reaching the nasopharynx, remove swab and try the other side.
    b. Once maximum insertion has been achieved, rotate the swab gently 360° in one direction. Wait approximately 5 seconds. Rotate the swab slowly 360° in the opposite direction. Wait approximately 5 seconds.
    c. Carefully remove the swab from the nasal cavity and immediately place the swab into the plain sterile transport tube. Break the swab at the predetermined breaking point. Secure the screw cap on the pre-labeled sterile transport tube (ensuring the sampling area of the swab does not touch the wall of the tube).
3. Immediately transfer sample tubes to a -80°C freezer.
4. All samples will be retained at -80°C until the last sample is taken at Day 29.
5. Batch shipment on dry ice will occur after the last Day 29 sample and will include one (1) sample tube per subject per timepoint.

6. The remaining sample tubes will be retained at Optimal Research as back-up samples and shipped separately on dry ice to the testing lab.

All the nasopharyngeal samples will be sent to:

SriSai Biopharmaceutical Solutions, LLC, Attn: Tara Coldsmith, Operations Supervisor, 320 Montevue Lane, Frederick, MD 21702, Phone: 301-846-0188 ext 62. Email: tcoldsmith@srisaipharma.com.

Handling of Biological Samples for Subjects Withdrawn from the Study. The following options for storage of samples for potential future use include:

- All collected samples will be retained and used in accordance with the subject's original informed consent for storage of samples for future use.

- The subject may withdraw consent for storage of samples for potential future use and the samples will be destroyed and no further testing will occur. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the storage of leftover samples for future research and request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed. Details of the sample retention for research are presented in the ICF.

- The subject may withdraw consent for storage of samples for future use while remaining in the study. In such a case, the samples will be destroyed as described above. Details of the sample retention for research are presented in the ICF.

Future Research

Subjects who provide informed consent for the study will be informed that any residual samples may be retained for as yet undetermined additional immunogenicity studies. These studies may include HLA typing of the PBMC samples. Subjects participating will be asked explicitly to consent for such sample retention and potential future genetic research on their blood cells.

Subjects unwilling to have their blood samples stored for future use can consent to participate in this study without having their blood samples stored for future testing. In such case, their blood samples will be destroyed after all the tests specified for this study have been concluded.

Subjects can withdraw consent for sample retention at any time, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study-site contact about the withdrawal of consent for the storage of samples for future use and request sample destruction.

9. PHARMACOKINETIC ASSESSMENTS

None

10. SAFETY ASSESSMENTS

10.1. Adverse Events

All clinical AEs occurring after the subject checks-in to the clinical unit and up to the follow-up visit, whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event CRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Screening will be recorded as part of medical history. Report all serious AEs (SAEs) according to the procedures in Section 10.4, SAE Reporting-Procedure for Investigators. Always report diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Preplanned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 10.3 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the Investigator or designee will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed or reported spontaneously by the subject at each study visit. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.3. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded as an AE on the CRF, and if serious, reported as an SAE following the procedures in Section 10.

The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs including significant abnormal laboratory values at the EoS assessment, these events will be followed up until resolution or until they become clinically not relevant.

10.2. Safety Variables

Safety and tolerability of Fluzone Quadrivalent will be evaluated based on AE monitoring, limited physical examinations, and use of concomitant medications.

10.3. Definitions

10.3.1. Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the

use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal lab findings that should be considered AEs.

10.3.2. Serious Adverse Event

Any untoward medical occurrence that at any dose:

Results in death,

Is life-threatening,

Requires inpatient hospitalization or prolongation of existing hospitalization,

Results in persistent or significant disability/incapacity,

Is a congenital anomaly/birth defect, or

Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.

Preplanned (prior to signing the ICF) procedures or treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

10.3.3. AE Severity

Severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], Section 15.4)

10.3.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study product on the basis or his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

Related:

The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

Not Related:

The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

10.3.5. Adverse Event Outcome

1 = Recovered/Resolved

The subject fully recovered from the AE with no residual effect observed.

2 = Recovered/Resolved with Sequelae

The residual effects of the AE are still present and observable.

Include sequelae/residual effects.

3 = Not Recovered/Not Resolved

The AE itself is still present and observable.

4 = Fatal

5 = Unknown

6 = Not applicable

Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment

10.3.6. Other Action Taken for Event

1 = None

No treatment was required.

2 = Medication required

- Prescription and/or OTC medication was required to treat the AE.
- 3 = Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the adverse event, whether or not medication was required.

4 = Other

10.4. Serious Adverse Event Reporting–Procedure For Investigators

10.4.1. Initial Reports

All AEs and SAEs will be reported in the CRF.

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study center and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

Place the initial version of SAE in the subject's file.

10.4.2. Follow-up Reports

This is NEW information received on a previously reported SAE.

Within 24 hours of the receipt of new information for a reported SAE to the Medical Monitor:

10.4.3. Notifying Regulatory Authorities, Investigators, Institutional Review Board, and Competent Authorities

Spontaneously reported SAEs suspected to be associated with the vaccine, based on the FDA approved product labeling, will be reported to FDA using the Med Watch Form by the Sponsor. It is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

10.5. Clinical Laboratory Evaluations

10.5.1. Hematology

A 4-mL K_2EDTA tube will be collected for the following hematology assessments: hemoglobin, hematocrit, red blood cell (RBC) count (with indices, e.g. MCV, MCH, MCHC, RDW), white blood cell (WBC) count (with differential, neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count (MPV).

10.5.2. Serum Chemistry

- An 8.5-mL serum separating tube will be collected for the following serum chemistry assessments: sodium, potassium, chloride, calcium, AST, ALT, alkaline phosphatase, total bilirubin, glucose, creatinine, blood urea nitrogen (BUN), BUN/creatinine ratio (calculated), creatinine with GFR estimated, albumin, globulin (calculated), albumin/globulin ratio (calculated), total protein, albumin, and carbon dioxide.

10.5.3. Urinalysis

Standard UA, including a microscopic examination, will be conducted for all subjects and includes: specific gravity, pH, protein, glucose, ketones, blood, RBCs, WBCs, bilirubin, and urobilinogen.

10.5.4. Urine Drug Screen and Alcohol Breath Test

A urine screen for drugs of abuse (opiates, benzodiazepines, amphetamines, cocaine, barbiturates, and phencyclidine) and a alcohol breath test will be performed for all subjects at Screening and Day 1. A positive test result will disqualify a subject.

10.5.5. Other Laboratory Tests

- Two 8.5-mL serum separating tubes will be collected for the following assessments at Screening: HIV antibody, HBsAg, HCV antibody.
- Conduct a nasopharyngeal swab and process per standard methods

Urine pregnancy testing will be conducted for WOCBP at Screening and on Day 1, respectively as detailed in Section 15.2.

10.6. Vital Signs

Vital signs will be recorded at the time points indicated in Section 15.2. Vital signs will be recorded after at least 5 minutes in the supine position and will consist of pulse rate, DBP, SBP, and oral temperature.

10.7. Physical Examination

A complete physical examination, including body weight, height, and BMI will be performed at Screening. A medically qualified person will perform the physical examination, which will include an evaluation of the respiratory, cardiovascular, gastrointestinal, dermatological, musculoskeletal, psychiatric, and neurologic systems, as well as the head, eyes, ears, nose, and throat. A complete examination will be performed on Day 1 prior to administration of the vaccine to assess eligibility (Table 15.2). Additional exams maybe performed if needed depending on the type and severity of an AE during the 6-month follow-up period.

10.8. 12-Lead ECG

A single, 12-lead ECG will be performed at Screening and will be interpreted by the Investigator.

During the collection of the ECG, subjects should be in a supine position in a quiet setting without distractions (eg, television, cell phones). Subjects should rest for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.
Subjects will be excluded from the study if the Investigator determines any ECG findings to be clinically significant.

11. OTHER ASSESSMENTS

Not applicable

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1 Monitoring and Inspections

The Sponsor's monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., CRFs, source data, and other pertinent documents).

The monitor is responsible for visiting sites at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2 Data Collection

CRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. CRF will be completed, reviewed, and signed by the Investigator. The signature will indicate that the Investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications and agrees with the content.

12.3 Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications written by the Data Management CRO and approved by the Sponsor. Data will be vetted both electronically and manually for CRFs the data may be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. For CRFs, the data may be electronically vetted by programmed data rules within the application.

Data received from external sources such as central labs will be reconciled to the clinical database.

12.4 Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, microfiches, X-rays, and correspondence.

The Investigator or designee and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

Subject files containing completed CRFs, informed consents, and supporting copies of source documentation (if kept)

Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and the Sponsor

Records related to the IP, including acknowledgment of receipt at site, accountability records, and final reconciliation and applicable correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

12.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments; IRB correspondence and approvals; approved and signed ICFs; Investigator's Agreement; and clinical supplies receipts, distribution, and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13. FINANCING AND INSURANCE

13.1 Finances

Prior to starting the study, the Investigator and/or institution will sign a clinical study agreement with Altimmune, Inc. This agreement will include the financial information agreed upon by the parties.

13.2 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. References

1. Package Insert Fluzone Quadrivalent 2016
2. Ohmit SE; Petrie JG; Cross RT; Johnson E; Monto AS. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. J Infect Dis. 2011; 204(12):1879-85.

15. APPENDICES

15.1 Blood Collection Volume by Category and Total

Table 15.1: Blood Collection Volumes

Time Point	Test Item	Collection Volume (mL)	Frequency[a]	Total Volume (mL)
Screening	Hematology test	4.0	1	29.5
	Blood chemistry test	8.5		
	Hepatitis B & C	8.5		
	HIV	8.5	1	
Treatment Period	HAI titers	10	7	70
	PBMC	50	2	100
		Total	8	199.5

15.2 Schedule of Events

Table 15.2: Schedule of Events

Assessment	Screen	Study Day						
		1	4 ±1	8 ±1	15 ±1	29±1/ET[g]	91 ±10	181 ±10
Informed Consent	X							
Demographics	X							
Medical/Surgical History	X							
Physical Examination, height[h], weight[h], BMI	X	X						
Limited Physical Exam (as needed)			X	X	X	X	X	X
Vital Signs[a]	X	X						
12-Lead ECG	X							
Inclusion/Exclusion Criteria	X	X						
Clinical Laboratory Tests (Chemistry, Hematology, UA)[b]	X							
Drugs of abuse[c], alcohol test	X	X						
Serology (HIV, Hepatitis B And C)	X							
Pregnancy Test[d]	X	X						
Confirm eligibility for study[e]		X						
Influenza Vaccination		X						
Blood Sample (Immunogenicity)		X	X	X	X	X	X	X
PBMC sample collection and processing		X		X				
Nasopharyngeal swab		X				X		
Prior/Concomitant medications	X	X	X	X	X	X	X	X
Adverse Events[f]		X	X	X	X	X	X	X

[a] All vital signs BP, pulse rate, and body temperature) will be measured at Screening in the supine position. On Day 1, temperature, blood pressure and pulse rate will be assessed.
[b] See Section 10.5 for listing of tests
[c] Opiates, benzodiazepines, amphetamines, cocaine, barbiturates, phencyclidine
[d] At Screening and Day 1 WOCBP must have negative urine pregnancy test results
[e] Review inclusion/exclusion criteria and may also include a limited physical examination
[f] Any subject that experiences an AE (whether serious or non-serious) or has clinically significant abnormal laboratory tests will be followed until resolution or clinical stability up to 180 days after administration of the vaccine or longer if specified by the Investigator.
[g] ET= early termination for any subject that discontinues prior to Day 29 visit, ET occurs after Day 29, the procedures for Day 181 will be followed.
[h] Height and weight are not required at Day 1

15.3. Package Insert Fluzone Quadrivalent

Sanofi Pasteur
450/477 Fluzone® Quadrivalent

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fluzone® Quadrivalent safely and effectively. See full prescribing information for Fluzone Quadrivalent.

Fluzone Quadrivalent (Influenza Vaccine)
Suspension for Intramuscular Injection
2016-2017 Formula
Initial US Approval (Fluzone Quadrivalent): 2013

----------INDICATIONS AND USAGE----------

Fluzone Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)
Fluzone Quadrivalent is approved for use in persons 6 months of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- **For intramuscular use only** (2)

Age	Dose	Schedule
6 months through 35 months	One or two doses [a], 0.25 mL each	If 2 doses, administer at least 4 weeks apart
36 months through 8 years	One or two doses [a], 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines
"-" Indicates information is not applicable

---------- DOSAGE FORMS AND STRENGTHS ----------

Suspension for injection supplied in 4 presentations: prefilled single-dose syringe (pink plunger rod), 0.25 mL; prefilled single-dose syringe (clear plunger rod), 0.5 mL; single-dose vial, 0.5 mL; multi-dose vial, 5 mL. (3)

LE687

----------CONTRAINDICATIONS ----------

Severe allergic reaction (e.g., anaphylaxis) to any component of the vac egg protein, or after previous dose of any influenza vaccine. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- If Guillain-Barré syndrome (GBS) has occurred within 6 weeks foll influenza vaccination, the decision to give Fluzone Quadrivalent sh based on careful consideration of the potential benefits and risks. (

---------- ADVERSE REACTIONS ----------

- In children 6 months through 35 months of age, the most common injection-site reactions were pain (57%) or tenderness (54%), erytl and swelling (22%); the most common solicited systemic adverse r irritability (54%), abnormal crying (41%), malaise (38%), drowsine appetite loss (32%), myalgia (27%), vomiting (15%), and fever (14
- In children 3 years through 8 years of age, the most common (≥10 site reactions were pain (67%), erythema (34%), and swelling (25 common solicited systemic adverse reactions were myalgia (39%) (32%), and headache (23%). (6.1)
- In adults 18 years and older, the most common (≥10%) injection-s was pain (47%); the most common solicited systemic adverse reac myalgia (24%), headache (16%), and malaise (11%). (6.1)
- In adults 65 years of age and older, the most common (≥10%) inje reaction was pain (33%); the most common solicited systemic adv were myalgia (18%), headache (13%), and malaise (11%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Past at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of Fluzone Quadrivalent have not been e pregnant women or children less than 6 months of age. (8.4)
- Pregnancy: Pregnancy registry available. Call Sanofi Pasteur Inc. a 1-800-822-2463.
- Antibody responses to Fluzone Quadrivalent are lower in persons age than in younger adults. (8.5)

See **17 FOR PATIENT COUNSELING INFORMATION and FDA - appr**

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Fluzone® Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone Quadrivalent is approved for use in persons 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

- **For intramuscular use only**

2.1 Dose and Schedule

The dose and schedule for Fluzone Quadrivalent are presented in Table 1.

Table 1: Dose and Schedule for Fluzone Quadrivalent

Age	Dose	Schedule
6 months through 35 months	One or two doses*, 0.25 mL each	If 2 doses, administer at least 4 weeks apart
36 months through 8 years	One or two doses*, 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines
"-" indicates information is not applicable

2.2 Administration

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If any of these defects or conditions exist, Fluzone Quadrivalent should not be administered.

Before administering a dose of vaccine, shake the prefilled syringe or vial. Withdraw one dose of vaccine from the single-dose vial using a sterile needle and syringe. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle in persons ≥36 months of age. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously, intradermally, or subcutaneously.

Fluzone Quadrivalent should not be combined through reconstitution or mixed with any other vaccine.

3 DOSAGE FORMS AND STRENGTHS

Fluzone Quadrivalent is a suspension for injection.

Fluzone Quadrivalent is supplied in 4 presentations:
1) Prefilled single-dose syringe (pink syringe plunger rod), 0.25 mL, for persons 6 months through 35 months of age.
2) Prefilled single-dose syringe (clear syringe plunger rod), 0.5 mL, for persons 36 months of age and older.
3) Single-dose vial, 0.5 mL, for persons 36 months of age and older.
4) Multi-dose vial, 5 mL, for persons 6 months of age and older.

4 CONTRAINDICATIONS

Do not administer Fluzone Quadrivalent to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see *Description (11)*], including egg protein, or to a previous dose of any influenza vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. (See ref. 1) If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone Quadrivalent should be based on careful consideration of the potential benefits and risks.

5.2 Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Fluzone Quadrivalent.

5.3 Altered Immunocompetence

If Fluzone Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.4 Limitations of Vaccine Effectiveness

Vaccination with Fluzone Quadrivalent may not protect all recipients.

6 ADVERSE REACTIONS

In children 6 months through 35 months of age, the most common (≥10%) injection-site reactions were pain (57%)* or tenderness (54%)†, erythema (37%), and swelling (22%); the most common solicited systemic adverse reactions were irritability (54%)†, abnormal crying (41%)†, malaise (38%)*, drowsiness (38%)†, appetite loss (32%)†, myalgia (27%)*, vomiting (15%)†, and fever (14%). In children 3 years through 8 years of age, the most common (≥10%) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). In adults 18 years and older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). In adults 65 years of age and older, the most common (≥10%) injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%).

* Assessed in children 24 months through 35 months of age
† Assessed in children 6 months through 23 months of age

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine and may not reflect the rates observed in practice.

Children 6 Months Through 8 Years of Age

Study 1 (NCT01240746, see http://clinicaltrials.gov) was a single-blind, randomized, active-controlled multi-center safety and immunogenicity study conducted in the US. In this study, children 6 months through 35 months of age received one or two 0.25 mL doses of either Fluzone Quadrivalent or one of two formulations of a comparator trivalent influenza vaccine (TIV-1 or TIV-2), and children 3 years through 8 years of age received one or two 0.5 mL doses of either Fluzone Quadrivalent, TIV-1, or TIV-2. Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). For participants who received two doses, the doses were administered approximately 4 weeks apart. The safety analysis set included 1841 children 6 months through 35 months of age and 2506 children 3 years through 8 years of age. Among participants 6 months through 8 years of age in the three vaccine groups combined, 49.3% were female (Fluzone Quadrivalent, 49.2%; TIV-1, 49.9%; TIV-2, 49.4%), 58.4% Caucasian (Fluzone Quadrivalent, 58.4%; TIV-1, 58.9%; TIV-2, 57.8%), 20.2% Black (Fluzone Quadrivalent, 20.5%; TIV-1, 19.9%; TIV-2, 19.1%), 14.1% Hispanic (Fluzone Quadrivalent, 14.3%; TIV-1, 13.2%; TIV-2, 14.7%), and 7.3% were of other racial/ethnic groups (Fluzone Quadrivalent, 6.8%; TIV-1, 8.0%; TIV-2, 6.5%). Table 2 and Table 3 summarize solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events for 28 days after each dose and serious adverse events (SAEs) during the 6 months following the last dose.

Table 2: Study 1*: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Months of Age (Safety Analysis Set)†

	Fluzone Quadrivalent (N=1223)			TIV-1 (B Victoria) (N=310)			TIV-2 (B Yamagata) (N=308)		
	Any (%)	Grade 2 (%)	Grade 3 (%)	Any (%)	Grade 2 (%)	Grade 3 (%)	Any (%)	Grade 2 (%)	Grade 3 (%)
Injection-site adverse reactions									
Pain	57.0	10.2	1.0	52.3	11.5	0.8	50.3	5.4	2.7
Tenderness	54.1	11.3	1.9	48.4	8.2	1.9	49.7	10.3	0.0
Erythema	37.3	1.5	0.2	32.9	1.0	0.0	33.3	1.0	0.0
Swelling	21.6	0.8	0.2	19.7	1.0	0.0	17.3	0.0	0.0
Systemic adverse reactions									
Fever (≥100.4°F)	14.3	5.5	2.1	16.0	6.6	1.7	13.0	4.1	2.0
Malaise	38.1	14.5	4.6	35.2	14.8	4.7	32.4	12.8	6.8
Myalgia	26.7	6.6	1.9	20.6	9.4	1.6	25.0	6.8	2.7
Headache	8.9	2.5	0.6	9.4	3.9	0.0	12.2	4.7	0.0
Irritability	54.0	26.4	3.2	52.8	20.1	2.1	53.5	22.9	2.8
Crying abnormal	41.2	12.3	3.3	36.5	8.2	1.9	29.9	10.4	2.1
Drowsiness	37.7	8.4	1.3	32.1	3.8	0.6	31.9	5.6	0.7
Appetite loss	32.3	9.1	1.8	33.3	5.7	1.9	25.0	8.3	0.7
Vomiting	14.8	6.2	1.0	11.3	4.4	0.6	12.9	6.2	0.0

*NCT01240746
†The safety analysis set includes all persons who received at least one dose of study vaccine
Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
N is the number of participants in the safety analysis set
Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: >101.3°F to ≤103.1°F (6 months through 23 months); ≥101.2°F to ≤102.0°F (24 months through 35 months); Malaise, Myalgia, and Headache: some interference with activity; Irritability: requiring increased attention; Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal; Appetite loss: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours
Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site tenderness: cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: >103.1°F (6 months through 23 months); ≥102.1°F (24 months through 35 months); Malaise, Myalgia, and Headache: Significant; prevents daily activity; Irritability: inconsolable; Crying abnormal: >3 hours; Drowsiness: sleeping most of the time or difficult to wake up; Appetite loss: refuses ≥3 feeds/meals or refuses most feeds/meals; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration
Assessed in children 24 months through 35 months of age
Assessed in children 6 months through 23 months of age
Fever measured by any route

Table 3: Study 1[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety Analysis Set)[b]

	Fluzone Quadrivalent[c] (N[f]=1669)			TIV-1[d] (B Victoria) (N[f]=424)			TIV-2[e] (B Yamagata) (N[f]=413)		
	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)
Injection-site adverse reactions									
Pain	66.6	15.6	2.1	64.6	9.5	2.0	63.8	11.6	2.8
Erythema	34.1	2.9	1.8	36.8	3.4	1.2	35.2	2.5	1.8
Swelling	24.8	2.8	1.4	25.4	1.5	1.2	25.9	2.5	1.8
Systemic adverse reactions									
Fever (≥100.4°F)[i]	7.0	2.1	2.1	7.1	2.2	1.2	7.6	2.8	0.8
Headache	23.1	4.8	2.2	21.2	5.1	2.7	24.4	7.5	2.0
Malaise	31.9	11.2	5.5	32.8	11.4	5.6	33.4	10.8	5.0
Myalgia	28.6	12.2	3.3	34.1	9.0	2.7	28.4	11.1	2.8

[a]NCT01240746
[b]The safety analysis set includes all persons who received at least one dose of study vaccine
[c]Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
[d]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[e]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[f]N is the number of participants in the safety analysis set
[g]Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: ≥101.2°F to ≤102.0°F; Headache, Malaise, and Myalgia: some interference with activity
[h]Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: ≥102.1°F; Headache, Malaise, and Myalgia: Significant; prevents daily activity
[i]Fever measured by any route

Among children 6 months through 8 years of age, unsolicited non-serious adverse events were reported in 1360 (47.0%) recipients in the Fluzone Quadrivalent group, 352 (48.0%) recipients in the TIV-1 group, and 346 (48.0%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were cough, vomiting, and pyrexia. During the 28 days following vaccination, a total of 16 (0.6%) recipients in the Fluzone Quadrivalent group, 4 (0.5%) recipients in the TIV-1 group, and 4 (0.6%) recipients in the TIV-2 group experienced at least one SAE; no deaths occurred. Throughout the study period, a total of 41 (1.4%) recipients in the Fluzone Quadrivalent group, 7 (1.0%) recipients in the TIV-1 group, and 14 (1.9%) recipients in the TIV-2 group, experienced at least one SAE. Three SAEs were considered to be possibly related to vaccination: croup in a Fluzone Quadrivalent recipient and 2 episodes of febrile seizure, 1 each in a TIV-1 recipient and a TIV-2 recipient. One death occurred in the TIV-1 group (a drowning 43 days post-vaccination).

Adults

In study 2 (NCT00988143, see http://clinicaltrials.gov), a multi-centered randomized, open-label trial conducted in the US, adults 18 years of age and older received one dose of either Fluzone Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 570 recipients, half aged 18-60 years and half aged 61 years or older. Among participants in the three vaccine groups combined, 67.2% were female (Fluzone Quadrivalent, 68.4%; TIV-1, 67.9%; TIV-2, 65.3%), 88.4% Caucasian (Fluzone Quadrivalent, 91.1%; TIV-1, 86.8%; TIV-2, 87.4%), 9.6% Black (Fluzone Quadrivalent, 6.8%; TIV-1, 12.1%; TIV-2, 10.0%), 0.4% Hispanic (Fluzone Quadrivalent, 0.0%; TIV-1, 0.5%; TIV-2, 0.5%), and 1.7% were of other racial/ethnic groups (Fluzone Quadrivalent, 2.1%; TIV-1, 0.5%; TIV-2, 2.2%). Table 4 summarizes solicited injection-site and systemic adverse reactions reported within 3 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

Table 4: Study 2[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 3 Days After Vaccination in Adults 18 Years of Age and Older (Safety Analysis Set)[b]

	Fluzone Quadrivalent[c] (N[f]=190)			TIV-1[d] (B Victoria) (N[f]=190)			TIV-2[e] (B Yamagata) (N[f]=190)		
	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)
Injection-site adverse reactions									
Pain	47.4	6.8	0.5	52.1	7.9	0.5	43.2	6.3	0.0
Erythema	1.1	0.0	0.0	1.6	0.5	0.0	1.6	0.5	0.0
Swelling	0.5	0.0	0.0	2.2	0.5	0.0	1.1	0.0	0.0
Induration	0.5	0.0	0.0	1.6	0.5	0.0	0.5	0.0	0.0
Ecchymosis	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0	0.0
Systemic adverse reactions									
Myalgia	23.7	5.8	0.0	25.3	5.8	0.0	16.8	5.8	0.0
Headache	15.8	2.2	0.5	18.4	6.3	0.5	18.0	4.2	0.0
Malaise	10.5	1.6	1.1	14.7	3.2	1.1	12.1	4.7	0.5
Shivering	2.6	0.5	0.0	5.3	1.1	0.0	3.2	0.5	0.0
Fever (≥100.4°F)[i]	0.0	0.0	0.0	0.5	0.5	0.0	0.5	0.5	0.0

[a]NCT00988143
[b]The safety analysis set includes all persons who received study vaccine
[c]Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
[d]2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[e]2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed
[f]N is the number of participants in the safety analysis set
[g]Grade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, Malaise, and Shivering: some interference with activity
[h]Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, Malaise, and Shivering: Significant; prevents daily activity
[i]Fever measured by any route

Unsolicited non-serious adverse events were reported in 33 (17.4%) recipients in the Fluzone Quadrivalent group, 45 (23.7%) recipients in the TIV-1 group, and 45 (23.7%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were headache, cough, and oropharyngeal pain. In the follow-up period, there were two SAEs, 1 (0.5%) in the Fluzone Quadrivalent group and 1 (0.5%) in the TIV-2 group. No deaths were reported during the trial period.

Geriatric Adults

In Study 3 (NCT01218646, see http://clinicaltrials.gov), a multi-center, randomized, double-blind trial conducted in the US, adults 65 years of age and older received one dose of either Fluzone Quadrivalent, or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 675 recipients. Among participants in the three vaccine groups combined, 55.7% were female (Fluzone Quadrivalent, 57.3%; TIV-1, 56.0%; TIV-2, 53.8%), 89.5% Caucasian (Fluzone Quadrivalent, 87.6%; TIV-1, 89.8%; TIV-2, 91.1%), 2.2% Black (Fluzone Quadrivalent, 4.0%; TIV-1, 1.8%; TIV-2, 0.9%), 7.4% Hispanic (Fluzone Quadrivalent, 8.4%; TIV-1, 7.6%; TIV-2, 6.2%) and 0.9% were of other racial/ethnic groups (Fluzone Quadrivalent, 0.0%; TIV-1, 0.9%; TIV-2, 1.8%).

Table 5 summarizes solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

Table 5: Study 3[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Adults 65 Years of Age and Older (Safety Analysis Set)[b]

	Fluzone Quadrivalent[c] (N[f]=225)			TIV-1[d] (B Victoria) (N[f]=225)			TIV-2[e] (B Yamagata) (N[f]=225)		
	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)	Any (%)	Grade 2[g] (%)	Grade 3[h] (%)
Injection-site adverse reactions									
Pain	32.6	1.3	0.9	28.6	2.7	0.0	23.1	0.9	0.0
Erythema	2.7	0.9	0.0	1.3	0.0	0.0	1.3	0.4	0.0
Swelling	1.8	0.4	0.0	1.3	0.0	0.0	0.0	0.0	0.0
Systemic adverse reactions									
Myalgia	18.3	4.0	0.4	18.3	4.0	0.0	14.2	2.7	0.4
Headache	13.4	1.3	0.4	11.6	1.3	0.0	11.6	1.8	0.4
Malaise	10.7	4.5	0.4	6.3	0.4	0.0	11.6	2.7	0.9
Fever (≥100.4°F)[i]	1.3	0.0	0.4	0.0	0.0	0.0	0.9	0.4	0.4

[a]NCT01218646
[b]The safety analysis set includes all persons who received study vaccine
[c]Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
[d]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[e]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[f]N is the number of participants in the safety analysis set
[g]Grade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, and Malaise: some interference with activity
[h]Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema and Injection-site swelling: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, and Malaise: Significant; prevents daily activity
[i]Fever measured by any route

Unsolicited non-serious adverse events were reported in 28 (12.4%) recipients in the Fluzone Quadrivalent group, 22 (9.8%) recipients in the TIV-1 group, and 22 (9.8%) recipients in the TIV-2 group. The most commonly reported adverse events were oropharyngeal pain, rhinorrhea, injection-site induration, and headache. Three SAEs were reported during the follow-up period, 2 (0.9%) in the TIV-1 group and 1 (0.4%) in the TIV-2 group. No deaths were reported during the trial period.

6.2 Post-Marketing Experience

Currently, there are no post-marketing data available for Fluzone Quadrivalent vaccine.

The following events have been spontaneously reported during the post-approval use of

the trivalent formulation of Fluzone. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Fluzone.

- *Blood and Lymphatic System Disorders:* Thrombocytopenia, lymphadenopathy
- *Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- *Eye Disorders:* Ocular hyperemia
- *Nervous System Disorders:* Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- *Vascular Disorders:* Vasculitis, vasodilatation/flushing
- *Respiratory, Thoracic and Mediastinal Disorders:* Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* Pruritus, asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders:* Vomiting

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: A developmental and reproductive toxicity study has been performed in female rabbits at a dose approximately 20 times the human dose (on a mg/kg basis) and has revealed no evidence of impaired female fertility or harm to the fetus due to Fluzone Quadrivalent. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Fluzone Quadrivalent should be given to a pregnant woman only if clearly needed.

In the developmental and reproductive toxicity study, female rabbits were administered Fluzone Quadrivalent or control saline (each 0.5 mL/dose) by intramuscular injection 24 and 10 days before insemination, and on Days 6, 12, and 27 of gestation. The administration of Fluzone Quadrivalent did not result in systemic maternal toxicity (no adverse clinical signs and no change in body weight or food consumption). In addition, no adverse effects on pregnancy, parturition, lactation, or embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study.

Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Fluzone Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

8.3 Nursing Mothers

It is not known whether Fluzone Quadrivalent is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fluzone Quadrivalent is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Fluzone Quadrivalent in children below the age of 6 months have not been established.

8.5 Geriatric Use

Safety and immunogenicity of Fluzone Quadrivalent were evaluated in adults 65 years of age and older [See *Clinical Studies* (14.5)]. Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults.

11 DESCRIPTION

Fluzone Quadrivalent (Influenza Vaccine) for intramuscular injection is an inactivated influenza vaccine, prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100), producing a "split virus". The split virus is further purified and then suspended in sodium phosphate-buffered isotonic sodium chloride solution. The Fluzone Quadrivalent process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration. Antigens from the four strains included in the vaccine are produced separately and then combined to make the quadrivalent formulation.

Fluzone Quadrivalent suspension for injection is clear and slightly opalescent in color.

Antibiotics are not used in the manufacture of Fluzone Quadrivalent.

The Fluzone Quadrivalent prefilled syringe and vial presentations are not made with natural rubber latex.

Fluzone Quadrivalent is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following four influenza strains recommended for the 2016-2017 influenza season: A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Brisbane/60/2008 (B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 6. The single-dose, pre-filled syringe (0.25 mL and 0.5 mL) and the single-dose vial (0.5 mL) are manufactured and formulated without thimerosal or any other preservative. The 5 mL multi-dose vial presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury. Each 0.25 mL dose from the multi-dose vial contains 12.5 mcg mercury.

Table 6: Fluzone Quadrivalent Ingredients

Ingredient	Quantity (per dose)	
	Fluzone Quadrivalent 0.25 mL Dose	Fluzone Quadrivalent 0.5 mL Dose
Active Substance: Split influenza virus, inactivated strains[a]:	30 mcg HA total	60 mcg HA total
A (H1N1)	7.5 mcg HA	15 mcg HA
A (H3N2)	7.5 mcg HA	15 mcg HA
B (Victoria lineage)	7.5 mcg HA	15 mcg HA
B (Yamagata lineage)	7.5 mcg HA	15 mcg HA
Other:		
Sodium phosphate-buffered isotonic sodium chloride solution	QS[b] to appropriate volume	QS[b] to appropriate volume
Formaldehyde	≤50 mcg	≤100 mcg
Octylphenol ethoxylate	≤125 mcg	≤250 mcg
Preservative		
Single-dose presentations	-	-
Multi-dose presentation (thimerosal)	12.5 mcg mercury	25 mcg mercury

[a]per United States Public Health Service (USPHS) requirement
[b]Quantity Sufficient
"-" Indicates information is not applicable

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. Protection from influenza virus infection has not been correlated with a specific level of hemagglutination inhibition (HI) antibody titer post-vaccination. However, in some human studies, antibody titers ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects. (See ref. 2) (See ref. 3)

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains representing the influenza viruses likely to be circulating in the US during the influenza season.

Annual vaccination with the influenza vaccine is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluzone Quadrivalent has not been evaluated for carcinogenic or mutagenic potential. A reproductive study of female rabbits vaccinated with Fluzone Quadrivalent was performed and revealed no evidence of impaired female fertility [see *Pregnancy* (8.1)].

14 CLINICAL STUDIES

The effectiveness of Fluzone Quadrivalent was demonstrated based on clinical endpoint efficacy data for Fluzone (trivalent influenza vaccine) and on an evaluation of serum HI antibody responses to Fluzone Quadrivalent. Fluzone Quadrivalent, an inactivated influenza vaccine that contains the hemagglutinins of two influenza A subtype viruses and two influenza type B viruses, is manufactured according to the same process as Fluzone.

14.1 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Children 6 through 24 Months of Age

A randomized, double-blind, placebo-controlled study was conducted at a single US center during the 1999-2000 (Year 1) and 2000-2001 (Year 2) influenza seasons. The intent-to-treat analysis set included a total of 786 children 6 through 24 months of age. Participants received two doses of either Fluzone (N = 525) or a placebo (N = 261). Among all randomized participants in both years, the mean age was 13.8 months; 52.5% were male, 50.8% were Caucasian, 42.0% were Black, and 7.2% were of other racial groups. Cases of influenza were identified through active and passive surveillance for influenza-like illness or acute otitis media and confirmed by culture. Influenza-like illness was defined as fever with signs or symptoms of an upper respiratory infection. Vaccine efficacy against all influenza viral types and subtypes was a secondary endpoint and is presented in Table 7.

Table 7: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Culture-Confirmed Influenza in Children Aged 6 through 24 Months during the 1999-2000 and 2000-2001 Influenza Seasons – Intent-to-Treat Analysis Set[a]

	Fluzone[b]				Placebo[c]				Fluzone vs. Placebo	
Year	n[d]	N[e]	Rate (n/N)[f]	(95% CI)	n[d]	N[e]	Rate (n/N)[f]	(95% CI)	Relative Risk (95% CI)	Percent Relative Reduction[g] (95% CI)
Year 1[h] (1999-2000)	15	273	5.5	(3.1; 8.9)	22	138	15.9	(10.3; 23.1)	0.34 (0.18; 0.64)	66 (36; 82)
Year 2[i] (2000-2001)	9	252	3.6	(1.6; 6.7)	4	123	3.3	(0.9; 8.1)	1.10 (0.34; 3.50)	-10 (-250; 66)

[a]The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated
[b]Fluzone: 1999-2000 formulation containing A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage) and 2000-2001 formulation containing A/New

Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage)
Placebo: 0.4% NaCl
n is the number of participants with culture-confirmed influenza for the given year of study as listed in the first column
N is the number of participants randomly assigned to receive Fluzone or placebo for the given year of study as listed in the column headers (intent-to-treat analysis set)
Rate (%) = (n/N) * 100
Relative reduction in vaccine efficacy was defined as (1-relative risk) x 100
Includes all culture confirmed influenza cases throughout the study duration for Year 1 (12 months of follow-up)
Includes all culture-confirmed influenza cases throughout the study duration for Year 2 (6 months of follow-up)

14.2 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Adults

A randomized, double-blind, placebo-controlled study was conducted in a single US center during the 2007-2008 influenza season. Participants received one dose of either Fluzone vaccine (N=813), an active comparator (N = 814), or placebo (N = 325). The intent-to-treat analysis set included 1138 healthy adults who received Fluzone or placebo. Participants were 18 through 49 years of age (mean age was 23.3 years); 63.2% were female, 83.1% were Caucasian, and 16.9% were of other racial/ethnic groups. Cases of influenza were identified through active and passive surveillance and confirmed by cell culture and/or real-time polymerase chain reaction (PCR). Influenza-like illness was defined as an illness with at least 1 respiratory symptom (cough or nasal congestion) and at least 1 constitutional symptom (fever or feverishness, chills, or body aches). Vaccine efficacy of Fluzone against all influenza viral types and subtypes is presented in Table 8.

Table 8: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Influenza in Adults Aged 18 through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat Analysis Set

Laboratory-Confirmed Symptomatic Influenza	Fluzone (N=813)			Placebo (N=325)			Fluzone vs. Placebo	
	n	Rate (%)	(95% CI)	n	Rate (%)	(95% CI)	Relative Risk (95% CI)	Percent Relative Reduction (95% CI)
Positive culture	21	2.6	(1.6, 3.9)	31	9.5	(6.6, 13.2)	0.27 (0.16, 0.46)	73 (54, 84)
Positive PCR	28	3.4	(2.3, 4.9)	35	10.8	(7.6, 14.7)	0.32 (0.20, 0.52)	68 (48, 80)
Positive culture, positive PCR, or both	28	3.4	(2.3, 4.9)	35	10.8	(7.6, 14.7)	0.32 (0.20, 0.52)	68 (48, 80)

NCT00538512
The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated
Fluzone: 2007-2008 formulation containing A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (Victoria lineage)
Placebo: 0.9% NaCl
N is the number of participants randomly assigned to receive Fluzone or placebo
n is the number of participants satisfying the criteria listed in the first column
Rate (%) = (n/N) * 100
Relative reduction in vaccine efficacy was defined as (1 - relative risk) x 100

14.3 Immunogenicity of Fluzone Quadrivalent in Children 6 Months through 8 Years of Age

In Study 1 (NCT01240746) [see *Adverse Reactions (6.1)*], 1419 children 6 months through 35 months of age and 2101 children 3 years through 8 years of age were included in the per-protocol immunogenicity analysis. Participants received one or two 0.25 mL doses or one or two 0.5 mL doses, respectively of Fluzone Quadrivalent, TIV-1, or TIV-2. For participants who received two doses, the doses were administered approximately 4 weeks apart. The distribution of demographic characteristics was similar to that of the safety analysis [see *Adverse Reactions (6.1)*].

HI antibody geometric mean titers (GMTs) and seroconversion rates 28 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 9 and Table 10).

Table 9: Study 1: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age (Per-protocol Analysis Set)

Antigen Strain	Fluzone Quadrivalent N=2339	Pooled TIV N=1181		GMT Ratio (95% CI)
	GMT	GMT		
A (H1N1)	1124	1096		1.03 (0.93, 1.14)
A (H3N2)	822	828		0.99 (0.91, 1.08)
	Fluzone Quadrivalent N=2339	TIV-1 (B Victoria) N=582	TIV-2 (B Yamagata) N=599	GMT Ratio (95% CI)
	GMT	GMT	GMT	
B/Brisbane/60/2008 (B Victoria)	86.1	64.3	(19.5)	1.34 (1.20, 1.50)
B/Florida/04/2006 (B Yamagata)	61.5	(16.3)	58.3	1.06 (0.94, 1.19)

NCT01240746
Per-protocol analysis set included all persons who had no study protocol deviations
Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
N is the number of participants in the per-protocol analysis set
Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66
2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
TIV-2 did not contain B/Brisbane/60/2008
TIV-1 did not contain B/Florida/04/2006

Table 10: Study 1: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age (Per-protocol Analysis Set)

Antigen Strain	Fluzone Quadrivalent N=2339	Pooled TIV N=1181		Difference of Seroconversion Rates (95% CI)
	Seroconversion (%)			
A (H1N1)	92.4	91.4		0.9 (-0.9, 2.6)
A (H3N2)	88.0	84.2		3.8 (1.4, 6.3)
	Fluzone Quadrivalent N=2339	TIV-1 (B Victoria) N=582	TIV-2 (B Yamagata) N=599	Difference of Seroconversion Rates (95% CI)
	Seroconversion (%)			
B/Brisbane/60/2008 (B Victoria)	71.8	61.1	(20.0)	10.7 (6.4, 15.1)
B/Florida/04/2006 (B Yamagata)	66.1	(17.9)	64.0	2.0 (-2.2, 6.4)

NCT01240746
Per-protocol analysis set included all persons who had no study protocol deviations
Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
N is the number of participants in the per-protocol analysis set
Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10
Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >-10%
2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
TIV-2 did not contain B/Brisbane/60/2008
TIV-1 did not contain B/Florida/04/2006

Non-inferiority immunogenicity criteria based on HI antibody GMTs and seroconversion rates were also met when age subgroups (6 months to <36 months and 3 years to <9 years) were examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV and the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

14.4 Immunogenicity of Fluzone Quadrivalent in Adults ≥18 Years of Age

In Study 2 (NCT00988143) [see *Adverse Reactions (6.1)*], 565 adults 18 years of age and older who had received one dose of Fluzone Quadrivalent, TIV-1, or TIV-2 were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis [see *Adverse Reactions (6.1)*].

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 11).

Table 11: Study 2: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-protocol Analysis Set)

Antigen Strain	Fluzone Quadrivalent N=190	Pooled TIV N=375		GMT Ratio (95% CI)
	GMT	GMT		
A (H1N1)	161	151		1.06 (0.87, 1.31)
A (H3N2)	304	339		0.90 (0.70, 1.15)
	Fluzone Quadrivalent N=190	TIV-1 (B Victoria) N=187	TIV-2 (B Yamagata) N=188	GMT Ratio (95% CI)
	GMT	GMT	GMT	
B/Brisbane/60/2008 (B Victoria)	101	114	(44.0)	0.89 (0.70, 1.12)
B/Florida/04/2006 (B Yamagata)	155	(78.1)	135	1.15 (0.93, 1.42)

NCT00988143
Per-protocol analysis set included all persons who had no study protocol deviations
Fluzone Quadrivalent containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
N is the number of participants in the per-protocol analysis set
Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

[f]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >2/3
[g]2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[h]2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed
[i]TIV-2 did not contain B/Brisbane/60/2008
[j]TIV-1 did not contain B/Florida/04/2006

14.5 Immunogenicity of Fluzone Quadrivalent in Geriatric Adults ≥65 Years of Age

In Study 3 (NCT01218646) [see *Adverse Reactions (6.1)*], 660 adults 65 years of age and older were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis [see *Adverse Reactions (6.1)*].

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following TIV for all four strains, based on pre-specified criteria (see Table 12). Seroconversion rates 21 days following Fluzone Quadrivalent were non-inferior to those following TIV for H3N2, B/Brisbane, and B/Florida, but not for H1N1 (see Table 13). The HI antibody GMT following Fluzone Quadrivalent was higher than that following TIV-1 for B/Florida but not higher than that following TIV-2 for B/Brisbane, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV). Seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV, based on pre-specified criteria (the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

Table 12: Study 3[a]: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)[b]

Antigen Strain	Fluzone Quadrivalent[c] N[d]=220	Pooled TIV[e] N[d]=440		GMT Ratio (95% CI)[f]
	GMT	GMT		
A (H1N1)	231	270		0.85 (0.67, 1.09)
A (H3N2)	501	324		1.55 (1.25, 1.92)
	Fluzone Quadrivalent[c] N[d]=220	TIV-1[g] (B Victoria) N[d]=219	TIV-2[h] (B Yamagata) N[d]=221	GMT Ratio (95% CI)[f]
	GMT	GMT	GMT	
B/Brisbane/60/2008 (B Victoria)	73.8	57.9	(42.2)[i]	1.27 (1.05, 1.55)
B/Florida/04/2006 (B Yamagata)	61.1	(28.5)[j]	54.8	1.11 (0.90, 1.37)

[a]NCT01218646
[b]Per-protocol analysis set included all persons who had no study protocol deviations
[c]Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
[d]N is the number of participants in the per-protocol analysis set
[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
[f]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66
[g]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[h]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[i]TIV-2 did not contain B/Brisbane/60/2008
[j]TIV-1 did not contain B/Florida/04/2006

Table 13: Study 3[a]: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)[b]

Antigen Strain	Fluzone Quadrivalent[c] N[d]=220	Pooled TIV[e] N[d]=440		Difference of Seroconversion Rate (95% CI)[f]
	Seroconversion[g] (%)			
A (H1N1)	65.91	69.77		-3.86 (-11.50, 3.56)
A (H3N2)	69.09	59.32		9.77 (1.96, 17.20)
	Fluzone Quadrivalent[c] N[d]=220	TIV-1[h] (B Victoria) N[d]=219	TIV-2[i] (B Yamagata) N[d]=221	Difference of Seroconversion Rate (95% CI)[f]
	Seroconversion[g] (%)			
B/Brisbane/60/2008 (B Victoria)	28.64	18.72	(8.60)[j]	9.91 (1.96, 17.73)
B/Florida/04/2006 (B Yamagata)	33.18	(9.13)[k]	31.22	1.96 (-6.73, 10.60)

[a]NCT01218646
[b]Per-protocol analysis set included all persons who had no study protocol deviations
[c]Fluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
[d]N is the number of participants in the per-protocol analysis set
[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
[f]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >-10%
[g]Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10
[h]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[i]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[j]TIV-2 did not contain B/Brisbane/60/2008
[k]TIV-1 did not contain B/Florida/04/2006

15 REFERENCES

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2 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. Virus Res 2004;103:133-138.
3 Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single-dose, prefilled syringe (pink plunger rod), without needle, 0.25 mL (NDC 49281-516-00) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281- 516-25).

Single-dose, prefilled syringe (clear plunger rod), without needle, 0.5 mL (NDC 49281-416-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-416-50

Single-dose vial, 0.5 mL (NDC 49281-416-58) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-416-10)

Multi-dose vial, 5 mL (NDC 49281-625-78) (not made with natural rubber latex). Supplied as package of 1 (NDC 49281- 625-15). A maximum of ten doses can be withdrawn from the multi-dose vial.

16.2 Storage and Handling

Store all Fluzone Quadrivalent presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

Do not use after the expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information). Inform the vaccine recipient or guardian:

- Fluzone Quadrivalent contains killed viruses and cannot cause influenza.
- Fluzone Quadrivalent stimulates the immune system to protect against influenza, but does not prevent other respiratory infections.
- Annual influenza vaccination is recommended.
- Report adverse reactions to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967
- Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-822-2463.

Vaccine Information Statements must be provided to vaccine recipients or their guardians, as required by the National Childhood Vaccine Injury Act of 1986 prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

SANOFI PASTEUR

6872, 6879, 6883

15.4: National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]

DMID Toxicity Table for Use in Trials Enrolling Healthy Adults (2014)

The abbreviations used in the following tables are:
ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; AV block: atrioventricular block; bpm: beats per minute; BUN: blood urea nitrogen; CK: creatine kinase; CPK: creatine phosphokinase; FEV_1: forced expiratory volume in 1 second; g: gram; HI: high; HPF: high power field; IU: international unit; IV: intravenous; K/CUMM: $x10^3/mm^3$; LLN: lower limit of normal; LO: low; mEq: milliequivalent; mmHg: millimeter of mercury; ms: millisecond; N: normal; PT: prothrombin time; PTT: partial thromboplastin time; QTc: QT-interval corrected for heart rate; QTcB: Bazett's corrected QT interval; QTcF: Fridericia's corrected QT interval; RBC: red blood cell; Rx: therapy; s: second; U: unit; ULN: upper limit of normal

CLINICAL ADVERSE EVENTS

Cardiovascular	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Arrhythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, blood loss	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL, no transfusion required	Transfusion required
QTcF (Fridericia's correction) [a] or QTcB (Bazett's correction)	Asymptomatic, QTc interval 450-479 ms, *OR* Increase in interval<30 ms above baseline	Asymptomatic, QTc interval 480-499 ms, *OR* Increase in interval 30-50 ms above baseline	Asymptomatic, QTc interval ≥500 ms, *OR* Increase in interval ≥60 ms above baseline
PR interval (prolonged)	PR interval 0.21-0.25 s	PR interval >0.25 s	Type II 2nd degree AV block *OR* Ventricular pause >3.0 s
Respiratory	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient-no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, acute	Transient; no treatment; FEV_1 71%-80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 60%-70% (of peak flow)	No normalization with bronchodilator; FEV_1 <60% of peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment

[a] Inclusion dependent upon protocol requirements

Gastrointestinal	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	6 or more loose or watery stools or >800 g/24 hours or requires IV hydration
Reactogenicity	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Local reactions			
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness [a]	2.5-5 cm	5.1-10 cm	>10 cm
Induration/swelling [b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All other conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

LABORATORY AND VITAL SIGNS TOXICITY GRADING

Blood, Serum, or Plasma Chemistries [a,b]	LO/HI/N [c]	Mild (Grade 1) [d]	Moderate (Grade 2)	Severe (Grade 3)
Sodium (mEq/L or mmol/L)	LO	132-<LLN	130-131	<130
	HI	>ULN-148	149-150	>150
Potassium (mEq/L or mmol/L) [e]	LO	<LLN-3.2	<3.2-3.1	<3.1
	HI	>ULN-5.6	>5.6-5.7	>5.7
Glucose (mg/dL)	LO	65-67	55-64	<55
	HI [f]	>ULN-120	121-130	>130
	HI [g]	140-159	160-200	>200
Blood urea nitrogen	HI	23-26 (mg/dL) or 8.3-9.4 (mmol/L)	27-31 (mg/dL) or 9.5- 11.2 (mmol/L)	>31 (mg/dL) or >11.2 (mmol/L)
Creatinine	N	>ULN-1.7 (mg/dL) or >ULN-151 (µmol/L)	1.8-2.0 (mg/dL) or 152-177 (µmol/L)	>2.0 (mg/dL) or > 177 (µmol/L)
Calcium (mg/dL)	LO	8.0-<LLN	7.5-7.9	<7.5
	HI	>ULN-11.0	11.1-11.5	>11.5
Magnesium (mg/dL)	LO	1.3-1.5	1.1-1.2	<1.1
Phosphorous (mg/dL)	LO	2.3-2.5	2.0-2.2	<2.0
Creatinine kinase (CPK or CK) (IU/L)	N	400-1000	1001-1500	>1500
Albumin (g/dL)	LO	2.8-3.0	2.5-2.7	<2.5
Total protein (g/dL)	LO	5.2-<LLN	5.0-5.4	<5.0
Alkaline phosphatase (U/L)	N	132-240	241-360	>360
AST (U/L)	HI	44-105	106-175	>175
ALT (U/L)	HI	44-105	106 -175	>175
Bilirubin, serum total (mg/dL)	HI	1.3-2.0	2.1-2.5	>2.5
Bilirubin, serum total (mg/dL) when ALT ≥105 (Hy's law)	HI	1.3-1.5	1.6-2.0	>2.0
Amylase (U/L)	N	200-270	271-360	>360
Lipase (U/L)	N	176-270	271-360	>360

[a] Depending upon the laboratory used, references ranges, eligibility ranges and grading may be split out by sex and/or age.
[b] Cardiac troponin I increase by factor: >ULN-<2.0xULN; ≥2.0-<5.0xULN; ≥5.0xULN. (This footnote is added by the sponsor).
[c] Low, High, Not Graded.
[d] If initial bound of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.
[e] Modified according to the laboratory range using a standardization formula (Tinazzi et al, 2014).**Error! Reference source not found.**
[f] Fasting.
[g] Non-fasting.

Hematology	LO/HI/N [a]	Mild (Grade 1) [b]	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (women) (g/dL)	LO	11.0-11.5	9.5-10.9	<9.5
Hemoglobin (men) (g/dL)	LO	12.0-12.5	10.0-11.9	<10.0
White blood cell count (K/CUMM)	HI	11.00-15.00	15.00-20.00	>20.00
	LO	2.50-3.50	1.50-2.49	<1.50
Lymphocytes (K/CUMM)	LO	0.75-1.00	0.50-0.75	<0.5
Neutrophils (K/CUMM)	LO	1.50-2.00	1.00-1.49	<1.00
Eosinophils (K/CUMM)	HI	0.50-0.75	0.75-1.50	>1.50
Platelets (K/CUMM)	LO	120-130	100-120	<100
Coagulation				
Prothrombin time (PT, seconds)	HI	> ULN-14.4	14.5-15.7	>15.7
Partial thromboplastin time (PTT or aPTT, seconds)	HI	>ULN-42.1	42.2-50.0	>50.0
Fibrinogen (mg/dL)	HI	>ULN-500	501-600	>600
	LO	<LLN-140	125-139	<125
Urine*				
Protein (dipstick)	HI	1+	2+	>2+
Ketones (dipstick) [c]	HI	1+	2+	>2+
Glucose (dipstick)	HI	1+	2+	>2+
Blood (microscopic) - red blood cells per high power field (RBC/HPF)	HI	5-10	11-50	>50 and/or gross blood

[a] Low, High, Not Graded.
[b] If initial bound of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.
[c] This grading is added by the sponsor.

16. REGISTRATION OF CLINICAL STUDIES AND DISCLOSURE OF RESULTS

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The study will be listed in clinicaltrials.gov within 21 days after enrollment of the first trial participant.