NCT04109222

Collection of Serum Samples From Children 6 Months to < 9 Years of Age Who Received Fluzone® Quadrivalent and Adults ≥ 65 Years of Age Who Received Fluzone® High-Dose, Influenza Vaccines, 2019–2020 Formulations

Phase IV, multi-center, open-label study to collect serum samples from children 6 months to < 9 years of age who received Fluzone® Quadrivalent vaccine and adults ≥ 65 years of age who received Fluzone® High-Dose vaccine for submission to CBER

Clinical Study Protocol

Health Authority File Number(s):	BB-IND #: 4518
WHO Universal Trial Number (UTN):	U1111-1225-1118
Study Code:	GRC00097
Development Phase:	Phase IV
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Products:	Fluzone® Quadrivalent, Influenza Vaccine (2019–2020 formulation) Fluzone® High-Dose, Influenza Vaccine (2019–2020 formulation)
Form/Route:	Liquid/Intramuscular
Indication For This Study:	The obtain serum samples for submission to CBER to aid in the influenza vaccine strain selection process. Children 6 months to < 9 years of age will receive the 2019–2020 formulation of Fluzone Quadrivalent vaccine and adults ≥ 65 years of age will receive the 2019–2020 formulation of Fluzone High-Dose vaccine, with all study vaccines given by the intramuscular route.
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officers:	[redacted]
Global Safety Officer:	[redacted]
Clinical Trial Manager:	[redacted]
Version and Date of the Protocol:	Version 1.0 dated 06 August 2019

History of Protocol Versions

Not applicable as this is the first version of the protocol.

Table of Contents

Synopsis

Company:	Sanofi Pasteur
Investigational Products:	Fluzone® Quadrivalent and Fluzone® High-Dose Influenza Vaccines (2019–2020 Formulations)
Active Substances:	For Fluzone Quadrivalent vaccine, influenza virus surface antigens of the following strains: • A/Brisbane/02/2018 (H1N1) • A/Kansas/14/2017 (H3N2) • B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; B Victoria lineage) • B/Phuket/3073/2013 (B Yamagata lineage) For Fluzone High-Dose, influenza virus surface antigens of the following strains: • A/Brisbane/02/2018 (H1N1) • A/Kansas/14/2017 (H3N2) • B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; B Victoria lineage)

Title of the Trial:	Collection of Serum Samples From Children 6 Months to < 9 Years of Age Who Received Fluzone® Quadrivalent and Adults ≥ 65 Years of Age Who Received Fluzone® High-Dose, Influenza Vaccines, 2019–2020 Formulations
Development Phase:	Phase IV
Coordinating Investigator:	[redacted]
Study Sites:	This will be a multi-center study conducted in 2 sites in the United States. The study centers, the Investigators at each center, including the Principal Investigators, are provided in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	First Visit, First Subject: September 2019 Last Visit, Last Subject: December 2019
Study Design, Schedule of Study Procedures, and Methodology:	This will be a Phase IV, multi-center, open-label study of a planned 90 subjects to provide serum samples from subjects who receive Fluzone Quadrivalent vaccine (children 6 months to < 9 years of age) or Fluzone High-Dose vaccine (adults ≥ 65 years of age). Each subject will be assigned to a vaccine group based on the subject's age at the time of enrollment. • Group 1: Children 6 to < 36 months of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (30 subjects planned) • Group 2: Children 3 to < 9 years of age assigned to receive a 0.5-mL

	dose of Fluzone Quadrivalent vaccine (30 subjects planned) • Group 3: Adults ≥ 65 years of age assigned to receive a 0.5-mL dose of Fluzone High-Dose vaccine (30 subjects planned) An approximately equal number of subjects from each group will be enrolled at each site. ***Vaccination*** All subjects will receive a 0.5-mL intramuscular injection of the study vaccine associated with their assigned group at Visit 1. For subjects 6 months to < 9 years of age for whom 2 doses of influenza vaccine are recommended per Advisory Committee on Immunization Practices guidance, a second intramuscular injection of Fluzone Quadrivalent vaccine will be administered at Visit 2 (28 [window, 28–35] days after Visit 1). ***Blood Sampling and Collection of Safety Data*** Study sites, at their discretion, may apply a topical analgesic to the venipuncture site prior to obtaining serum samples. However, topical analgesic agents must <u>not</u> be applied at the site of vaccine administration. <u>Subjects 6 months to < 9 years of age (Group 1 and Group 2):</u> Blood specimens (approximately 5 mL) will be obtained from all subjects prior to the first vaccination at Visit 1 (Day 0) and 28 (window, 28–35) days following the final vaccination (Visit 2, if no study vaccine is administered at Visit 2; or Visit 3, if a second dose of study vaccine is administered at Visit 2). Staff will observe subjects for 20 minutes following study vaccine administration and will record the occurrence of any serious adverse events (SAEs). Subjects' parents/guardians will record information to allow for the collection of any medical events that might represent SAEs, suspected unexpected serious adverse reactions (SUSARs), or adverse events of special interest (AESIs) from Visit 1 through Visit 2 for subjects receiving 1 dose of study vaccine, and from Visit 1 through Visit 3 for subjects receiving 2 doses of study vaccine. Parents/guardians will be asked to record this information in the diary card and to bring the diary card with them to the next visit. Staff will contact parents/guardians by telephone 21 (window, 19–23) days after each vaccination to remind them of their next visit and to ask them to notify the site immediately if a serious medical event (eg, hospital visit), which might represent an SAE, SUSAR, or AESI, occurs. In addition, parents/guardians will be reminded to record information about any medical events that might represent SAEs, SUSARs, or AESIs, and any concomitant medications taken from the most recent visit to the next visit. Staff will review the Visit 1 through Visit 2 safety data for all vaccinated subjects with parents/guardians at Visit 2. Staff will also review the Visit 2 through Visit 3 safety data with parents/guardians at Visit 3 for subjects receiving 2 doses of study vaccine. <u>Subjects ≥ 65 years of age (Group 3):</u> Blood specimens (approximately 20 mL) will be obtained from all subjects prior to vaccination at Visit 1 and 21 (window, 21–28) days post-vaccination (Visit 2). Staff will observe subjects for 20 minutes following study vaccine administration and will record the occurrence of SAEs. Subjects will record information to allow for the collection of any medical events that might

	represent SAEs, SUSARs, or AESIs from Visit 1 through Visit 2. Subjects will be asked to record this information in the diary card and to bring the diary card with them to the next visit. Staff will contact subjects by telephone 14 (window, 12–16) days after study vaccine administration to remind them of their next visit and to ask them to notify the site immediately if a serious medical event (eg, hospital visit), which might represent an SAE, SUSAR, or AESI, occurs. In addition, subjects will be reminded to record information about any medical events that might represent SAEs, SUSARs, or AESIs, and any concomitant medications taken from the most recent visit to the next visit. Staff will review the Visit 1 through Visit 2 safety data for all vaccinated subjects at Visit 2.
Interruption of the Study:	The study may be discontinued if new data about the investigational product(s) resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the institutional review board(s) (IRB[s]), or the governing regulatory authorities in the country where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRB(s), the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory requirements. The Investigator shall promptly inform the study subjects or subjects' parents/guardians, as appropriate, and should assure appropriate subject therapy and/or follow-up.
Objective:	To provide serum samples (collected from subjects before vaccination [Blood Sample 1] and after final vaccination [Blood Sample 2]) to the Center for Biologics Evaluation and Research for further analysis by the World Health Organization, the Centers for Disease Control and Prevention, and the Food and Drug Administration to support formulation recommendations for subsequent influenza vaccines. In addition, serum samples from adult subjects may be further analyzed by the Sponsor to assess breadth of immune response induced by the study vaccines.
Endpoint:	There are no endpoints for this objective.
Planned Sample Size:	The study will enroll approximately 90 subjects: approximately 30 subjects 6 to < 36 months of age will be administered Fluzone Quadrivalent vaccine (Group 1), approximately 30 subjects 3 to < 9 years of age will be administered Fluzone Quadrivalent vaccine (Group 2), and approximately 30 subjects ≥ 65 years of age will be administered Fluzone High-Dose vaccine (Group 3). No study power assessment will be done for this study. Only descriptive statistical analyses will be conducted in this study.
Duration of Participation in the Study:	Subjects 6 months to < 9 years of age: 28 (window, 28–35) days following the last dose of influenza vaccine, including SAE/AESI follow-up. No additional safety follow-up beyond Visit 2 (for subjects receiving 1 dose) or Visit 3 (for subjects receiving 2 doses) is planned. Subjects ≥ 65 years of age: 21 (window, 21–28) days after vaccination, including SAE/AESI follow-up. No additional safety follow-up beyond Visit 2 is planned.

Licensed Study Product 1:	Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2019–2020 formulation
Form:	Liquid – pre-filled syringes
Composition:	Each 0.5 mL dose of vaccine contains 15 µg hemagglutinin (HA) of each antigen: • A/Brisbane/02/2018 (H1N1) • A/Kansas/14/2017 (H3N2) • B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; B Victoria lineage) • B/Phuket/3073/2013 (B Yamagata lineage)
Route:	Intramuscular
Batch Number:	TBD
Licensed Study Product 2:	Fluzone High-Dose vaccine, 2019–2020 formulation
Form:	Liquid – pre-filled syringes
Composition:	Each 0.5 mL dose of vaccine contains 60 µg HA of each antigen: • A/Brisbane/02/2018 (H1N1) • A/Kansas/14/2017 (H3N2) • B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; B Victoria lineage)
Route:	Intramuscular
Batch Number:	TBD
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Aged 6 months to < 9 years or ≥ 65 years of age on the day of first study vaccination (study product administration). 2) For subjects 6 to < 12 months of age, born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 5.5 lbs (2.5 kg). 3) Informed consent form (ICF) has been signed and dated by subjects ≥ 65 years of age. 4) Assent form has been signed and dated by subjects 7 to < 9 years of age, and ICF has been signed and dated by parent(s) or guardian(s) for subjects 6 months to < 9 years of age. 5) Subject and parent/guardian (of subjects 6 months to < 9 years of age) are able to attend all scheduled visits and to comply with all study procedures.
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure. **Note:** Subjects may be considered eligible for enrollment if no

	intervention for the other study occurred within the 30 days prior to the first study vaccination and none are planned before the subject would complete safety surveillance for the present study. 2) Receipt of any vaccine in the 30 days preceding the first study vaccination, or planned receipt of any vaccine before Visit 2 for subjects receiving 1 dose of influenza vaccine or Visit 3 for subjects receiving 2 doses of influenza vaccine. 3) Previous vaccination against influenza (in the 2019–2020 influenza season) with either study vaccine or another vaccine. 4) Receipt of immune globulins, blood, or blood-derived products in the 3 months preceding planned inclusion. 5) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the 6 months preceding planned inclusion; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the 3 months preceding planned inclusion). 6) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to study vaccine or to a vaccine containing any of the same substances. **Note:** The list of vaccine components is included in the Prescribing Information for each study vaccine. 7) Thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator. 8) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination. 9) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily. 10) Current alcohol abuse or drug addiction. 11) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion. 12) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of planned vaccination or febrile illness (temperature ≥ 100.4°F [38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 13) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) or in-laws of the Investigator or employee with direct involvement in the proposed study. 14) History of serious adverse reaction to any influenza vaccine. 15) Personal history of Guillain-Barré syndrome. 16) Any condition that in the opinion of the Investigator would pose a health risk to the subject if enrolled or could interfere with the evaluation of the vaccine.

	17) Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder. 18) Known seropositivity for human immunodeficiency virus, hepatitis B, or hepatitis C. **Note:** Subjects enrolled into this study will not be prohibited from donating blood for non-interventional studies or other purposes.
Statistical Methods:	Summaries of baseline demographic characteristics of the study subjects will be presented. The number of subjects enrolled and their age at enrollment (mean, median, and minimum and maximum), sex, race, and ethnic origin will be summarized, along with the number and description of protocol deviations. Listings of subjects by age group, sex, vaccine received, and history of vaccination in the previous season will be provided. Listings or tables of SAEs, SUSARs, and AESIs, will also be provided. No hypotheses will be tested.

Table of Study Procedures

Study Flow Chart for Subjects 6 Months to < 9 Years of Age: 2 or 3 Visits, 1 or 2 Vaccinations

	All Subjects		Subjects Receiving 1 Dose of Influenza Vaccine	Subjects Receiving 2 Doses of Influenza Vaccine		
Visit Number	**Visit 1**	**Telephone Contact**	**Visit 2**	**Visit 2**	**Telephone Contact**	**Visit 3**
Study Timelines	**Day 0**	**Visit 1 + 21 days**	**Visit 1 + 28 days**	**Visit 1 + 28 days**	**Visit 2 + 21 days**	**Visit 2 + 28 days**
Time Windows	**-**	**+ 19 to 23 days**	**+ 28 to 35 days**	**+ 28 to 35 days**	**+ 19 to 23 days**	**+ 28 to 35 days**
Informed consent/assent[a]	X					
Inclusion & Exclusion Criteria	X					
Demographic data	X					
Medical history	X					
Influenza vaccination history	X					
History-directed physical examination	X			X		
Temperature[b]	X			X		
Review contraindications for vaccination				X		
Allocation of subject number	X					
Blood sample (BL)[c]	BL1		BL2			BL2
Vaccination[d]	X			X		
Immediate surveillance (20 minutes)	X			X		
Diary card (DC) provided	DC1			DC2		
Telephone contact[e]		X			X	
Diary card reviewed			DC1	DC1		DC2
Diary card collected			DC1	DC1		DC2
Interim history			X	X		X
Reporting medical events to allow for the collection of SAEs, SUSARs, and AESIs	To be reported throughout the study period					
Collection of reportable concomitant medications	X		X	X		X
Termination of study[f]			X			X

AESI: adverse event of special interest; SAE: serious adverse event; SUSAR: suspected unexpected serious adverse reaction

[a] Informed consent form will be signed and dated by parent(s) or guardian(s) for subjects 6 months to < 9 years of age and assent form will be signed and dated by subjects 7 to < 9 years of age.

[b] The preferred route for this study is rectal for subjects 6 to < 36 months of age, and oral for subjects 3 to < 9 years of age. The axillary route may be used when a rectal or oral temperature cannot be obtained.

[c] A blood sample, approximately 5 mL, will be collected from all subjects at Visit 1, prior to vaccination, and at either Visit 2 (for subjects receiving 1 influenza vaccine dose) or at Visit 3 (for subjects receiving 2 influenza vaccine doses).

[d] One or 2 doses of influenza vaccine will be administered according to the Advisory Committee on Immunization Practices guidance in effect during the study. If 2 doses of influenza vaccine are indicated, 1 dose will be administered during Visit 1 and the second dose will be administered approximately 28 days later during Visit 2.

[e] The subject's parent/guardian will be contacted by telephone 21 (window, 19–23) days after vaccination as a reminder to notify the site immediately if a serious medical event (eg, hospital visit) occurs and to complete the diary card and to bring it with them to the next visit.

[f] The End of Study case report form will be completed at Visit 2 for subjects receiving 1 dose of influenza vaccine or at Visit 3 for subjects receiving 2 doses of influenza vaccine.

Study Flow Chart for Subjects ≥ 65 Years of Age: 2 Visits, 1 Vaccination

Visit Number	**Visit 1**	**Telephone Contact**	**Visit 2**
Study Timelines	**Day 0**	**Visit 1 + 14 days**	**Visit 1 + 21 days**
Time Windows	**-**	**+ 12 to 16 days**	**+ 21 to 28 days**
Informed consent	X		
Inclusion/exclusion criteria	X		
Demographic data	X		
Medical history	X		
Influenza vaccination history (previous season)	X		
History-directed physical examination	X		
Temperature[a]	X		
Allocation of subject number	X		
Blood sampling (BL)[b]	BL1		BL2
Vaccination	X		
Immediate surveillance (20 minutes)	X		
Diary card provided	X		
Telephone contact[c]		X	
Diary card reviewed and collected			X
Reporting of medical events to allow for the collection of SAEs, SUSARs, and AESIs	To be reported throughout the study period		
Collection of reportable concomitant medications	X		X
Termination of study			X

AESI: adverse event of special interest; SAE: serious adverse event; SUSAR: suspected unexpected serious adverse reaction

[a] The preferred route for this study for subjects ≥ 65 years of age is oral.

[b] A blood sample, approximately 20 mL, will be collected at Visit 1 and Visit 2.

[c] Subjects will be contacted by telephone 14 (window, 12–16) days after vaccination as a reminder to notify the site immediately if a serious medical event (eg, hospital visit) occurs and to complete the diary card and to bring it with them to Visit 2.

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Event of Special Interest
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDM	Clinical Data Management
CRA	Clinical Research Associate
CRB	Case Report Book
CRF	Case Report Form
DTaP	Diphtheria-Tetanus-Acellular-Pertussis
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FVFS	First Visit, First Subject
GBS	Guillain-Barré Syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance Department
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IIV3	Trivalent Inactivated Influenza Vaccine
IME	Important Medical Event
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
LVLS	Last Visit, Last Subject
µg	Microgram
NA	Neuraminidase
PCV	Pneumococcal Conjugate Vaccine
RMO	Responsible Medical Officer
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

US	United States
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1 Introduction

1.1 Background

This is a study using the 2019–2020 formulations of quadrivalent inactivated influenza vaccine (Fluzone® Quadrivalent, Influenza Vaccine) and high-dose trivalent inactivated influenza vaccine (Fluzone® High-Dose, Influenza Vaccine).

Influenza viruses types A and B belong to the genus *Orthomyxoviridae* and are characterized as enveloped, negative-strand, segmented ribonucleic acid (RNA) viruses. The viral envelope contains 2 virus-coded glycoprotein spikes, the hemagglutinin (HA) and neuraminidase (NA) proteins, which are key antigens in the host response to influenza virus in both natural infection and vaccination. A third protein, M2, is a minor envelope component of the A-strain viruses (1).

Influenza is transmitted through inhalation of virus-containing droplets from infected individuals. The incubation period is usually 1 to 2 days (2). The virus multiplies in the ciliated columnar epithelium of the upper and lower respiratory tract, causing cellular necrosis and sloughing (1). Virus shedding typically begins just before illness onset (within 24 hours), rapidly peaks, and remains elevated for 1 to 2 days before rapidly declining to low levels. Usually, virus shedding lasts a total of 5 to 10 days (2).

There is considerable variation in the severity of illness in different individuals, partly due to age, general health, and immune status relative to previous influenza infections and vaccination. The classic symptoms include rapid onset (12 hours or less) of malaise, fever, myalgia, headache, and a non-productive cough or sore throat. Most symptoms last several days, but malaise and cough may last for a week or more (2). Complications of influenza include primary viral pneumonia, secondary bacterial pneumonia, and exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and congestive heart failure.

While influenza affects all age groups, the elderly, children younger than 5 years of age, and persons with underlying health problems are at increased risk for complications. Members of high-risk groups who become ill with influenza are more likely than the general population to require hospitalization. Among infants and younger children, estimated rates of influenza-associated hospitalization are substantially higher than among older children and are similar to rates for other groups considered at higher risk for influenza-related complications, including persons ≥ 65 years of age who are at increased risk due to immunosenescence and adults 50–64 years of age and older who are at increased risk because they are likely to have chronic medical conditions that could lead to severe influenza illness (3).

Antigenic variation is an important feature of the influenza virus. The viral HA and NA surface antigens are subject to continuous and sequential evolution within immune or partially immune populations. Antigenic drift results from mutation(s) affecting the RNA segment coding for either HA or NA, but more commonly HA. As a result, there is alteration in protein structure involving 1 or a few amino acids, resulting in minor changes in antigenicity. Antigenic variants within a subtype (e.g., H1 or H3) emerge and through natural selection gradually become the more predominant circulating virus strain, while the preceding antigenic variant is suppressed by

specific immunity in the population. In contrast to antigenic drift, antigenic shift represents the emergence of completely new subtypes, typically through gene reassortment with other circulating strains and acquisition of antigenically different gene sequences. Antigenic shift occurs at irregular intervals and may lead to pandemics (1) (2). While influenza B appears to be more genetically stable than influenza A, the dominant circulating B strain typically varies from season to season. For over a decade, both Yamagata and Victoria lineages have co-circulated during each season with varying prevalence (4). The large antigenic divergence between the 2 influenza B lineages limits antigenic cross-reactivity; therefore, immunity to 1 B lineage may not provide adequate protection against the other. Accordingly, switching from a trivalent vaccine to a quadrivalent vaccine is expected to prevent additional morbidity and mortality associated with mismatched influenza B strains that may occur with trivalent vaccines (4). With this in mind, Fluzone Quadrivalent vaccine was developed.

Vaccination with influenza vaccine is the primary method for preventing influenza and its severe complications. It has been shown to be effective in reducing influenza-associated morbidity and mortality in groups at increased risk for influenza-related complications such as infants and young children and persons 50 years of age and older. Of note, immune responses to the vaccine are lower in seniors than those in young healthy adults (3). Strategies to improve immune responses to the vaccine in the elderly population could provide substantial additional reductions in influenza-associated morbidity and mortality. One approach is to increase the dose of HA in inactivated vaccines. Previous studies evaluating the immune responses in terms of hemagglutination inhibition (HAI) antibodies with higher doses of HA per strain in different influenza vaccines support a dose-response effect (5).

Fluzone High-Dose vaccine contains 60 µg HA per virus strain per dose, which is 4 times the amount of HA per strain per dose in Fluzone vaccine. It was developed for use in the elderly to elicit enhanced immune responses against influenza through the use of higher antigen content, with the goal of providing older adults with improved protection against the disease.

During this study, Fluzone Quadrivalent or Fluzone-High-Dose vaccine will be administered according to the guidelines in the Prescribing Information and only to persons for whom the respective vaccine is indicated.

The objective of this study is to provide serum samples collected from children 6 months to < 9 years of age who receive Fluzone Quadrivalent vaccine and adults ≥ 65 years of age who receive Fluzone High-Dose vaccine to the Center for Biologics Evaluation and Research (CBER). The serum samples are used for further analysis by the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) to support formulation recommendations for subsequent influenza vaccines. In addition, serum samples from adult subjects may be further analyzed by the Sponsor to assess breadth of immune response induced by the study vaccines.

1.1.1 Epidemiology

Influenza is noted for occurring in epidemics. Typically, localized influenza epidemics begin abruptly, peak in 2 to 3 weeks, and last 5 to 6 weeks, although this can vary considerably by season. The first sign of influenza in a community is usually reports of increased numbers of children with febrile respiratory illness, although a nursing home outbreak may be the first

indication. Outbreaks in children are usually followed by the occurrence of influenza-like illness among adults. Following this is an increase in hospital admissions for pneumonia, exacerbation of chronic obstructive pulmonary disease, croup, and congestive heart failure. Increased absenteeism from school and the workplace occur as a late indicator. Finally, an increased number of deaths due to pneumonia and influenza are a highly specific indicator of influenza. However, due to the reporting delay and time course from infection to death, this indicator lags behind the others (2).

As with other viral respiratory infections, influenza is a seasonal disease. In the Northern Hemisphere, influenza is most likely to occur from November to April, and in the Southern Hemisphere from May to October. In tropical regions, it is more endemic, with periods of increased activity occurring more than once a year.

The public health impact of influenza is dramatic. Annually, from the 2010–2011 through 2017–2018 influenza season in the United States (US), the CDC estimated that influenza resulted in 9.3–49.0 million illnesses, 140,000–960,000 hospitalizations, and 12,000–79,000 deaths (6). Estimated annual overall hospitalizations and deaths attributable to influenza during this period in the United States were higher compared to historical data, with annual estimated hospitalizations ranging from approximately 55,000 to 431,000 per season (mean: 226,000) from 1979–1980 through 2000–2001 and deaths ranging from 3,000 to 49,000 each season from 1976–1977 through 2006–2007 (7) (8). During the 2010–2011 through 2017–2018 influenza seasons, annual estimates for influenza-related hospitalizations and deaths were highest (45%–72% and 69%–89% of overall estimates, respectively) among adults ≥ 65 years of age (9). During the 2017–2018 season, rates of hospitalization in all age groups were the highest seasonal rates seen since hospital-based surveillance was expanded in 2005 to include all ages, with an estimated 11.5 million cases of influenza in children, 30 million cases of influenza in adults 18–64 years of age, and more than 7.3 million cases in adults ≥ 65 years of age (10).

In the United States, death associated with laboratory-confirmed influenza virus infection among children < 18 years of age has been a nationally reportable condition since 2004. Since reporting began, the total number of influenza-associated deaths among children during 1 season has ranged from 37 (during the 2011–2012 season) to 186 (during the 2017–2018 season, as of April 19, 2019); this excludes the 2009 pandemic, when 358 pediatric deaths from 15 April 2009 through 2 October 2010 were reported to the CDC (11). During the 2009 pandemic, the majority of children who died had 1 or more underlying medical conditions previously associated with conferring a greater risk for influenza complications (12). During the 2017–2018 season, approximately 80% of the deaths occurred in children who had not received the 2017–2018 influenza vaccine (11).

Based on current understanding, the epidemiology of influenza B is characterized by major epidemics every 2–4 years. It causes infections in all age groups, including children, young adults, and the elderly. While influenza affects all age groups, young children remain at increased risk for complications and are more likely than the general population to require hospitalization. Influenza B has been associated with myalgia, myositis, pneumonia, and leukopenia in children (13) (14) (15). Influenza B infection in older adults leads to excess mortality in some annual epidemics. Across all ages, the burden of disease from influenza B is less than that from A/H3N2 but greater than that from A/H1N1. Overall, it is a significant cause of absenteeism, clinic visits, hospitalizations, and deaths (4).

1.1.2 Prevention and Control of Infection Among Humans

Currently, the most effective measure for reducing the impact of influenza is to vaccinate persons at risk each year before the onset of the influenza season, especially persons at high risk for influenza-related complications. The Advisory Committee on Immunization Practices (ACIP) of the CDC recommends that all eligible persons 6 months of age and older receive annual vaccination against influenza (3).

Influenza vaccine has been effective in reducing influenza-related morbidity and mortality. The effectiveness of the influenza vaccine in preventing or attenuating influenza illness depends in part on the age and immune competence of the vaccine recipient and on the similarity between the virus strains present in the vaccine and those circulating in the community. Most vaccinated children and young adults develop high post-vaccination HAI antibody titers. These antibodies are protective against illness caused by strains similar to those in the vaccine or the related variants that may emerge during outbreak periods. Elderly persons and persons with certain chronic diseases may develop lower post-vaccination antibody titers than healthy young adults and thus may remain susceptible to influenza-related upper respiratory infections. However, even if such older persons develop influenza illness despite vaccination, the vaccine can be effective in preventing lower-respiratory tract involvement or other secondary complications, thereby reducing the risk of hospitalization and death (3).

Annually, from the 2011–2012 through 2018–2019[a] influenza seasons in the United States, overall vaccine effectiveness ranged from 19% to 52%, for children 6 months to < 9 years of age it ranged from 25% to 68%, and for adults ≥ 65 years of age it ranged from 17% to 50% (16). The CDC estimated that influenza vaccination prevented 23% of influenza-related hospitalizations during the 2015–2016[b] season and averted 2882 pneumonia and influenza deaths among adults ≥ 65 years of age. In this same period, for persons < 18 years of age, an estimated 167 pneumonia and influenza deaths were averted (17).

1.1.3 The Advisory Committee on Immunization Practices Recommendations

Because children 6 to < 24 months of age are at substantially increased risk for influenza-related hospitalizations, and children 24 through 59 months of age are at increased risk for influenza-related clinic and emergency department visits, ACIP has recommended annual vaccination of all eligible children in these age groups. In recent years, ACIP further expanded the age groups targeted for vaccination, and now recommends that all eligible persons 6 months of age and older receive annual influenza vaccination (3). The ACIP continues to emphasize the importance of vaccinating persons ≥ 6 months of age who have high-risk medical conditions (3).

If a child 6 months to < 9 years of age is receiving influenza vaccine for the first time, based on ACIP recommendations, 2 doses of influenza vaccine should be administered 4 weeks apart during the current season. This recommendation is based on studies demonstrating that vaccine effectiveness is lower among children who have never received influenza vaccine previously or

[a] Preliminary estimates for 2018–2019.

[b] Latest data available.

who received only 1 dose in their first year of vaccination than it is among those children who received 2 doses in their first year of being vaccinated. Children 6 months to < 9 years of age who are adequately primed, based on influenza vaccination history, should receive 1 dose during the current season as per ACIP recommendations (3).

1.2 Background of the Investigational Product

Vaccine Testing and Release

Before being released for clinical use, the 2019–2020 formulations of Fluzone Quadrivalent and Fluzone High-Dose vaccines will have passed all approved release-testing requirements.

Previous Clinical Experience: Fluzone Vaccine

Fluzone vaccine was licensed in the United States in 1947 as a whole-virus preparation and it has been available since 1980 as a split-virus preparation. Numerous clinical trials have demonstrated its safety, immunogenicity, and effectiveness. Clinical trials, in which Fluzone vaccine was used as a comparator, have also demonstrated the safety and immunogenicity, and/or effectiveness of Fluzone High-Dose and Fluzone Quadrivalent vaccines.

Fluzone Quadrivalent Vaccine

In pre-licensure studies, Fluzone Quadrivalent vaccine, which contains 4 influenza strains (A/H1N1, A/H3N2, and 2 B strains [1 each from the Yamagata and Victoria lineages]), induced antibody responses that were comparable to those induced by trivalent Fluzone vaccine with respect to the strains contained in each vaccine. Pre-licensure studies also demonstrated that the safety profile of Fluzone Quadrivalent vaccine was similar to that of trivalent Fluzone vaccine. Accordingly, Fluzone Quadrivalent vaccine offers the possibility of protecting against both B lineages simultaneously, without compromising vaccine safety (18) (19).

Fluzone High-Dose Vaccine

Fluzone High-Dose vaccine, a trivalent formulation with 60 µg HA per viral strain, has been shown in pre-licensure studies to elicit a higher immune response in the elderly than does Fluzone vaccine (15 µg HA per viral strain) (20) (21) (22). Solicited injection site and systemic reactions were reported more frequently with Fluzone High-Dose vaccine; however, these events were generally mild to moderate in intensity and transient. No safety concerns were identified. Moreover, a large-scale efficacy trial, which was conducted during 2 influenza seasons (2011–2012 and 2012–2013) and involved more than 30,000 persons, showed that Fluzone High-Dose vaccine was 24.2% more effective than Fluzone vaccine in preventing laboratory-confirmed symptomatic influenza in persons 65 years of age and older. The results of the study met the FDA-agreed criteria for demonstrating the superiority of Fluzone High-Dose vaccine compared with Fluzone vaccine for prevention of influenza disease in older adults (23).

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

The benefit to subjects participating in this study is potential protection from influenza disease following the receipt of the 2019–2020 formulation of Fluzone Quadrivalent or Fluzone High-Dose vaccine.

1.3.2 Potential Risks to Subjects

The most frequent side effect of influenza vaccination is pain or tenderness at the injection site that usually resolves within 3 days. Injection site reactions are generally mild.

Systemic findings such as malaise, myalgia, headache, shivering, fever, and other side effects can occur following vaccination and most often affect persons who have had no prior exposure to the virus antigens in the vaccine (e.g., young children) (24). These reactions begin 6 to 12 hours after vaccination and usually resolve within 3 days. Placebo-controlled trials suggest that in elderly persons and in healthy young adults, split-virus influenza vaccine is not associated with higher rates of systemic symptoms when compared with placebo injection (25).

Immediate allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component (26) (27) (28).

Guillain-Barré syndrome (GBS) is a very rare, acute, and frequently severe polyneuropathy characterized by ascending fulminant muscle paralysis. The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was < 10 cases/1,000,000 persons vaccinated. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for such a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10–20 cases per 1,000,000 adults and stretches the limits of epidemiologic investigation (29).

The reasons why swine influenza vaccine triggered GBS in 1976 to 1977 have never been discovered. In subsequent annual influenza vaccine programs in the United States, from 1977 to 1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of the studies. However, in a study of the 1992–1993 and 1993–1994 seasons, the overall relative risk for GBS was 1.7 (95% confidence interval = 1.0–2.8; P = 0.04) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS for each 1,000,000 persons vaccinated. The combined number of GBS cases peaked 2 weeks after vaccination. A meta-analysis provided a similar risk estimate for GBS following receipt of 2009 influenza A (H1N1) monovalent inactivated influenza vaccine (30). Thus, investigations to date indicate that there is no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976) and that, if influenza vaccine does pose a risk, it is probably slightly more than 1 additional case per 1,000,000 persons vaccinated. Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately 1 additional case/1,000,000 persons vaccinated is

substantially less than the risk for severe influenza, which could be prevented by vaccination in all age groups and especially in persons ≥ 65 years of age and those who have medical indications for influenza vaccination.

Neurological disorders temporally associated with influenza vaccination such as myelitis (including encephalomyelitis and transverse myelitis), optic neuritis/neuropathy, partial facial paralysis, and brachial neuritis have been reported. However, no causal relationship has been established. Almost all persons affected were adults, and the described clinical reactions began as soon as a few hours and as late as 2 weeks after vaccination. Full recovery was almost always reported (31).

Analysis of reports collected by the Vaccine Adverse Events Reporting System during the 2010–2011 influenza season suggested an increased risk of febrile seizures among children younger than 2 years of age who received trivalent inactivated influenza vaccine (IIV3) (32). Using data collected through the CDC-sponsored Vaccine Safety Datalink (VSD) project, Tse et al (33) found an increased risk of fever-associated seizure occurring on the day of and 1 day after influenza vaccination in children 6 months through 4 years of age during the 2010–2011 influenza season. The risk was higher among children who received concomitant IIV3 vaccine and pneumococcal conjugate vaccine (PCV) 13-valent, and peaked at approximately age 16 months (44.9 cases per 100,000 doses). In a subsequent study that included VSD data collected over 5 influenza seasons (2005–2011), Duffy et al (34) reported that inactivated influenza vaccination in children 6–23 months of age was not an independent risk factor for febrile seizures, but revealed an increased risk of febrile seizure when influenza vaccine was given with either PCV or a diphtheria-tetanus-acellular-pertussis (DTaP)-containing vaccine. The maximum estimated absolute excess risk due to concomitant administration of IIV3, PCV, and DTaP-containing vaccines compared with administration of these vaccines on separate days was 30 cases per 100,000 vaccinees. According to CDC, the risk of febrile seizure following influenza vaccination is small (35).

Cases of demyelinating disorders (e.g., incident multiple sclerosis in adults, acute disseminated encephalomyelitis, transverse myelitis), have been reported following influenza vaccines, although the Institute of Medicine concluded that the evidence is inadequate to accept or reject a causal relationship (31).

Cases of vasculitis have been reported following influenza immunization. A cause-and-effect relationship has not been determined (31).

A Phase III study performed in persons ≥ 65 years of age demonstrated increased rates of solicited injection site and systemic reactions in subjects receiving Fluzone High-Dose vaccine compared to persons receiving Fluzone vaccine but were typically mild and transient (22). Safety monitoring of Fluzone High-Dose vaccine during the first year after licensure indicated a higher than expected number of gastrointestinal events compared with standard-dose vaccine, but otherwise no new safety concerns were identified (36).

There may be other risks not yet identified.

Please refer to the US Prescribing Information for the vaccine administered for other adverse events (AEs).

1.4 Rationale for the Study

The aim of Study GRC00097 is to obtain serum samples for submission to CBER to aid in the influenza vaccine strain selection process. Children 6 months to < 9 years of age will receive the 2019–2020 formulation of Fluzone Quadrivalent vaccine and adults ≥ 65 years of age will receive the 2019–2020 formulation of Fluzone High-Dose vaccine.

Serum samples from subjects will be supplied to CBER after the completion of this study (i.e., after the last subject completes the last study visit). In turn, CBER will distribute the serum samples to CDC and other WHO-collaborating laboratories for evaluation against circulating influenza viral strains. It is expected that the immunologic and surveillance data will be presented at WHO meetings where the vaccine strain selections will be made for the Southern and Northern hemispheres and at the FDA Vaccines and Related Biological Products Advisory Committee meeting for selection of strains for influenza vaccines, including those to be distributed in the United States.

No early safety data review is planned for this study.

2 Study Objective

To provide serum samples (collected from subjects before vaccination [Blood Sample 1] and after final vaccination [Blood Sample 2]) to CBER for further analysis by the WHO, the CDC, and the FDA to support formulation recommendations for subsequent influenza vaccines. In addition, serum samples from adult subjects may be further analyzed by the Sponsor to assess breadth of immune response induced by the study vaccines.

There are no endpoints for this objective.

3 Investigators and Study Organization

This study will be conducted in 2 centers in in the United States. Details of the study centers, the Investigators at each center, including the Principal Investigators, are provided in the "List of Investigators and Centers Involved in the Trial" document.

The Sponsor's Responsible Medical Officers (the RMOs; the persons authorized to sign this protocol and any amendments on behalf of the Sponsor) are [redacted] and [redacted] or such delegate(s) as may be identified in their absence.

4 Independent Ethics Committee/Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form(s) (ICF[s]), assent form(s) (subjects 7 to < 9 years of age must sign an assent form), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and/or receive favorable opinion from, the appropriate Institutional Review Board(s) (IRB[s]).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and/or the Sponsor are responsible for obtaining this approval and/or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IRB(s) (the names and qualifications of the members attending and voting at the meetings).

The Investigator will submit written summaries of the status of the study to the IRB(s) annually, or more frequently if requested. All serious adverse events (SAEs)/adverse events of special interest (AESIs) occurring during the study that are related to the product administered will be reported by the Investigator to the IRB(s), according to the IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This will be a Phase IV, multi-center, open-label study of a planned 90 subjects to provide serum samples from subjects who receive Fluzone Quadrivalent vaccine (children 6 months to < 9 years of age) or Fluzone High-Dose vaccine (adults ≥ 65 years of age).

Each subject will be assigned to a vaccine group based on the subject's age at the time of enrollment.

- Group 1: Children 6 to < 36 months of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (30 subjects planned)
- Group 2: Children 3 to < 9 years of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (30 subjects planned)
- Group 3: Adults ≥ 65 years of age assigned to receive a 0.5-mL dose of Fluzone High-Dose vaccine (30 subjects planned)

An approximately equal number of subjects from each group will be enrolled at each site.

5.1.2 Justification of the Study Design

See Section 1.4 for the justification for the selection of subjects and the choice of groups.

5.1.3 Study Plan

Vaccination

All subjects will receive a 0.5-mL intramuscular injection of the study vaccine associated with their assigned group at Visit 1. For subjects 6 months to < 9 years of age for whom 2 doses of influenza vaccine are recommended per ACIP guidance, a second intramuscular injection of

Fluzone Quadrivalent vaccine will be administered at Visit 2 (28 [window, 28–35] days after Visit 1).

Blood Sampling and Collection of Safety Data

- Subjects 6 months to < 9 years of age (Group 1 and Group 2): blood specimens (approximately 5 mL) will be obtained from all subjects prior to the first vaccination at Visit 1 (Day 0) and 28 (window, 28–35) days following the final vaccination (Visit 2, if no study vaccine is administered at Visit 2; or Visit 3, if a second dose of study vaccine is administered at Visit 2). Staff will observe subjects for 20 minutes following study vaccine administration and will record the occurrence of any SAEs/AESIs. Subjects' parents/guardians will record information to allow for the collection of any medical events that might represent SAEs, suspected unexpected serious adverse reactions (SUSARs), or AESIs from Visit 1 through Visit 2 for subjects receiving 1 dose of study vaccine, and from Visit 1 through Visit 3 for subjects receiving 2 doses of study vaccine.
- Subjects ≥ 65 years of age (Group 3): blood specimens (approximately 20 mL) will be obtained from all subjects prior to vaccination at Visit 1 and 21 (window, 21–28) days post-vaccination (Visit 2). Staff will observe subjects for 20 minutes following study vaccine administration and will record the occurrence of any SAEs/AESIs. Subjects will record information to allow for the collection of any medical events that might represent SAEs, SUSARs, or AESIs from Visit 1 through Visit 2.

5.1.4 Visit Procedures

Medical procedures (injections, examinations, etc.) must be conducted by appropriately licensed or credentialed study site staff working within the scope of their licenses/credentials.

Visit 1 (Day 0): Inclusion and Vaccination

1) Explain the study objectives and design to the subject/subject's parent/guardian, including but not limited to its objectives, design, and risks and benefits, and answer any questions the subject/subject's parent/guardian may have.
2) Obtain a written informed consent from the subject/subject's parent/guardian and assent (if required as per IRB regulations). The Investigator or delegate will also sign and date the ICF and assent form, retain the originals, and give copies of the signed and dated form(s) to the subject/subject's parent/guardian.
3) Check eligibility of the subject by reviewing applicable inclusion and exclusion criteria.
4) Collect relevant demographic information (date of birth, sex, race, and ethnic origin).
5) Obtain significant medical history (see Section 5.2.6 for details). For subjects 6 months to < 9 years of age, collect influenza vaccination history to determine vaccination schedule (1 dose versus 2 doses) per ACIP recommendations in effect during the study.
6) For subjects ≥ 65 years of age, collect influenza vaccination history from previous season, including name of product if known.
7) Perform a directed physical examination, if indicated, based on medical history.

8) Measure the temperature by the preferred route (rectal for subjects 6 to < 36 months of age and oral for subjects 3 to < 9 years of age and ≥ 65 years of age) and record this information in the source document. If the subject has a temperature ≥ 100.4°F (38.0°C) defer enrollment until the subject has been afebrile for at least 24 hours (see Section 5.2.7.1).

9) If subject meets all inclusion and no exclusion criteria, receive subject number and vaccine and dose to be administered based on subject's age.

10) Obtain a pre-vaccination blood sample:

    a. approximately 5 mL for subjects 6 months to < 9 years of age

    b. approximately 20 mL for subjects ≥ 65 years of age

    Note: see Section 7.1 for detailed instructions regarding the collection of blood samples.

11) Prepare the vaccine to be administered based on the information provided in Section 6.1.1.2 and Section 6.1.2.2.

12) Within 30 minutes of removing the assigned vaccine from the refrigerator, inject 1 dose of assigned study vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle, as appropriate (see Section 6.1.1.2 and Section 6.1.2.2).

13) Observe subject for 20 minutes following the injection for the occurrence of any SAEs/AESIs.

14) Provide to the subject/subject's parent/guardian an age-appropriate diary card, for the purpose of capturing medical events that might represent SAEs, SUSARs, or AESIs, as well as any concomitant medications (see Section 6.7) from Visit 1 through Visit 2.

15) Schedule Visit 2.

16) Remind the subject/subject's parent/guardian that they will be contacted by telephone (14 [window, 12–16] days post-vaccination for subjects ≥ 65 years of age and 21 [window, 19–23] days post-vaccination for subjects 6 months to < 9 years of age) to remind them to complete the diary card and to bring the completed diary card with them to Visit 2.

17) Remind the subject/subject's parent/guardian to notify the site immediately if a serious medical event (eg, hospital visit), which might represent an SAE, SUSAR, or AESI, occurs.

18) Collect reportable concomitant medications (see Section 6.7).

19) Complete the relevant case report forms (CRFs) for this visit.

Telephone Contact – Visit 1 + 14 (Window, 12–16) for Subjects ≥ 65 Years of Age, Visit 1 + 21 (window, 19–23) Days for Subjects 6 Months to < 9 Years of Age

Note: If Day 14 (subjects ≥ 65 years of age) or Day 21 (subjects 6 months to < 9 years of age) falls on a weekend or a holiday, the telephone call may be made the following business day. If the subject or subject's parent/guardian is not available, the study staff should document the attempts to make contact.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.

2) Remind the subject/subject's parent/guardian to do the following:

- Complete the diary card as needed, and bring it to Visit 2.
- Notify the site immediately if a serious medical event (eg, hospital visit), which might represent an SAE, SUSAR, or AESI, occurs.

Visit 2 (Visit 1 + 21 [Window, 21–28] Days) – Subjects ≥ 65 Years of Age – Collection of Safety Information and Blood Sample

1) Review the diary card with the subject and collect it as a source document.
2) Review interim health history, including any medical events that might represent SAEs, SUSARs, or AESIs, medications, or therapy that occurred since vaccination. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.
3) Obtain the second blood sample (approximately 20 mL; see Section 7.1 for detailed instructions regarding the collection of blood samples).
4) Complete the relevant CRFs for this visit and the End of Study CRF.

Visit 2 (Visit 1 + 28 [Window, 28–35] Days) – Subjects 6 Months to < 9 Years of Age Receiving 1 Dose of Influenza Vaccine – Collection of Safety Information and Blood Sample

1) Review Diary Card 1 with the subject's parent/guardian for accuracy and collect it as the source document.
2) Review interim health history, including any medical events that might represent SAEs, SUSARs, or AESIs, medications, or therapy that occurred since vaccination. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.
3) Obtain the second blood sample (approximately 5 mL; see Section 7.1 for detailed instructions regarding the collection of blood samples).
4) Complete the relevant CRFs for this visit and the End of Study CRF.

Visit 2 (Visit 1 + 28 [Window, 28–35] Days) – Subjects 6 Months to < 9 Years of Age Receiving 2 Doses of Influenza Vaccine[a] – Second Vaccination and Collection of Safety Information

1) Review Diary Card 1 with the subject's parent/guardian for accuracy and collect it as the source document.
2) Review interim health history, including medical events that might represent SAEs, SUSARs, or AESIs, medications, or therapy that occurred since vaccination. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.
3) Perform a history-directed physical examination.
4) Measure temperature by the preferred route (rectal for subjects 6 to < 36 months of age and oral for subjects 3 to < 9 years of age) and record this information in the source document. If the subject has a temperature ≥ 100.4°F (≥ 38.0°C) defer vaccination until the subject has been afebrile for at least 24 hours (see Section 5.2.7.1).

[a] As per ACIP guidance.

5) Prepare the vaccine to be administered based on the information provided in Section 6.1.1.2.
6) Within 30 minutes of removing the vaccine from the refrigerator, inject subject with the vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle, as appropriate (see Section 6.1.1.2).
7) Observe subject for 20 minutes following the injection for the occurrence of any SAEs/AESIs.
8) Provide age-appropriate Diary Card 2 to the subject's parent/guardian for the purpose of capturing medical events that might represent SAEs, SUSARs, or AESIs, as well as any concomitant medications (see Section 6.7) from Visit 2 through Visit 3.
9) Schedule Visit 3.
10) Remind the subject's parent/guardian that they will be contacted by telephone 21 [window, 19–23] days post-vaccination to remind them to complete the diary card and to bring the completed diary card with them to Visit 3.
11) Remind the subject's parent/guardian to notify the site immediately if a serious medical event (eg, hospital visit), which might represent an SAE, SUSAR, or AESI, occurs.
12) Collect reportable concomitant medications (see Section 6.7).
13) Complete the relevant CRFs for this visit.

Telephone Contact – Visit 2 +21 (Window, 19–23) Days – Subjects 6 Months to < 9 Years of Age Receiving 2 Doses of Influenza Vaccine[a]

Note: If Day 21 falls on a weekend or a holiday, the telephone call may be made the following business day. If the subject or subject's parent/guardian is not available, the study staff should document the attempts to make contact.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.
2) Remind the subject or subject's parent/guardian to do the following:
   - Complete the diary card as needed, and bring it to Visit 2.
   - Notify the site immediately if a serious medical event (eg, hospital visit), which might represent an SAE, SUSAR, or AESI, occurs.

Visit 3 (Visit 2 + 28 [Window, 28–35] Days) – Subjects 6 Months to < 9 Years of Age Receiving 2 Doses of Influenza Vaccine[a] ***– Collection of Safety Information and Blood Sample***

1) Review Diary Card 2 with the subject's parent/guardian for accuracy and collect it as the source document.

[a] As per ACIP guidance.

2) Review interim health history, including any medical events that might represent SAEs, SUSARs, or AESIs, medications, or therapy that occurred since vaccination. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.
3) Obtain blood sample (approximately 5 mL; see Section 7.1 for detailed instructions regarding the collection of blood samples).
4) Complete the relevant CRFs for this visit and the End of Study CRF.

Collection of Diary Cards

If the subject/subject's parent/guardian does not return for Visit 2 or Visit 3, and the diary card is not received at the site, site personnel will contact the subject/subject's parent/guardian by telephone. During the telephone call, the subject/subject's parent/guardian will be reminded to return the diary card to the study site. Telephone calls will be recorded on the subject's source documents. If study personnel are unable to contact the subject or subject's parent/guardian by telephone with 3 attempts, study personnel will follow instructions given in Section 5.2.9.

Follow-up of subjects with SAEs, SUSARs, and AESIs That Led to Study/Vaccination Discontinuation:

Unless a subject/subject's parent/guardian refuses further contact, each subject who experiences an SAE[a]/AESI during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the subject's participation in the study) if *either* of the following is true:

- The SAE/AESI is considered by the Investigator to be related to the product administered (SUSARs, by definition, are considered related to the product administered).
- The SAE/AESI caused the discontinuation of the subject from the study or from vaccination.

5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained.

Planned study period: FVFS (first visit, first subject) to LVLS (last visit, last subject), September 2019 to December 2019

Planned end of study: December 2019

Planned date of final clinical study report: approximately 10 months after LVLS

[a] The classification of an SAE as an SUSAR is determined by the GPV Department and RMO(s) at Sanofi Pasteur.

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Subjects may be recruited from the general population. The site will ensure that any advertisements used to recruit subjects (informational brochures, parent letters, posters, and other advertisements) are submitted to Sanofi Pasteur prior to submission to the IRB(s) for approval.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject voluntarily confirms his or her willingness to participate in a particular study, or a parent/guardian confirms their willingness to allow their child to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF. In addition to the ICF that is signed by the subject or subject's parent/guardian, subjects 7 to < 9 years of age will be asked to review and sign a study assent form.

In accordance with GCP, prior to signing and dating the consent form, the subject or the subject's parent(s)/guardian(s) (of subjects 6 months to < 9 years of age) must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions. The same must also be done for subjects 7 to < 9 years of age prior to their signing and dating the assent form.

The actual ICF used at each center may differ, depending on local regulations and IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the form being used.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, or the willingness of a parent/guardian (of subjects 6 months to < 9 years of age) to have their child continue participation in the study, this will be communicated to the subject or subject's parent/guardian (as appropriate) in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF (and assent form).

Informed consent forms and assent forms will be provided in duplicate, or a photocopy of the signed consent/assent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject or subject's parent/guardian.

Documentation of the consent (and assent) process should be recorded in the source documents.

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment:

1) Aged 6 months to < 9 years or ≥ 65 years of age on the day of first study vaccination (study product administration).[a]
2) For subjects 6 to < 12 months of age, born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 5.5 lbs (2.5 kg).
3) Informed consent form has been signed and dated by subjects ≥ 65 years of age.
4) Assent form has been signed and dated by subjects 7 to < 9 years of age, and ICF has been signed and dated by parent(s) or guardian(s) for subjects 6 months to < 9 years of age.
5) Subject and parent/guardian (of subjects 6 months to < 9 years of age) are able to attend all scheduled visits and to comply with all study procedures.

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from study enrollment:

1) Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.

   Note: Subjects may be considered eligible for enrollment if no intervention for the other study occurred within the 30 days prior to the first study vaccination and none are planned before the subject would complete safety surveillance for the present study.
2) Receipt of any vaccine in the 30 days preceding the first study vaccination, or planned receipt of any vaccine before Visit 2 for subjects receiving 1 dose of influenza vaccine or Visit 3 for subjects receiving 2 doses of influenza vaccine.
3) Previous vaccination against influenza (in the 2019–2020 influenza season) with either study vaccine or another vaccine.
4) Receipt of immune globulins, blood, or blood-derived products in the 3 months preceding planned inclusion.
5) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the 6 months preceding planned inclusion; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the 3 months preceding planned inclusion).
6) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to study vaccine or to a vaccine containing any of the same substances.

[a] "6 months to < 9 years" means from the 6th month after birth to the day before the 9th year. "≥ 65 years" means from the day of the 65th birthday onwards.

Note: The list of vaccine components is included in the Prescribing Information for each study vaccine.

7) Thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator.

8) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination.

9) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

10) Current alcohol abuse or drug addiction.

11) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion.[a]

12) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of planned vaccination or febrile illness (temperature ≥ 100.4°F [38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

13) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) or in-laws of the Investigator or employee with direct involvement in the proposed study.

14) History of serious adverse reaction to any influenza vaccine.

15) Personal history of GBS.

16) Any condition that in the opinion of the Investigator would pose a health risk to the subject if enrolled or could interfere with the evaluation of the vaccine.

17) Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.

18) Known seropositivity for human immunodeficiency virus, hepatitis B, or hepatitis C.

Note: Subjects enrolled into this study will not be prohibited from donating blood for non-interventional studies or other purposes.

If the subject has a primary physician who is not the Investigator, the site should contact this physician with the subject's/subject's parent's/guardian's consent to inform him/her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

[a] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, autoimmune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases.

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE/AESI or to repetitive outpatient care will be collected in the case report book (CRB). The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. Its purpose is to assist in the later interpretation of safety data collected during the study.

5.2.7 Contraindications for Subsequent Vaccinations

5.2.7.1 Temporary Contraindications

Should a subject experience one of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the Table of Study Procedures.

1) Febrile illness (temperature ≥ 100.4°F [≥ 38.0°C]) or moderate or severe acute illness/infection on the day of vaccination, according to Investigator

5.2.7.2 Definitive Contraindications

Should a subject experience 1 or more of the conditions listed below, after the first dose of study vaccine, the Investigator will not administer the second dose of vaccine that has been allocated for use in the study (i.e., study vaccine); however, the Investigator may administer a second dose of licensed, non-study influenza vaccine in accordance with standard clinical care.

Definitive contraindications include but are not limited to:

1) An anaphylactic or other significant allergic reaction to the previous dose of vaccine
2) Receipt of any non-study vaccine (including a non-study dose of 2019–2020 influenza vaccine), immune globulins, blood, or blood-derived products between Visit 1 and Visit 2.
3) Bleeding disorder, receipt of anticoagulants, or thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator.

4) Development of any condition that in the opinion of the Investigator would pose a health risk to the subject or could interfere with the evaluation of the study vaccine (including GBS, clinically significant developmental delay, neurologic disorder, seizure disorder, human immunodeficiency virus infection, hepatitis B, or hepatitis C).

5) Development of immunodeficiency; or receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy; or receipt of long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks).

6) Adverse events that are considered a contraindication for further participation in the study.

Subjects with a definitive contraindication will continue to be followed up for the study-defined safety assessments, as applicable. Therefore, in this study, subjects with a definitive contraindication will be discontinued from the study (and, accordingly, will not have a post-vaccination blood sample collected), but will continue to be followed for study-defined safety assessments.

5.2.8 Conditions for Withdrawal

Subjects/subjects' parents/guardians will be informed that they have the right to withdraw/withdraw their child from the study at any time.

A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without permission from the subject/subject's parent/guardian.
- At the request of the subject/subject's parent/guardian (dropout).

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant non-compliance with the protocol, based on the Investigator's judgment

The reason for a withdrawal or dropout should be clearly documented in the source documents and in the CRB.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "Adverse Event") or for another reason.

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (i.e., documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant

to the least significant (refer to the CRF completion instructions for additional details and examples):

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE/AESI), as defined in Section 9.1.2.2. This category also applies if the subject experiences a definitive contraindication that is an SAE/AESI or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the Investigator and returned unsigned, and the subject or parent/guardian did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (e.g., deviation of the Inclusion/Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is not an SAE/AESI or AE. • The subject or the parent/guardian signed the certified letter sent by the Investigator, but did not give any other news and did not come to any following visit.
Withdrawal by Subject or Parent/Guardian/Legally Acceptable Representative	To be used: • When the subject or parent/guardian indicated unwillingness to continue in the study • When the subject or parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AESI or AE (e.g., subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the study because of an AE or a protocol deviation.

For subjects where the reason for early termination was lost to follow-up or if the subject withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the subject's status at the end of the study is "Withdrawal by Subject or Parent/Guardian/Legally Acceptable Representative", the site will attempt to contact them except if they specified that they do not want to be contacted again and it is documented in the source document.

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMOs for advice on how to address any study related medical question or problem. The RMOs will be available 24 hours a day, 7 days a week, as needed. Contact information for each of the RMOs is provided in the Operating Guidelines.

This process does not replace the need to report an SAE/AESI. The Investigator is still required to follow the protocol-defined process for reporting SAEs/AESIs to the Global Pharmacovigilance (GPV) Department (please refer to Section 10).

5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (e.g., those that affect the conduct of the study or the safety of subjects) require IRB approval, and must also be forwarded to regulatory authorities.

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. Administrative changes do not require IRB approval; however, the IRB(s) must be notified whenever one is made.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IRB approval has already been given, are not initiated without IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.5 Interruption of the Study

The study may be discontinued if new data about the investigational product(s) resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IRB(s), or the governing regulatory authorities in the country where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRB(s), the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory requirements. The Investigator shall promptly inform the study subjects or subjects' parents/guardians, as appropriate, and should assure appropriate subject therapy and/or follow-up.

6 Vaccines Administered

Subjects 6 to < 36 months of age and subjects 3 to < 9 years of age will be administered Fluzone Quadrivalent vaccine and subjects ≥ 65 years of age will be administered Fluzone High-Dose vaccine.

- Fluzone Quadrivalent vaccine (subjects 6 months to < 9 years of age):
  15 µg/HA of each antigen per 0.5-mL dose (total HA content per dose: 60 µg)
- Fluzone High-Dose vaccine (subjects ≥ 65 years of age):
  60 µg/HA of each antigen per 0.5-mL dose (total HA content per dose: 180 µg)

Subjects will receive an intramuscular injection of the product that they are assigned to receive. For subjects 6 months to < 9 years of age, 1 or 2 doses of influenza vaccine will be administered according to ACIP guidance in effect during the study. If 2 doses of influenza vaccine are indicated, 1 dose will be administered during Visit 1 and the second dose of Fluzone Quadrivalent vaccine will be administered approximately 28 days later, during Visit 2.

6.1 Identity of the Investigational Products

The 2019–2020 formulations of Fluzone Quadrivalent and Fluzone High-Dose vaccines are sterile suspensions prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing fluid is harvested and the virus inactivated with formaldehyde. The influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted producing a split antigen. The split antigen is then suspended in sodium phosphate-buffered isotonic sodium chloride solution. Neither antibiotics nor preservatives are used in the manufacture of the vaccine formulations used in this study. Fluzone Quadrivalent and Fluzone High-Dose vaccines are clear and slightly opalescent in color.

6.1.1 Identity of Licensed Study Product 1

Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2019–2020 formulation

6.1.1.1 Composition

Each 0.5 mL dose of vaccine contains 15 µg HA of each antigen:

- A/Brisbane/02/2018 (H1N1)
- A/Kansas/14/2017 (H3N2)
- B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; B Victoria lineage)
- B/Phuket/3073/2013 (B Yamagata lineage)

6.1.1.2 Preparation and Administration

Fluzone Quadrivalent vaccine is a liquid preparation; as such, no diluent is required. This product is provided in 0.5-mL pre-filled, single-dose syringes. The vaccine will be administered

intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle, as appropriate. The vaccine must be administered within 30 minutes of removing the vaccine from the refrigerator.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and/or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered; another dose is to be used, and the event is to be reported to the Sponsor.

Subjects must be kept under observation for 20 minutes after each vaccination to ensure their safety, and any SAEs/AESIs during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

Fluzone Quadrivalent vaccine will be administered at Visit 1 (Day 0) as a single 0.5-mL dose to subjects 6 to < 36 months of age (Group 1) and subjects 3 to < 9 years of age (Group 2) assigned to receive this vaccine. For subjects 6 months to < 9 years of age for whom 2 doses of influenza vaccine are recommended per ACIP guidance, a second dose of Fluzone Quadrivalent will be administered at Visit 2 (28 [window, 28–35] days after Visit 1).

6.1.2 Identity of Licensed Study Product 2

Fluzone High-Dose vaccine, 2019–2020 formulation

6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains 60 µg HA of each antigen:

- A/Brisbane/02/2018 (H1N1)
- A/Kansas/14/2017 (H3N2)
- B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; B Victoria lineage)

6.1.2.2 Preparation and Administration

Fluzone High-Dose vaccine is a liquid preparation; as such, no diluent is required. This product is provided in 0.5-mL, pre-filled, single-dose syringes. The vaccine will be administered intramuscularly into the deltoid muscle of choice using a needle of appropriate length. To ensure intramuscular vaccination, the subject will be instructed to relax the arm; the needle will be inserted straight into the deltoid muscle, centered between the shoulder and the axilla and midway between the posterior and anterior aspects of the arm. The vaccine must be administered within 30 minutes of its removal from the refrigerator.

Additional procedures for preparing and administering Fluzone High-Dose vaccine are the same as those described for Fluzone Quadrivalent vaccine in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

Fluzone High-Dose vaccine will be administered as a single 0.5-mL dose given at Visit 1 (Day 0) to subjects ≥ 65 years of age assigned to receive this vaccine (Group 3).

6.1.3 Identity of Control Products

Not applicable.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

All study vaccines will be supplied by the Sponsor. Fluzone Quadrivalent and Fluzone High-Dose vaccines will be supplied with their manufacturer's commercial labeling and packaging.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C and should be protected from light. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the study site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.3.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the study site, product inventory at the site, the dose(s) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRB. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the study site's product accountability records against the record of administered doses in the CRBs.

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.3.3 Replacement Doses

If a replacement dose is required (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

Unused or wasted products will be returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the study period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

This is an open-label study.

6.5 Randomization and Allocation Procedures

Subjects will not be randomized. Each subject will be assigned to a vaccine group based on the subject's age at the time of enrollment.

Subject numbers will be 12 digits long, with a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier. The 5-digit subject identifier will correspond to the chronological order of enrollment in the center. For example, Subject 840000100001 is the first subject enrolled in Center Number 1 (in the US) and Subject 840000200002 is the second subject enrolled in Center Number 2 (in the US).

Subject numbers should not be reassigned for any reason.

6.6 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified study personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the study site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications and other therapies (e.g., blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during study participation.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of each vaccination to the end of the follow-up period (i.e., from Visit 1 through Visit 2 for subjects receiving 1 dose of study vaccine or from Visit 1 through Visit 3 for subjects receiving 2 doses of study vaccine).

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. As Category 1 medications are NOT reportable for this study, there are 2 standard categories of reportable medications, defined as follows:

- Category 2: medications impacting or that may have an impact on the immune response (e.g., other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Global Clinical Immunology [GCI] department, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors).
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (e.g., steroids/corticosteroids)

The information reported in the CRB for each reported medication will be limited to:

- Trade name
- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Medication category (2 or 3)
- Start and stop dates

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded.

Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 3 medication.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples will be collected at Visit 1 and at Visit 2 for subjects receiving 1 dose of study vaccine or at Visit 1 and Visit 3 for subjects receiving 2 doses of study vaccine. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

A total of 2 blood samples (each approximately 5 mL for subjects 6 months to < 9 years of age or approximately 20 mL for subjects ≥ 65 years of age) will be collected from all subjects. The first blood sample will be collected at Visit 1 prior to vaccination. The second blood sample will be collected at Visit 2, if no study vaccine is administered at Visit 2; or at Visit 3, if study vaccine is administered at Visit 2. Blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label, and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C up to a maximum of 24 hours. The samples should then be centrifuged, and the serum should be transferred to the appropriate number of aliquoting tubes. These tubes should be pre-labeled with adhesive labels that identify the study code, the subject's number, and the sampling stage or visit number (see Section 5.1.3 and Section 7.1).

The subject's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and consent from the subject/subject's parent/guardian for future use of the subject's samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

Shipments to the laboratory will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to GCI at Sanofi Pasteur. The address is provided in the Operating Guidelines.

7.4 Future Use of Stored Biological Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 25 years after the end of the study. These samples are being retained in long-term storage to support answers to potential regulatory questions related to the product's licensure and the potential revalidation of the study results.

In addition, subjects/parents/guardians (of subjects 6 months to < 9 years of age) will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, diary cards, and other study documents, as well as with the following study materials: all study vaccines, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, and shipping containers.

The means for performing Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and/or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent

countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Endpoints and Assessment Methods

9.1.1 Sample Collection

The study objective is presented in Section 2.

There are no endpoints for the objective of this study.

9.1.2 Safety

9.1.2.1 Safety Endpoints

There are no safety endpoints for this study.

Serious adverse events[a] and AESIs will be collected from Visit 1 through Visit 2 for subjects receiving 1 dose of study vaccine, and from Visit 1 to Visit 3 for subjects receiving 2 doses of study vaccine.

9.1.2.2 Safety Definitions

The following definitions are taken from the International Council for Harmonisation (ICH) E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

[a] The classification of an SAE as an SUSAR is determined by the GPV Department and RMO(s) at Sanofi Pasteur.

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability/incapacity[c]
- Is a congenital anomaly/birth defect
- Is an important medical event (IME)

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or autoimmune disease.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions.

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

Adverse Event of Special Interest (AESI):

An AESI is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (e.g., regulators) might also be warranted.

9.1.2.3 Safety Assessment Methods

At each visit, the Investigator or a delegate will perform a directed physical examination, if indicated, based on interim history and will ask the subject or subject's parent/guardian about any medical events that might represent SAEs, SUSARs, or AESIs recorded in the diary card that may

[a] The term "life-threatening" 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.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.1.2.3.1 SAEs, SUSARs, and AESIs

Subjects or parents/guardians (of subjects 6 months to < 9 years of age) will be instructed to record information about any medical events that might represent SAEs, SUSARs, or AESIs that may occur from Visit 1 through Visit 2 (Diary Card 1) for all subjects and from Visit 2 through Visit 3 (Diary Card 2) for subjects receiving 2 doses of study vaccine. Space will be provided in the diary card for this purpose.

Information on SAEs[a]/AESIs will be collected and assessed throughout the study, from Visit 1 through Visit 2 for subjects receiving 1 dose of study vaccine, and from Visit 1 through Visit 3 for subjects receiving 2 doses of study vaccine.

Any SAE/AESI occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the Safety Complementary Information CRFs. All information concerning the SAE/AESI is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). See Section 10 for further details on SAE/AESI reporting.

For each SAE/AESI, the following information is to be recorded:

- Start and stop dates[b]
- Action taken for each SAE/AESI (e.g., medication)

  The action(s) taken by the subject/subject's parent(s)/guardian(s) to treat and/or manage any SAEs/AESIs will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination
- For each SAE/AESI, the Investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)

---

[a] The classification of an SAE as an SUSAR is determined by the GPV Department and RMO(s) at Sanofi Pasteur.

[b] The stop date of all related SAEs/AESIs will be actively solicited. For other events, the Investigator will provide the stop date when it becomes available. Serious adverse events/AESIs for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

- Whether the SAE/AESI caused study discontinuation

9.1.2.3.2 Adverse Events of Special Interest

Adverse events of special interest will be captured as SAEs. These include new onset of GBS, encephalitis/myelitis (including transverse myelitis), neuritis (including Bell's palsy, optic neuritis, and brachial neuritis), thrombocytopenia, vasculitis, convulsions (including febrile convulsions [children only]), and anaphylaxis or other hypersensitivity/allergic reactions from Visit 1 through Visit 2 for subjects receiving 1 dose of vaccine, or from Visit 1 through Visit 3 for subjects receiving 2 doses of vaccine.

9.1.2.3.3 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each SAE/AESI and the product administered as either ***not related*** or ***related***, based on the following definitions:

Not related – The SAE/AESI is clearly/most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the SAE/AESI is incompatible with a causal relationship; or the SAE/AESI started before the first vaccination (screening phase, if applicable)

Related – There is a "reasonable possibility" that the SAE/AESI was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all SAEs involving the injection site are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

Serious adverse events/AESIs that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

9.1.3 Immunogenicity

No immunogenicity data will be obtained in this trial.

9.1.4 Efficacy

No clinical efficacy data will be obtained in the trial.

10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs/AESIs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following

sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational products. It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy report) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

Serious adverse events occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE/AESI must be reported, even if the Investigator considers that it is not related to the vaccine. The investigator (licensed physician [MD or DO]) must validate the information entered on the AE CRF by completing the investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the RMOs with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the operating guidelines.

The Investigator must complete the paper copies of the SAE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by 1 of the following means:

- By fax, to the following number: 1-570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address:
- Sanofi Pasteur, Inc.
  Reception & Triage – Case Management
  Global Pharmacovigilance Department
  Discovery Drive, Swiftwater, PA 18370

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

If there is need for urgent consultation, the Investigator is to contact 1 of the RMOs as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE/AESI (e.g., outcome, precise description of medical history, results of the investigation). All relevant information must be

included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and to the CRA. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE/AESI that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), other products (e.g., a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE/AESI and the product administered will be evaluated by the Investigator as described in Section 9.1.2.3.3.

Following this, the Sponsor's Global Safety Officer will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs/IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs/AESIs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor's RMOs will notify the Investigators in writing of the occurrence of any reportable SAEs/AESIs. The Investigators/Sponsor will be responsible for informing the IRB(s) that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of safety information on a daily basis as described in Section 9.1.2.3.

At specified intervals, the Investigator or an authorized designee will interview the subjects/subjects' parents/guardians to collect the information recorded in the diary card, and will

attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records/Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

The Investigator is responsible for the timeliness, completeness, and accuracy of the information in the CRBs; must provide explanations for all missing information; and must sign the CRB using an e-signature.

11.2 Data Management

Management of SAE Data

During the study, SAE/AESI data (reported on the AE and Safety Complementary Information CRFs) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer and the RMOs. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information from the GPV database cases will be reconciled with that in the clinical database.

Management of Clinical and Laboratory Data

Clinical data, defined as all data reported in the CRB, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and/or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical

data will be submitted to the investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency but will not be integrated into the clinical Datawarehouse.

After integration of all corrections in the complete set of data, and after the SAE/AESI information available from CDM and the GPV Department has been reconciled, the database will be released for statistical analysis.

11.3 Data Review

A review of the data is anticipated through the data review process led by Data Management before database lock.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Summaries of baseline demographic characteristics of the study subjects will be presented. The number of subjects enrolled and their age at enrollment (mean, median, and minimum and maximum), sex, race, and ethnic origin will be summarized, along with the number and description of protocol deviations. Listings of subjects by age group, sex, vaccine received, and history of vaccination in the previous season will be provided. Listings or tables of SAEs, SUSARs, and AESIs, will also be provided. No hypotheses will be tested.

12.2 Analysis Sets

12.2.1 All Vaccinated Population

The All Vaccinated Population is defined as those subjects who have received at least 1 dose of the study vaccine.

12.2.2 Populations Used in Analyses

All analyses will be performed on the All Vaccinated Population.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

Not applicable.

12.3.3 Efficacy

Not applicable.

12.4 Interim/Preliminary Analysis

No interim analyses are planned.

12.5 Determination of Sample Size and Power Calculation

The study will enroll approximately 90 subjects: approximately 30 subjects 6 to < 36 months of age will be administered Fluzone Quadrivalent vaccine (Group 1), approximately 30 subjects 3 to < 9 years of age will be administered Fluzone Quadrivalent vaccine (Group 2), and approximately 30 subjects ≥ 65 years of age will be administered Fluzone High-Dose vaccine (Group 3).

No study power assessment will be done for this study. Only descriptive statistical analyses will be conducted in this study.

13 Ethical and Legal Issues and Investigator/Sponsor Responsibilities

13.1 Ethical Conduct of the Study/Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and/or national regulations and directives.

13.2 Source Data and Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent/assent forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a diary card, the study coordinator will obtain verbal clarification from the subject, enter the response into the "Comments Per Visit" page of the diary card, and transfer the information to the CRB.

The subject pre-screening log should list all individuals contacted by the Investigators to participate/have their child participate in the study, regardless of the outcome.

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the investigational site, it is the responsibility of the Investigator to obtain those records if needed.

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations, including the GDPR (Global Data Protection Regulation). Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Each subject's race and ethnicity will be collected in this study because these data are required by certain regulatory agencies (e.g., the US FDA and the Pharmaceuticals and Medical Devices Agency in Japan).

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (i.e., before the inclusion of the first subject in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB, and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

After the start of the study, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject medical files and CRBs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs/AESIs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs/AESIs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department (CQA) or by independent auditors to verify that the study has been

conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to study documents during these inspections and audits.

13.4.3 Archiving

The Investigator and the study site shall retain and preserve 1 copy of the study file containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- such longer period as required by applicable regulatory requirements

If during the Retention Period, the study site is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the study site shall contact the Sponsor to organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, the Investigator and/or the study site are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the study will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement will be signed by all the parties involved in the study's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and/or the study protocol.

13.6 Stipends for Participation

Subjects may be provided with a stipend according to local practice to compensate for the time and travel required for study visits and procedures.

13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study at least 90 days prior to submission for publication/presentation.

Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this study are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

14 Reference List

1 Fiore AE, Bridges CB, Katz JM, Cox NJ. Inactivated influenza vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6th ed. Edinburgh, UK: Elsevier/Saunders; 2012;257-93.

2 Treanor JT. Influenza viruses, including avian influenza and swine influenza. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th ed. New York, NY: Churchill Livingstone; 2010:2265-88.

3 Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal Influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices - United States, 2016-17 influenza season. MMWR Recomm Rep. 2016;65(No. RR-5):1-54.

4 Belshe RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine. 2010;28(suppl 4):D45-53.

5 Monto AS, Ansaldi F, Aspinall R, et al. Influenza control in the 21st century: optimizing protection of older adults. Vaccine. 2009;27(37):5043-53.

6 Centers for Disease Control and Prevention Website. Disease burden of influenza. Available at: https://www.cdc.gov/flu/about/burden/index.html. Accessed July 19, 2019.

7 Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292(11):1333-40.

8 Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza-United States, 1976-2007. MMWR. 2010;59(33):1057-62.

9 Centers for Disease Control and Prevention Website. Past seasons estimated influenza disease burden. Available at: https://www.cdc.gov/flu/about/burden/past-seasons.html. Accessed July 19, 2019.

10 Centers for Disease Control and Prevention Website. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States - 2017-2018 influenza season. Available at: https://www.cdc.gov/flu/about/burden/2017-2018.htm. Accessed July 19, 2019.

11 Centers for Disease Control and Prevention Website. Summary of the 2017-2018 influenza season. Available at: https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm. Accessed July 19, 2019.

12 Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2013-14. MMWR. 2013;62(RR07):1-43.

13 Hu JJ, Kao CL, Lee PI, et al. Clinical features of influenza A and B in children and association with myositis. J Microbiol Immunol Infect. 2004;37(2):95-8.

14 Hite LK, Glezen WP, Demmler GJ, Munoz FM. Medically attended pediatric influenza during the resurgence of the Victoria lineage of influenza B virus. Int J Infect Dis. 2007;11(1):40-7.

15 Glezen WP, Couch RB, Taber LH, et al. Epidemiologic observations of influenza B virus infections in Houston, Texas, 1976-1977. Am J Epidemiol. 1980;111(1):13-22.

16 Centers for Disease Control and Prevention Website. Past seasons vaccine effectiveness. Available at: https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html. Accessed July 19, 2019.

17 Centers for Disease Control and Prevention Website. 2015-2016 season burden estimates. Available at: https://www.cdc.gov/flu/about/burden-averted/2015-16.htm. Accessed July 19, 2019.

18 Greenberg DP, Robertson CA, Landolfi VA, Bhaumik A, Senders SD, Decker MD. Safety and immunogenicity of an inactivated quadrivalent influenza vaccine in children 6 months through 8 years of age. Pediatr Infect Dis J. 2014;33(6):630-6.

19 Greenberg DP, Robertson CA, Noss MJ, Blatter MM, Biedenbender R, Decker MD. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. Vaccine. 2013;31(5):770-6.

20 Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med. 2006;166(10):1121-7.

21 Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine. 2007;25(44):7656-63.

22 Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis. 2009;200(2):172-80.

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

24 Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. MMWR. 2007;56(RR-6):1-54.

25 Mitchell DK, Ruben FL, Gravenstein S. Immunogenicity and safety of inactivated influenza virus vaccine in young children in 2003-2004. Pediatr Infect Dis J. 2005;24(10):925-7.

26 Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington D.C. Public Health Foundation, 2015.

27 Woo EJ. Allergic reactions after egg-free recombinant influenza vaccine: reports to the US Vaccine Adverse Event Reporting System. Clin Infect Dis. 2015;60(5):777-80.

28 Woo EJ, Moro PL, Cano M, Jankosky C. Postmarketing safety surveillance of trivalent recombinant influenza vaccine: Reports to the Vaccine Adverse Event Reporting System. Vaccine. 2017;35(42):5618-21.

29 Seneviratne U. Guillain-Barré syndrome. Postgrad Med J. 2000;76(902):774-82.

30 Salmon DA, Proschan M, Forshee R, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. Lancet. 2013;381(9876):1461-8.

31 Stratton K, Ford A, Rush E, et al. Committee to Review Adverse Effects of Vaccines Board on Population Health and Public Health Practice: adverse effects of vaccines evidence of causality. Washington, D.C.: The National Academies Press; 2012. Available at: https://www.nap.edu/read/13164/chapter/1. Accessed May 7, 2018.

32 Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the Vaccine Adverse Event Reporting System. Vaccine. 2012;30(11):2020-3.

33 Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine. 2012;30(11):2024-31.

34 Duffy J, Weintraub E, Hambidge SJ, et al. Febrile seizure risk after vaccination in children 6 to 23 months. Pediatrics. 2016;138(1):e20160320.

35 Center for Disease Control and Prevention Website. Childhood Vaccines and Febrile Seizures. Available at: https://www.cdc.gov/vaccinesafety/concerns/febrile-seizures.html. Accessed May 7, 2018.

36 Moro PL, Arana J, Cano M, et al. Postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010. Clin Infect Dis. 2012;54(11):1608-14.

15 Signature Page

Document Number CLI_00206681	**Version Number** 1.0
Project Code Flu seasonal	
Arficact Name Protocol Body	

	Approver Name	**Date** (Universal Time)	**Reason for Signature**
Approval	[redacted]		