

NCT number: NCT03308825

Safety and Immunogenicity of Fluzone® Quadrivalent and Fluzone® High-Dose, Influenza Vaccines, 2017–2018 Formulations

Phase IV, multi-center, open-label trial to assess the safety and immunogenicity of Fluzone® Quadrivalent vaccine in children and adults and Fluzone® High-Dose vaccine in older adults

Clinical Trial Protocol

Health Authority File Number:

BB-IND #: 4518

WHO Universal Trial Number (UTN):

U1111-1183-5816

Trial Code:

GRC73

Development Phase:

Phase IV

Sponsor:

Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Investigational Product(s):

Fluzone® Quadrivalent, Influenza Vaccine (2017–2018 formulation)
Fluzone® High-Dose, Influenza Vaccine (2017–2018 formulation)

Form/Route:

Liquid/Intramuscular

Indication For This Study:

To evaluate the safety and immunogenicity of the 2017–2018 formulations of Fluzone Quadrivalent vaccine (intramuscular route) in children 6 months to < 9 years of age and adults 18 to < 65 years of age, and Fluzone High-Dose vaccine (intramuscular route) in adults ≥ 65 years of age

Manufacturer:

Same as Sponsor

Coordinating Investigator:

To be determined.

Sponsor's Responsible Medical Officers:

Sanofi Pasteur Inc.

Tel: [REDACTED]

Fax: [REDACTED]

Sanofi Pasteur Inc.

Tel: [REDACTED]

Fax: [REDACTED]

Product Safety Officer:

Sanofi Pasteur Inc.

Tel: [REDACTED]; Fax: [REDACTED]

Clinical Trial Manager:

Sanofi Pasteur Inc.

Tel: [REDACTED]; Fax: [REDACTED]

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Synopsis

Company:	Sanofi Pasteur
Investigational Products:	Fluzone® Quadrivalent and Fluzone® High-Dose Influenza Vaccines (2017–2018 Formulations)
Active Substances:	<p>Influenza virus surface antigens of the following strains:</p> <ul style="list-style-type: none">• A/Michigan/45/2015 X-275 (H1N1)• A/Hong Kong/4801/2014 X-263B (H3N2)• B/Brisbane/60/2008 (B Victoria lineage)• B/Phuket/3073/2013 (B Yamagata lineage [in Fluzone Quadrivalent vaccine only])
Title of the Trial:	Safety and Immunogenicity of Fluzone® Quadrivalent and Fluzone® High-Dose, Influenza Vaccines, 2017–2018 Formulations
Development Phase:	Phase IV
Coordinating Investigator:	To be determined.
Trial Centers:	This study will be conducted in 3 centers in the United States. Investigators and sites are listed in the “List of Investigators, Trial Centers, and Sponsor’s Personnel Involved in the Trial” document.
Planned Trial Period:	First Visit, First Subject: September 2017 Last Visit, Last Subject: December 2017
Trial Design and Methodology:	<p>This will be a Phase IV, multi-center, open-label study of a planned 240 subjects to describe the safety and immunogenicity of Fluzone Quadrivalent vaccine in children 6 months to < 9 years of age and adults 18 to < 65 years of age, and to describe the safety and immunogenicity of Fluzone High-Dose vaccine in adults ≥ 65 years of age. Each subject will be assigned to the appropriate age group based on the subject’s age at the time of enrollment. An approximately equal number of subjects from each age group will be enrolled at each site.</p> <ul style="list-style-type: none">• Group 1: Children 6 to < 36 months of age assigned to receive a 0.25-mL pediatric dose of Fluzone Quadrivalent vaccine (60 subjects planned)• Group 2: Children 3 to < 9 years of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (60 subjects planned)• Group 3: Adults 18 to < 65 years of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (60 subjects planned)• Group 4: Adults ≥ 65 years of age assigned to receive a 0.5-mL dose of Fluzone High-Dose vaccine (60 subjects planned) <p>All subjects will receive an intramuscular dose of their assigned vaccine during 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 (ACIP) guidance, a second dose of the same volume of Fluzone Quadrivalent vaccine as the first dose will be administered at Visit 2 (28 [window, 28–35] days after Visit 1).</p>

	<p>Subjects 6 months to < 9 years of age (Group 1 and Group 2): blood specimens will be obtained from all subjects prior to the first vaccination and 28 (window, 28–35) days following the final vaccination (Visit 2 for subjects receiving 1 dose; Visit 3 for subjects receiving 2 doses) and assayed for immunogenicity. Solicited adverse reaction (AR) information will be collected for 7 days following each vaccination. Unsolicited non-serious adverse event (AE) and serious adverse event (SAE) information will be collected from Visit 1 through Visit 2 for subjects receiving 1 dose or from Visit 1 through Visit 3 for those subjects receiving 2 doses.</p> <p>Subjects ≥ 18 years of age (Group 3 and Group 4): blood specimens will be obtained from all subjects prior to vaccination and 21 (window, 21–28) days post-vaccination (Visit 2). Solicited AR information will be collected for 7 days following vaccination. Unsolicited non-serious AE and SAE information will be collected from Visit 1 through Visit 2.</p>
Early Safety Data Review:	<p>This study will not include an early review of safety data. However, it may be interrupted at any time if new data about the investigational products become available, and/or on advice of the Sponsor, the Institutional Review Board(s) (IRB[s]), or the Food and Drug Administration (FDA).</p> <p>If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IRB(s), and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects or subjects' parents/guardians, as appropriate, and should assure appropriate therapy and follow-up.</p>
Observational Objectives:	<p><i>Safety</i></p> <p>To describe the safety of the 2017–2018 formulation of Fluzone Quadrivalent vaccine in children 6 to < 36 months of age and 3 to < 9 years of age, and in adults 18 to < 65 years of age, and the safety of the 2017–2018 formulation of Fluzone High-Dose vaccine in adults ≥ 65 years of age.</p> <p><i>Immunogenicity</i></p> <p>To describe the immunogenicity of the 2017–2018 formulation of Fluzone Quadrivalent vaccine in children 6 to < 36 months of age and 3 to < 9 years of age, and in adults 18 to < 65 years of age, and the immunogenicity of the 2017–2018 formulation of Fluzone High-Dose vaccine in adults ≥ 65 years of age.</p> <p><i>Serum Collection</i></p> <p>To submit available sera (collected before vaccination [Blood Sample 1] and after final vaccination [Blood Sample 2]) from approximately 120 subjects (30 subjects from each age group) 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 FDA to support formulation recommendations for subsequent influenza vaccines.</p>
Endpoints:	<p><i>Safety</i></p> <p>1) Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 20 minutes after vaccination.</p>

	<p>2) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited injection site reactions (prelisted in the subject's diary card and electronic case report form [eCRF]) occurring from Day 0 through Day 7 after vaccination.</p> <p>3) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions (prelisted in the subject's diary card and eCRF) occurring from Day 0 through Day 7 after vaccination.</p> <p>4) Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs from Visit 1 through Visit 2 for subjects receiving 1 dose or from Visit 1 through Visit 3 for subjects receiving 2 doses.</p> <p>5) Occurrence, nature (MedDRA preferred term), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs from Visit 1 through Visit 2 for subjects receiving 1 dose or from Visit 1 through Visit 3 for subjects receiving 2 doses.</p> <p>Adverse events of special interest will be captured as SAEs. These include new onset of Guillain-Barré syndrome (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.</p>
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Immunogenicity

Immunogenicity will be evaluated in all subjects by analyzing sera collected prior to vaccination on Day 0 (Visit 1) and after final vaccination (28 [window, 28–35] days post-final vaccination for subjects 6 months to < 9 years of age [Visit 2 for subjects receiving 1 dose; Visit 3 for subjects receiving 2 doses]; or 21 [window, 21–28] days post-vaccination for subjects ≥ 18 years of age) using the hemagglutination inhibition (HAI) assay technique.

For each influenza vaccine strain (i.e., 3 strains for Fluzone High-Dose vaccine [a trivalent vaccine] and 4 strains for Fluzone Quadrivalent vaccine), HAI assay titers at pre-vaccination (Day 0) and after the final vaccination will be determined in duplicate.

The derived endpoints^a are:

- Geometric means of HAI assay titers at pre-vaccination and post-final vaccination
- Ratios of post-final vaccination titers divided by pre-vaccination titers.
- Seroprotection: a titer ≥ 40 (1/dilution [dil]) at pre-vaccination and at post-final vaccination
- Seroconversion: either a pre-vaccination titer < 10 (1/dil) and a post-final vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4-fold increase in post-final vaccination titer

	<p>^a Post-final vaccination in each of the derived endpoints is defined as 28 (window, 28–35) days post-final vaccination for subjects 6 months to < 9 years of age, and 21 (window, 21–28) days post-vaccination for subjects ≥ 18 years of age</p> <p>Serum Collection</p> <p>There are no observational endpoints for the serum collection objective.</p>
Planned Sample Size:	<p>The study will enroll approximately 240 subjects: approximately 60 subjects 6 to < 36 months of age will be administered Fluzone Quadrivalent vaccine (Group 1), approximately 60 subjects 3 to < 9 years of age will be administered Fluzone Quadrivalent vaccine (Group 2), approximately 60 subjects 18 to < 65 years of age will be administered Fluzone Quadrivalent vaccine (Group 3), and approximately 60 subjects ≥ 65 years of age will be administered Fluzone High-Dose vaccine (Group 4).</p> <p>No study power assessment will be done for this study. Only descriptive statistical analyses will be conducted in this study.</p>
Schedule of Study Procedures:	<p>Vaccination</p> <p>All subjects will receive either a 0.25-mL (subjects 6 to < 36 months of age [Group 1]) or a 0.5-mL (subjects 3 to < 9 years of age and ≥ 18 years of age [Groups 2, 3, and 4]) intramuscular injection of study vaccine based on 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 (same 0.25-mL or 0.5-mL volume as administered at Visit 1) will be administered at Visit 2.</p> <p>Blood Sampling</p> <p>A total of 2 blood samples (each approximately 5 mL for subjects 6 months to < 9 years of age or approximately 10 mL for subjects ≥ 18 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 for subjects receiving 1 dose of study vaccine; or at Visit 3 for subjects receiving 2 doses of study vaccine (with the first dose administered at Visit 1 and the second dose administered at Visit 2).</p> <p>Study sites, at their discretion, may apply a topical analgesic prior to venipuncture. However, topical analgesic agents must <u>not</u> be applied at the site of vaccine administration.</p> <p>Collection of Safety Data</p> <p>Staff will observe subjects for 20 minutes following study vaccine administration and will record the occurrence of any immediate unsolicited systemic AEs.</p> <p>Subjects or subjects' parents/guardians will record information about solicited injection site and systemic reactions from Day 0 through Day 7 post-vaccination, and will record information about unsolicited non-serious AEs and SAEs 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.</p> <p>Staff will contact subjects or parents/guardians by telephone on Day 8 (window, Days 8–10) after any study vaccine administration to remind them to record any AEs experienced and any concomitant medications taken from the most recent visit to the next visit in the diary card and to bring the diary card with them to the next visit. Subjects or parents/guardians will also be</p>

	<p>reminded to notify the site immediately if an SAE occurs.</p> <p>Staff will review the Visit 1 through Visit 2 safety data for all vaccinated subjects with subjects or 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 6 months to < 9 years of age receiving 2 doses of study vaccine.</p>
Duration of Participation in the Trial:	<p>Subjects 6 months to < 9 years of age: 28 (window, 28–35) days following the last dose of influenza vaccine, including immunogenicity and safety 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.</p> <p>Subjects ≥ 18 years of age: 21 (window, 21–28) days after vaccination, including immunogenicity and safety follow-up. No additional safety follow-up beyond Visit 2 is planned.</p>
Licensed Product 1:	<p>Fluzone Quadrivalent vaccine, No Preservative: Pediatric Dose (0.25-mL dose), 2017–2018 formulation</p> <p>or</p> <p>Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2017–2018 formulation</p>
Form:	Liquid – pre-filled syringes
Composition:	<p>Each 0.25-mL dose contains 7.5 µg hemagglutinin (HA) of each antigen, and each 0.5-mL dose contains 15 µg HA of each antigen:</p> <ul style="list-style-type: none"> • A/Michigan/45/2015 X-275 (H1N1) • A/Hong Kong/4801/2014 X-263B (H3N2) • B/Brisbane/60/2008 (B Victoria lineage) • B/Phuket/3073/2013 (B Yamagata lineage)
Route:	Intramuscular
Batch Number:	TBD
Licensed Product 2:	Fluzone High-Dose vaccine, 2017–2018 formulation
Form:	Liquid – pre-filled syringes
Composition:	<p>Each 0.5-mL dose contains 60 µg HA of each antigen:</p> <ul style="list-style-type: none"> • A/Michigan/45/2015 X-275 (H1N1) • A/Hong Kong/4801/2014 X-263B (H3N2) • B/Brisbane/60/2008 (B Victoria lineage)
Route:	Intramuscular
Batch Number:	TBD
Inclusion Criteria:	<p>An individual must fulfill all of the following criteria in order to be eligible for study enrollment:</p> <ol style="list-style-type: none"> 1) Aged 6 months to < 9 years or ≥ 18 years 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 ≥ 2.5 kg (5.5 lbs). 3) Informed consent form has been signed and dated by subjects ≥ 18 years of age.

	<ol style="list-style-type: none">4) Assent form has been signed and dated by subjects 7 to < 9 years of age, and informed consent form 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:	<p>An individual fulfilling <i>any</i> of the following criteria is to be excluded from study enrollment:</p> <ol style="list-style-type: none">1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be pre-menarche, or post-menopausal for at least 1 year, or surgically sterile.2) 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. <p>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.</p> <ol style="list-style-type: none">3) 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.4) Previous vaccination against influenza (in the 2017–2018 influenza season) with either study vaccine or another vaccine.5) Receipt of immune globulins, blood, or blood-derived products in the 3 months preceding planned inclusion.6) 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).7) 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. <p>Note: The list of vaccine components is included in the Prescribing Information for each study vaccine.</p> <ol style="list-style-type: none">8) Thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator.9) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination.10) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

	<ol style="list-style-type: none">11) Current alcohol abuse or drug addiction.12) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion.13) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of planned vaccination or febrile illness (temperature $\geq 100.4^{\circ}\text{F}$ [38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.14) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study (subjects ≥ 18 years of age) or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study (all subjects).15) History of serious AR to any influenza vaccine.16) Personal history of GBS.17) 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.18) Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.19) Known seropositivity for human immunodeficiency virus, hepatitis B, or hepatitis C. <p>Note: Subjects enrolled into this study will not be prohibited from donating blood for non-interventional studies or other purposes.</p>
Statistical Methods:	<p>Summaries of the recruitment and 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 violations.</p> <p>For the main safety and immunogenicity parameters, 95% confidence intervals (CIs) of point estimates of proportions will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. All analyses will be descriptive; no hypotheses will be tested.</p> <p><i>Safety</i></p> <p>The Safety Analysis Set will be used for the safety analyses. Subjects will be analyzed according to the vaccine they actually received.</p> <p><i>Immunogenicity</i></p> <p>The immunogenicity analyses will be performed on both the Full Analysis Set and the Per-Protocol Analysis Set. Data will be summarized and presented for each age group.</p>

	<p>The following immunogenicity parameters^a will be calculated for each influenza strain with 95% CIs:</p> <ul style="list-style-type: none">• Geometric mean HAI assay titers at pre-vaccination and post-final vaccination• Geometric means of titer ratios (post-final vaccination divided by pre-vaccination).• Seroprotection rates: The percentages of subjects with a titer ≥ 40 (1/dil) at pre-vaccination and at post-final vaccination• Seroconversion rates: The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-final vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4-fold increase in post-final vaccination titer <p>^a Post-final vaccination in each of the immunogenicity parameters is defined as 28 (window, 28–35) days post-final vaccination for subjects 6 months to < 9 years of age, and 21 (window, 21–28) days post-vaccination for subjects ≥ 18 years of age.</p>
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Tables of Study Procedures

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

Visit Number	All Subjects		Subjects Receiving 1 Dose of Influenza Vaccine	Subjects Receiving 2 Doses of Influenza Vaccine		
	Visit 1	Telephone Contact		Visit 2	Telephone Contact	Visit 3
Study Timelines	Day 0	Visit 1 + 8 days	Visit 1 + 28 days	Visit 1 + 28 days	Visit 2 + 8 days	Visit 2 + 28 days
Time Windows	--	+ 8 to 10 days	+ 28 to 35 days	+ 28 to 35 days	+ 8 to 10 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 and collected			DC1	DC1		DC2
Interim history			X	X		X
Termination record ^f			X			X
Serious adverse events	To be reported throughout the study period					

^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 (same 0.25-mL or 0.5-mL volume of Fluzone Quadrivalent vaccine as administered at Visit 1) will be administered approximately 28 days later during Visit 2.

^e The subject's parent/guardian will be contacted by telephone on Day 8 (window, Days 8–10) after vaccination as a reminder to complete the diary card and to bring it with them to the next visit. The termination 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 ≥ 18 Years of Age: 2 Visits, 1 Vaccination

Visit Number	Visit 1	Telephone Contact	Visit 2
Study Timelines	Day 0	Visit 1 + 8 days	Visit 1 + 21 days
Time Windows		+ 8 to 10 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		
Urine or serum pregnancy test ^b	X		
Allocation of subject number	X		
Blood sampling (BL) ^c	BL1		BL2
Vaccination	X		
Immediate surveillance (20 minutes)	X		
Diary card provided	X		
Telephone contact ^d		X	
Diary card reviewed and collected			X
Termination record			X
Serious adverse events	To be reported throughout the study period		

^a The preferred route for this study for subjects ≥ 18 years of age is oral.

^b Only for women of child-bearing potential.

^c A blood sample, approximately 10 mL, will be collected at Visit 1 and Visit 2.

^d Subjects will be contacted via telephone on Day 8 (window, Days 8–10) as a reminder 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
AR	Adverse Reaction
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDM	Clinical Data Management
CI	Confidence Interval
CRA	Clinical Research Associate
CTA	Clinical Trial Agreement
dil	Dilution
DTaP	Diphtheria-Tetanus-Acellular-Pertussis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
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
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IIV3	Trivalent Inactivated Influenza Vaccine
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
LLT	Lowest Level Term
LLOQ	Lower Limit of Quantification
LVLS	Last Visit, Last Subject
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
PCV	Pneumococcal Conjugate Vaccine
PPAS	Per-Protocol Analysis Set
RBC	Red Blood Cell
RMO	Responsible Medical Officer

RNA	Ribonucleic acid
SAE	Serious Adverse Event
ULOQ	Upper Limit of Quantification
US	United States
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1 Introduction

1.1 Background

This is a study using the 2017–2018 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 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. 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 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 aged ≥ 65 years (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, and immunity to 1 B lineage does 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 high-risk groups such as persons aged ≥ 65 years. However, 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 significant 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.

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 it is indicated.

The objectives of this study are to describe the safety and immunogenicity of Fluzone Quadrivalent vaccine in children 6 months to < 9 years of age and adults 18 to < 65 years of age, and to describe the safety and immunogenicity of Fluzone High-Dose vaccine in adults ≥ 65 years of age. An additional objective of the study is to submit sera from selected subjects to the Center for Biologics Evaluation and Research (CBER) 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.

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. 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. During seasonal influenza epidemics from 1979–1980 through 2000–2001, the estimated annual overall number of influenza-associated hospitalizations in the United States (US) ranged from approximately 55,000 to 431,000 per annual epidemic (mean: 226,000) (3) (6). Between the 1976–1977 season and 2006–2007 season, estimated annual deaths attributable to influenza ranged from 3,000 to 49,000 each season (3) (7). Approximately 90% of the deaths attributed to pneumonia and influenza during these periods occurred among persons \geq 65 years of age (3). From the 1976–1977 season through the 2006–2007 season, an estimated yearly average of 21,098 influenza-related deaths occurred among adults aged \geq 65 years, compared with an estimated 124 deaths among persons $<$ 19 years of age and 2385 deaths among persons 19 through 64 years of age (3) (7).

In the United States, death associated with laboratory-confirmed influenza virus infection among children aged $<$ 18 years has been a nationally reportable condition since 2004. Since reporting began, the annual number of influenza-associated pediatric deaths during regular influenza seasons has ranged from 37 to 171 deaths per season (3). However, between 15 April 2009 and 02 October 2010 (the period of the 2009 H1N1 influenza pandemic), 358 deaths attributed to laboratory-confirmed 2009 H1N1 influenza occurred among children aged $<$ 18 years, the majority of whom had 1 or more underlying medical conditions previously associated with conferring a greater risk for influenza complications (3).

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 (8) (9) (10). 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).

In 1 meta-analysis, influenza vaccine was shown to prevent illness in 59% (95% confidence interval [CI] = 51%–67%) of adults aged 18 through 65 years in 8 of 12 seasons analyzed. Another meta-analysis of randomized clinical trial results among healthy persons aged 16 through 65 years suggested that when vaccine and circulating influenza viruses strains were well-matched, efficacy against influenza symptoms was 73% (95% CI = 54%–84%) whereas it was 44% (95% CI = 23%–59%) when they were not well-matched. The only large randomized placebo-controlled trial conducted among community-dwelling persons aged ≥ 60 years reported a vaccine efficacy of 58% (95% CI = 26%–77%) against serologically confirmed influenza illness during a season when the vaccine strains were considered to be well-matched to circulating strains (3).

Some observational studies that have provided estimates of vaccine effects for serious complications of influenza infections among community-dwelling older persons have found large reductions in hospitalizations or deaths. For example, in 1 case-control study conducted during the 1999–2000 season in persons aged < 65 years with underlying medical conditions, vaccination was reported to reduce deaths attributable to any cause by 78% and reduce hospitalizations attributable to respiratory infections or cardiopulmonary diseases by 87% (3). Recent studies using methods to account for unmeasured confounding factors (e.g., dementia and difficulties with self-care) have indicated that vaccine effectiveness among community-dwelling older persons for nonspecific serious outcomes such as pneumonia/influenza hospitalizations or all-cause mortality is $< 10\%$, which is much more plausible than higher estimates from earlier studies (11).

1.1.3 The Advisory Committee on Immunization Practices Recommendations

Because children 6 through 23 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 through 8 years of age is receiving influenza vaccine for the first time, based on ACIP recommendations, 2 doses of influenza vaccine should be administered 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 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 through 8 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 2017–2018 formulation of Fluzone Quadrivalent and Fluzone High-Dose vaccines will have passed all approved release-testing requirements.

Previous Clinical Experience

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 (12) (13).

Fluzone High-Dose Vaccine

Fluzone High-Dose vaccine, 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) (14) (15) (16). 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 (17).

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

The benefit to subjects participating in this study is the receipt of the 2017–2018 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) (18). 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 (19).

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 (20).

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 (21).

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% CI = 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 (22). 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 (23).

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) (24). Using data collected through the CDC-sponsored Vaccine Safety Datalink (VSD) project, Tse et al. (25) 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. (26) 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 (27).

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 (23).

Cases of vasculitis have been reported following influenza immunization. A cause-and-effect relationship has not been determined (23).

A Phase III study performed in persons \geq 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 (16). 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 (28).

There may be other risks not yet identified.

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

1.4 Rationale for the Trial

Historically, annual safety and immunogenicity studies of Fluzone vaccine have been conducted in the United States in support of licenses held by Sanofi Pasteur in various countries and to obtain serum samples for submission to CBER to aid in the influenza vaccine strain selection process. The aim of the GRC73 study is to evaluate the safety and immunogenicity of the 2017–2018 formulation of Fluzone Quadrivalent vaccine in children 6 months to $<$ 9 years of age and in adults 18 to $<$ 65 years of age, and of the 2017–2018 formulation of Fluzone High-Dose vaccine in adults \geq 65 years of age.

Samples of sera from vaccine 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 sera 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 to be distributed in the United States.

2 Trial Objectives

2.1 Observational Objectives

2.1.1 Safety

To describe the safety of the 2017–2018 formulation of Fluzone Quadrivalent vaccine in children 6 to < 36 months of age and 3 to < 9 years of age, and in adults 18 to < 65 years of age, and the safety of the 2017–2018 formulation of Fluzone High-Dose vaccine in adults ≥ 65 years of age.

The endpoints for the observational safety objective are presented in Section 9.3.1.2.

2.1.2 Immunogenicity

To describe the immunogenicity of the 2017–2018 formulation of Fluzone Quadrivalent vaccine in children 6 to < 36 months of age and 3 to < 9 years of age, and in adults 18 to < 65 years of age, and the immunogenicity of the 2017–2018 formulation of Fluzone High-Dose vaccine in adults ≥ 65 years of age.

The endpoints for the observational immunogenicity objective are presented in Section 9.3.2.1.

2.1.3 Serum Collection

To submit available sera (collected before vaccination [Blood Sample 1] and after final vaccination [Blood Sample 2]) from approximately 120 subjects (30 subjects from each age group) to CBER for further analysis by the WHO, the CDC, and the FDA to support formulation recommendations for subsequent influenza vaccines.

There are no endpoints for the serum collection objective.

3 Investigators and Trial Organization

This study will be conducted in 3 centers in the United States. Details of the study centers, the Investigators at each center, and the Coordinating Investigator(s) are provided in the “List of Investigators and Centers Involved in the Trial” document.

The Sponsor’s Responsible Medical Officers (RMOs; the persons authorized to sign this protocol and any amendments on behalf of the Sponsor) are [REDACTED], [REDACTED] and [REDACTED], [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) occurring during the study that are related to vaccination will be reported by the Investigator to the IRB(s), according to the IRB policy.

5 Investigational Plan

5.1 Description of the Overall Trial Design and Plan

5.1.1 Trial Design

5.1.2 Justification of the Trial Design

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

5.1.3 Trial Plan

This will be a Phase IV, multi-center, open-label study of a planned 240 subjects to describe the safety and immunogenicity of Fluzone Quadrivalent vaccine in children 6 months to < 9 years of age and adults 18 to < 65 years of age, and to describe the safety and immunogenicity of Fluzone High-Dose vaccine in adults ≥ 65 years of age. Each subject will be assigned to the appropriate age group based on the subject's age at the time of enrollment. An approximately equal number of subjects from each age group will be enrolled at each site.

- Group 1: Children 6 to < 36 months of age assigned to receive a 0.25-mL pediatric dose of Fluzone Quadrivalent vaccine (60 subjects planned)
- Group 2: Children 3 to < 9 years of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (60 subjects planned)

- Group 3: Adults 18 to < 65 years of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (60 subjects planned)
- Group 4: Adults \geq 65 years of age assigned to receive a 0.5-mL dose of Fluzone High-Dose vaccine (60 subjects planned)

All subjects will receive an intramuscular dose of their assigned vaccine during 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 dose of the same volume of Fluzone Quadrivalent vaccine as the first dose will be administered at Visit 2 (28 [window, 28–35] days after Visit 1).

Subjects 6 months to < 9 years of age (Group 1 and Group 2): blood specimens will be obtained from all subjects prior to the first vaccination and 28 (window, 28–35) days following the final vaccination (Visit 2 for subjects receiving 1 dose; Visit 3 for subjects receiving 2 doses) and assayed for immunogenicity. Solicited adverse reaction (AR) information will be collected for 7 days following each vaccination. Unsolicited non-serious AE and SAE information will be collected from Visit 1 through Visit 2 for subjects receiving 1 dose or from Visit 1 through Visit 3 for those subjects receiving 2 doses.

Subjects \geq 18 years of age (Group 3 and Group 4): blood specimens will be obtained from all subjects prior to vaccination and 21 (window, 21–28) days post-vaccination (Visit 2). Solicited AR information will be collected for 7 days following vaccination. Unsolicited non-serious AE and SAE information will be collected from Visit 1 through Visit 2.

Pregnancy Testing

A urine human chorionic gonadotropin pregnancy test or a serum pregnancy test supplied by Sanofi Pasteur will be used to test females of child-bearing potential for pregnancy prior to vaccination. Subjects will not participate in the study if the initial pregnancy test is positive.

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 or subject's parent/guardian, including but not limited to its objectives, design, and risks and benefits, and answer any questions the subject or subject's parent/guardian may have.
- 2) Obtain a written informed consent from the subject or 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 or 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).

- 6) 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.
- 7) For subjects \geq 18 years of age, collect influenza vaccination history from previous season, including name of product if known.
- 8) Perform a directed physical examination, if indicated, based on medical history.
- 9) Measure the temperature by the preferred route (see Section 9.3.1.3.2) and record this information in the source document. If the subject has a temperature \geq 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).
- 10) When applicable, obtain a urine or serum pregnancy test.
- 11) If subject meets all inclusion and no exclusion criteria, connect to the Interactive Response Technology (IRT) system to enter required data to receive subject number and vaccine and dose to be administered based on subject's age.
- 12) Obtain a pre-vaccination blood sample (approximately 5 mL for subjects 6 months to < 9 years of age, approximately 10 mL for subjects \geq 18 years of age; see Section 7.1 for detailed instructions regarding the collection of blood samples).
- 13) Prepare the vaccine to be administered based on the information provided in Section 6.1.1.2 and Section 6.1.2.2.
- 14) 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).
- 15) Observe subject for 20 minutes following the injection for the occurrence of allergic and anaphylactic reactions and immediate injection site and systemic reactions.
- 16) Provide to the subject or subject's parent/guardian an age-appropriate diary card, a digital thermometer, and a flexible ruler, along with instructions for their use, to record solicited injection site and systemic reactions from Day 0 through Day 7 post-vaccination, and unsolicited AEs, SAEs, as well as any concomitant medications (see Section 6.7) from Visit 1 through Visit 2.
- 17) Schedule Visit 2.
- 18) Remind the subject or subject's parent/guardian that they will be contacted by telephone on or about Day 8 post-vaccination to remind them to complete the diary card and to bring the completed diary card with them to Visit 2.
- 19) Remind the subject or subject's parent/guardian to notify the site immediately if an SAE occurs.
- 20) Complete the relevant electronic case report form (eCRF) pages for this visit.

Telephone Contact – Visit 1 + 8 (window, 8–10) days

Eight days after the study vaccination at Visit 1, a delegated staff member from the study site will telephone the subject or subject's parent/guardian to perform the following:

- 1) Remind the subject or subject's parent/guardian to record on the diary card any AEs and any concomitant medications (see Section 6.7) from Visit 1 until Visit 2.
- 2) Remind the subject or subject's parent/guardian to notify the site immediately if an SAE occurs. If an SAE occurs, follow the instructions in Section 10 for reporting it.
- 3) Confirm the date of the appointment of Visit 2, instruct the subject or subject's parent/guardian to return at this time, and to bring the completed diary card with them to the study site.

Note: If Day 8 falls on a weekend or a holiday, the telephone call may be placed preferably on 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.

Visit 2 (Visit 1 + 21 [window, 21–28] days) – Subjects 18 Years of Age and Older – 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 AEs, medications, or therapy that occurred since vaccination.
- 3) Obtain the second blood sample (approximately 10 mL; see Section 7.1 for detailed instructions regarding the handling of blood samples).
- 4) Complete the relevant eCRF forms for this visit as well as the termination record in the eCRF.

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 AEs, medications, or therapy that occurred since vaccination.
- 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 eCRF pages for this visit as well as the termination record in the eCRF.

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 any AEs, medications, or therapy that occurred since vaccination.
- 3) Perform a history-directed physical examination.
- 4) Measure temperature by the preferred route (see Section 9.3.1.3.2) and record this information in the source document. If the subject has a temperature $\geq 100.4^{\circ}\text{F}$ ($\geq 38.0^{\circ}\text{C}$) defer vaccination until the subject has been afebrile for at least 24 hours (see Section 5.2.7.1).
- 5) Connect to the IRT system to confirm vaccine and dose to be administered based on subject's age. The second vaccine dose should be the same as the first dose (i.e., same 0.25-mL or 0.5-mL volume of Fluzone Quadrivalent vaccine) administered at Visit 1.
- 6) Prepare the vaccine to be administered based on the information provided in Section 6.1.1.2.
- 7) 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 (Section 6.1.1.2).
- 8) Observe subject for 20 minutes following the injection for the occurrence of allergic and anaphylactic reactions and immediate injection site and systemic reactions.
- 9) Provide age-appropriate Diary Card 2 to the subject's parent/guardian to record solicited injection site and systemic reactions from Day 0 through Day 7 post-vaccination, and unsolicited AEs, SAEs, as well as any concomitant medications (see Section 6.7) from Visit 2 through Visit 3.
- 10) Schedule Visit 3.
- 11) Remind the subject's parent/guardian that they will be contacted by telephone on or about Day 8 post-vaccination to remind them to complete the diary card and to bring the completed diary card with them to Visit 3.
- 12) Remind the subject's parent/guardian to notify the site immediately if an SAE occurs.
- 13) Complete the relevant eCRF pages for this visit.

Telephone Contact – Visit 2 + 8 (window, 8–10) days

Eight days after the study vaccination at Visit 2 (for subjects receiving a second vaccination), a delegated staff member from the study site will telephone the subject's parent/guardian to perform the following:

- 1) Remind the subject's parent/guardian to record on the diary card any AEs and any concomitant medications (see Section 6.7) from Visit 2 until study termination Visit 3.

^a As per ACIP guidance.

- 2) Remind the subject's parent/guardian to notify the site immediately if an SAE occurs. If an SAE occurs, follow the instructions in Section 10 for reporting it.
- 3) Confirm the date of the appointment of Visit 3. Instruct the subject's parent/guardian to return at this time and to bring the completed diary card with them to the study site.

Note: If Day 8 falls on a weekend or a holiday, the telephone call may be placed preferably on the following business day. If the subject's parent/guardian is not available, the study staff should document the attempts to make contact.

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.
- 2) Review interim health history, including any AEs, medications, or therapy that occurred since vaccination.
- 3) Obtain blood sample (approximately 5 mL; see Section 7.1 for detailed instructions regarding the collection of blood samples).
- 4) Complete the relevant eCRF pages for this visit as well as the termination record in the eCRF.

Collection of Diary Cards

If the subject or 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 or subject's parent/guardian by telephone. During the telephone call, the subject or 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.

Serious Adverse Events and Adverse Events That Are Related to Vaccination or That Led to Discontinuation:

At any time during the study, a subject who experiences an SAE or an AE must be followed if *either* of the following is true:

- The SAE or AE is considered by the Investigator to be related to vaccination, and is not resolved by the end of the subject's participation in the study
- The subject has been discontinued from the study because of the SAE or AE

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

^a As per ACIP guidance

5.1.5 Planned Trial 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 2017 to December 2017

Planned end of study: December 2017

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

5.1.6 Early Safety Data Review

This study will not include an early review of safety data. However, it may be interrupted at any time if new data about the investigational products become available, and/or on advice of the Sponsor, the IRB(s), or the FDA.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IRB(s), and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects or subjects' parents/guardians, as appropriate, and should assure appropriate therapy and follow-up.

5.2 Enrollment and Retention of Trial 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 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 (and assent form) 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 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 in order to be eligible for study enrollment:

- 1) Aged 6 months to < 9 years or ≥ 18 years 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 ≥ 2.5 kg (5.5 lbs).
- 3) Informed consent form has been signed and dated by subjects ≥ 18 years of age.
- 4) Assent form has been signed and dated by subjects 7 to < 9 years of age, and informed consent form 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) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at

^a “6 months to < 9 years” means from the 6 month after birth to the day before the 9th year. “ ≥ 18 years” means from the day of the 18th birthday onwards.

least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be pre-menarche,^a or post-menopausal for at least 1 year, or surgically sterile.

- 2) 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.

- 3) 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.
- 4) Previous vaccination against influenza (in the 2017–2018 influenza season) with either study vaccine or another vaccine.
- 5) Receipt of immune globulins, blood, or blood-derived products in the 3 months preceding planned inclusion.
- 6) 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).
- 7) 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.

- 8) Thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator.
- 9) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination.
- 10) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.
- 11) Current alcohol abuse or drug addiction.
- 12) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion.^a

^a Pre-menarche females will declare by themselves that they have not yet started menstruation. If a young female subject reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward.

- 13) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of planned vaccination or febrile illness (temperature $\geq 100.4^{\circ}\text{F}$ [38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
- 14) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study (subjects ≥ 18 years of age) or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study (all subjects).
- 15) History of serious AR to any influenza vaccine.
- 16) Personal history of GBS.
- 17) 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.
- 18) Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.
- 19) 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.

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 medical history (reported as diagnosis) including conditions for which the subject is or has been followed by a physician or conditions that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the eCRF. The significant medical history section of the eCRF 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^b)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms 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

^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

^b Investigators are highly encouraged to evaluate signs and symptoms to establish and report a diagnosis whenever feasible; reporting only signs and symptoms in lieu of a unifying diagnosis is strongly discouraged.

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.

- Febrile illness (temperature $\geq 38.0^{\circ}\text{C}$ [$\geq 100.4^{\circ}\text{F}$]) or moderate or severe acute illness/infection on the day of vaccination, according to Investigator judgment

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:

- An anaphylactic or other significant allergic reaction to the previous dose of vaccine.
- Receipt of any non-study vaccine (including a non-study dose of 2017–2018 influenza vaccine), immune globulins, blood, or blood-derived products between Visit 1 and Visit 2.
- Bleeding disorder, receipt of anticoagulants, or thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator.
- 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).
- Development of an 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).
- Adverse events that are considered a contraindication for further participation in the study.

Subjects with a definitive contraindication will continue to be followed for the study-defined safety and immunogenicity assessments, as applicable. Therefore, in this study subjects with a definitive contraindication will be discontinued from the study; but, will continue to be followed for study-defined safety assessments. For safety follow-up of subjects who experience definitive contraindications, see Section 5.2.11.

5.2.8 Conditions for Withdrawal

Subjects or subjects' parents/guardians will be informed that they have the right to withdraw or 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 the subject's or parent's/guardian's permission.
- At the request of the subject or 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 on the eCRF.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "SAE" or "other AE" as appropriate) 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 eCRF and in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Trial

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the eCRF. Reasons are listed below from the most significant to the least significant (refer to the eCRF completion guidelines for additional details and examples):

- **Serious adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an SAE, as defined in Section 9.3.1.1.
- **Other adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an AE other than an SAE, as defined in Section 9.3.1.1.
- **Non-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow the protocol, including when it is retrospectively discovered that a subject did not fulfill the eligibility criteria. The Investigator will provide a comment as to the specific cause of non-compliance.

- **Lost to follow-up:** To be used when the Investigator withdraws a subject from the study because of failure to establish contact, as outlined in Section 5.2.9. The Investigator will provide documentation that contact was attempted (i.e., return of unsigned certified letter receipt).
- **Voluntary withdrawal not due to an adverse event:** To be used when a subject drops out of the study for any reason other than those listed above.

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 SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definitive contraindications.

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.

For subjects where the reason for early termination is voluntary withdrawal, 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.

5.2.12 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy and if at least one dose of the study vaccine(s) has been administered, the subject will not be discontinued from the study and will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable). However, no additional vaccination will be administered.

All pregnancy cases should be reported if they occurred during the study. To report the pregnancy case, the Investigator must fill out a Pregnancy Reporting Form in the electronic data capture (EDC) system and send it to the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome—i.e., details about the delivery and the newborn, or about pregnancy termination—and must update the electronic Pregnancy Reporting Form. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the Global Pharmacovigilance (GPV) Department regardless of when the SAE occurs (e.g., even after the end of the study).

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 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. The investigator is still required to follow the protocol defined process for reporting SAEs to GPV (Please refer to Section 10).

5.4 Modification of the Trial 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., 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 or logistical aspect of the study but does not affect its design or objectives or have an impact on the subjects' safety. Regulatory authorities need only be notified about administrative changes. 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 Trial

The study may be discontinued if new data about the investigational products resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, and/or the IRB(s). If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the regulatory authorities, and the IRB(s) of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The Investigator shall promptly inform the study subjects or subjects' parents/guardians, as appropriate, and assure appropriate therapy for and follow-up of subjects.

6 Vaccines Administered

The vaccine to be administered is based on the age of the subject at enrollment into the study. Subjects 6 to < 36 months of age, subjects 3 to < 9 years of age, and subjects 18 to < 65 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, pediatric dose (subjects 6 to < 36 months of age):
7.5 µg/HA of each antigen per 0.25-mL dose (total HA content per dose: 30 µg)
- Fluzone Quadrivalent vaccine (subjects 3 to < 9 years of age and 18 to < 65 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 (same 0.25-mL or 0.5-mL volume of Fluzone Quadrivalent vaccine as administered at Visit 1) will be administered approximately 28 days later, during Visit 2.

6.1 Identity of the Investigational Products

The 2017–2018 formulations of Fluzone Quadrivalent (0.25-mL and 0.5-mL pre-filled syringe presentations) 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 Trial Product 1

Fluzone Quadrivalent vaccine, No Preservative: Pediatric Dose (0.25-mL dose),
2017–2018 formulation

or

Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2017–2018 formulation

6.1.1.1 Composition

Each 0.25-mL dose contains 7.5 µg HA of each antigen, and each 0.5-mL dose contains 15 µg HA of each antigen:

- A/Michigan/45/2015 X-275 (H1N1)
- A/Hong Kong/4801/2014 X-263B (H3N2)
- B/Brisbane/60/2008 (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 0.25-mL and 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.

See Section 6.1.3 for general preparation and administration instructions.

6.1.1.3 Dose Selection and Timing

Fluzone Quadrivalent vaccine will be administered as a single 0.25-mL or 0.5-mL dose, as appropriate, given on Day 0 at Visit 1 to all subjects 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 the same volume of Fluzone Quadrivalent vaccine as the first dose will be administered at Visit 2 (28 [window, 28–35] days after Visit 1).

6.1.2 Identity of Licensed Trial Product 2

Fluzone High-Dose vaccine, 2017–2018 formulation

6.1.2.1 Composition

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

- A/Michigan/45/2015 X-275 (H1N1)
- A/Hong Kong/4801/2014 X-263B (H3N2)
- B/Brisbane/60/2008 (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 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.

See Section 6.1.3 for general preparation and administration instructions.

6.1.2.3 Dose Selection and Timing

Fluzone High-Dose vaccine will be administered as a single 0.5-mL dose given on Day 0 at Visit 1 to all subjects assigned to receive this vaccine.

6.1.3 General Preparation and Administration Instructions

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 reactions during this period will be documented in the eCRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

6.1.4 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 in order 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. 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 eCRF. 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 eCRFs and the communication from the IRT system.

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 either contact the IRT system to receive the replacement dose verification or 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. On the day of enrollment, subjects who meet all inclusion criteria and no exclusion criteria will be assigned to 1 of 4 age groups (60 subjects each) based on their age at enrollment (6 to < 36 months of age [Group 1], 3 to < 9 years of age [Group 2], 18 to < 65 years of age [Group 3], or ≥ 65 years of age [Group 4]); see Section 6 for details of vaccine administered to each age group. Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data (including the number of doses) in response to IRT system prompts. The IRT system will then provide the subject number and vaccine and dose to be administered based on subject's age and have the site staff confirm it. The full detailed procedures for using the IRT system are described in the Operating Guidelines. If the subject is not eligible to participate in the study, information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IRT system will consist of an 8-digit string (a 3-digit study center identifier and a 5-digit subject identifier connected by "-"). For example, Subject 001-00001 is the first subject enrolled in center number 1. 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 including 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 eCRF of concomitant medication will be limited to specific categories of medication of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the eCRF from the day of vaccination to the end of the solicited and unsolicited 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) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

The “reportable” medications are distributed according to 2 categories. These are:

- Category 1: antipyretics, analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, and other immune modulators.

Note: inhaled and topical steroids should not be captured.

- Category 2: Other reportable medications as specified in the protocol (i.e., medications related to exclusion criteria) and other medications as noted here. All non-study vaccines, immune globulins, and blood or blood-derived products are included in this category. Other medications include topical analgesics applied to the site of the blood draw; allergy hyposensitization therapy received within 30 days before study vaccination and/or during the safety 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); and statin therapy. These therapies are permissible but nonetheless should be recorded as Category 2 medications. 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 1 medication in this specific instance, not as a Category 2 medication.

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

- Trade name
- Given as treatment or as prophylaxis
- Medication category
- Start and stop dates

Dosage and administration route will not be recorded. Homeopathic medication will not be recorded. Topical treatment will not be recorded. Topical medication, except for topical analgesics applied to the site of the blood draw or inadvertently applied to the vaccination site (see categorization instructions above), will not be recorded.

The fact that a medication was given in response to an AE will be captured in the “Action Taken” column of the AE only. No details will be recorded in the concomitant medication module of the eCRF unless the medication received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses 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 10 mL for subjects \geq 18 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 and will attach the pre-printed label that contains that subject's number and the sampling stage to the tube. It is preferred that the blood be taken from the limb opposite to the one that will be used for vaccination, but it is not required.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of antibody 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 are then centrifuged, and the serum is 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 (see Section 7.1).

The subject's number and the date of sampling, the number of aliquots obtained, and the subject or subject's parent's/guardian's consent for future use of his/her samples are to be specified on a sample identification list. All these items, as well as the date and time of preparation, are to be recorded in the source document. Space is provided on the sample identification 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 Global Clinical Immunology (GCI) 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 International Air Transport Association 602 regulations.

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

7.4 Future Use of Stored Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 5 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

Subjects or subjects' parents/guardians 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. In any case, 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 laboratory methods. Human genetic tests will never be performed on these samples without individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, eCRFs, SAE reporting forms, diary cards, memory aids, 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, shipping containers, rulers, and digital thermometers.

The means for performing 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 phlebotomy (except for the blood collection tubes, which are provided by the Sponsor), 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 Primary Endpoints and Assessment Methods

9.1.1 Safety

There are no primary objectives for safety.

9.1.2 Immunogenicity

There are no primary objectives for immunogenicity.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Safety

There are no secondary objectives for safety.

9.2.2 Immunogenicity

There are no secondary objectives for immunogenicity.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Safety

The observational safety objective is presented in Section 2.1.1.

9.3.1.1 Safety Definitions

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

Adverse Event:

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

Therefore an AE may be:

- A new illness
- The worsening of a concomitant illness

- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event:

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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient'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

- 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^d

^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 out-patient 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.

^d Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These 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.

Additionally, the following important medical events are to be considered as SAEs and reported to the Sponsor according to the procedure described in Section 10:

- 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

Adverse Reaction:

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

(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)

Unexpected Adverse Reaction:

An unexpected AR is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the eCRF. The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

Examples of solicited reactions include injection site pain from Day 0 through Day 7 post-vaccination, or headache from Day 0 through Day 7.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the eCRF and considered as related to vaccination.

Unsolicited Adverse Event/Adverse Reaction:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset post-vaccination (i.e., excluding solicited reactions). For example, if headache from Day 0 through Day 7 is a solicited reaction (i.e., prelisted in the eCRF), then a headache starting on Day 7 is a solicited reaction, whereas headache starting on Day 8 post-vaccination is an unsolicited AE.

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction^a is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

Systemic Adverse Event:

Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination site, e.g., erythema that is localized but that is not at the injection site.

Adverse Events of Special Interest:

Adverse events of special interest are AEs that are considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine.

9.3.1.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- 1) Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 20 minutes after vaccination.
- 2) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited injection site reactions (prelisted in the subject's diary card and eCRF) occurring from Day 0 through Day 7 after vaccination.
- 3) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions (prelisted in the subject's diary card and eCRF) occurring from Day 0 through Day 7 after vaccination.
- 4) Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs from Visit 1 through Visit 2 for subjects receiving 1 dose or from Visit 1 through Visit 3 for subjects receiving 2 doses.
- 5) Occurrence, nature (MedDRA preferred term), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs from Visit 1 through Visit 2 for subjects receiving 1 dose or from Visit 1 through Visit 3 for subjects receiving 2 doses.

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

^a All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

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.

9.3.1.3 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 solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the eCRF according to the instructions provided by the Sponsor.

9.3.1.3.1 Immediate Post-vaccination Surveillance Period

Subjects will be kept under observation for 20 minutes after each vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the eCRF, as follows:

- Any unsolicited systemic AE occurring during the first 20 minutes post-vaccination will be recorded on the eCRF as immediate unsolicited systemic AE.
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 20 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10.

9.3.1.3.2 Reactogenicity (Solicited Reactions From Day 0 Through Day 7 After Each Vaccination)

After each vaccination, subjects or subject's parent/guardian will be provided with a safety diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (i.e., Day 0 through Day 7) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event, if any (e.g., medication)

The action taken by the subject or subject's parent/guardian to treat any **solicited reactions** will be classified in the eCRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

- 3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)
- 4: Hospitalization (inpatient)

Subjects or subject's parent/guardian will be contacted by telephone 8 days after each vaccination to remind them to record all safety information in the diary card.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 9.1, Table 9.2, Table 9.3, Table 9.4, and Table 9.5 present the injection site reactions and systemic reactions that are prelisted in the diary cards and eCRF, together with the intensity scales.

Table 9.1: Solicited Injection Site Reactions: Terminology, Definitions, and Intensity Scales (Subjects 6 to < 36 Months of Age)

CRF term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition		Presence of redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale^a	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

^a For the subjective reaction of tenderness, parents/guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: Solicited Injection Site Reactions: Terminology, Definitions, and Intensity Scales (Subjects 3 to < 9 Years of Age)

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition		Presence of redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale ^a	Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

^a For the subjective reaction of pain, subjects or subject's parent/guardian will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.3: Solicited Injection Site Reactions: Terminology, Definitions, and Intensity Scales (Subjects 18 Years of Age and Older)

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition		Presence of redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale ^a	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

^a For the subjective reaction of pain, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 9.4: Solicited Systemic Reactions: Terminology, Definitions, and Intensity Scales (Subjects 6 to < 36 Months of Age)

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)	Vomiting does not include spitting up	Inconsolable crying without a reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale^a	Grade 1: $\geq 38.0^{\circ}\text{C}$ to $\leq 38.5^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$ to $\leq 101.3^{\circ}\text{F}$ Grade 2: $> 38.5^{\circ}\text{C}$ to $\leq 39.5^{\circ}\text{C}$ or $> 101.3^{\circ}\text{F}$ to $\leq 103.1^{\circ}\text{F}$ Grade 3: $> 39.5^{\circ}\text{C}$ or $> 103.1^{\circ}\text{F}$	Grade 1: 1 episode per 24 hours Grade 2: 2–5 episodes per 24 hours Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 1: < 1 hour Grade 2: 1–3 hours Grade 3: > 3 hours	Grade 1: Sleepier than usual or less interested in surroundings Grade 2: Not interested in surroundings or did not wake up for a feed/meal Grade 3: Sleeping most of the time or difficult to wake up	Grade 1: Eating less than normal Grade 2: Missed 1 or 2 feeds/meals completely Grade 3: Refuses ≥ 3 feeds/meals or refuses most feeds/meals	Grade 1: Easily consolable Grade 2: Requiring increased attention Grade 3: Inconsolable

^a For all reactions but fever, parents/guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.5: Solicited Systemic Reactions: Terminology, Definitions, and Intensity Scales (Subjects 3 to < 9 Years of Age and 18 Years of Age and Older)

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale^a	Grade 1: $\geq 38.0^{\circ}\text{C}$ to $\leq 38.4^{\circ}\text{C}$, or $\geq 100.4^{\circ}\text{F}$ to $\leq 101.1^{\circ}\text{F}$ Grade 2: $\geq 38.5^{\circ}\text{C}$ to $\leq 38.9^{\circ}\text{C}$, or $\geq 101.2^{\circ}\text{F}$ to $\leq 102.0^{\circ}\text{F}$ Grade 3: $\geq 39.0^{\circ}\text{C}$ or $\geq 102.1^{\circ}\text{F}$	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

^a For all reactions but fever, subjects or subjects' parents/guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Important notes for the accurate assessment of temperature:

Subjects or subject's parent(s)/guardian(s) are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the eCRF. 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 and ≥ 18 years of age. The axillary route may be used when a rectal or oral temperature cannot be obtained. Pre-vaccination temperature is also systematically collected by the investigator in the eCRF for all subjects. Tympanic thermometers must not be used.

9.3.1.3.3 Unsolicited Non-serious Adverse Events From Visit 1 Through Visit 2 or Visit 3

In addition to recording solicited reactions, subjects or subjects' parent(s)/guardian(s) will be instructed to record any other medical events 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.

For each unsolicited non-serious AE, the following information is to be recorded:

- Start and stop dates^a
- Intensity of the event:
 - For measurable unsolicited non-serious AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1, Table 9.2, Table 9.3, Table 9.4, and Table 9.5)
 - Other unsolicited non-serious AEs will be classified according to the following intensity scale:
 - Grade 1: No interference with activity
 - Grade 2: Some interference with activity
 - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

The action taken by the subject or subjects' parent(s)/guardian(s) to treat any **unsolicited AEs** will be classified in the eCRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

^a The stop date of all related AEs will be actively solicited. For other events, the Investigator will provide the stop date when it becomes available. Adverse events for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

- 2: Health care provider contact (no new medication prescribed)
- 3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to discontinuation
- Whether the AE was related to vaccination (for unsolicited systemic AEs)

9.3.1.3.4 Serious Adverse Events

Information on SAEs 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 occurring at any time during the study will be reported by the Investigator through the EDC system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE 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). The Investigator will assess the causal relationship between the SAE and the investigational product as either “Not related” or “Related”, as described in Section 9.3.1.3.6.

See Section 10 for further details on SAE reporting.

9.3.1.3.5 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.

9.3.1.3.6 Assessment of Causality

The Investigator will assess the *causal relationship* between each unsolicited systemic AE and vaccination as either not related or related, based on the following definitions^a:

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

^a ICH Guidelines, Clinical Safety Data Management E2A

1: Related – There is a “reasonable possibility” that the AE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all injection site AEs (solicited and unsolicited) and all solicited systemic reactions are considered to be related to vaccination and referred to as reactions, and therefore do not require the Investigator’s opinion on relatedness.

AEs likely to be related to the product, whether serious or not, 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.

9.3.2 Immunogenicity

The observational immunogenicity objective is presented in Section 2.1.2.

9.3.2.1 Immunogenicity Endpoints

Immunogenicity will be evaluated in all subjects by analyzing sera collected prior to vaccination on Day 0 (Visit 1) and after final vaccination (28 [window, 28–35] days post-final vaccination for subjects 6 months to < 9 years of age [Visit 2 for subjects receiving 1 dose; Visit 3 for subjects receiving 2 doses]; or 21 [window, 21–28] days post-vaccination for subjects \geq 18 years of age) using the HAI assay technique.

For each influenza vaccine strain (i.e., 3 strains for Fluzone High-Dose vaccine [a trivalent vaccine] and 4 strains for Fluzone Quadrivalent vaccine), HAI assay titers at pre-vaccination (Day 0) and after the final vaccination will be determined in duplicate.

The derived endpoints^a are:

- Geometric means of HAI assay titers at pre-vaccination and post-final vaccination
- Ratios of post-final vaccination titers divided by pre-vaccination titers.
- Seroprotection: a titer \geq 40 (1/dilution [dil]) at pre-vaccination and at post-final vaccination
- Seroconversion: either a pre-vaccination titer $<$ 10 (1/dil) and a post-final vaccination titer \geq 40 (1/dil), or a pre-vaccination titer \geq 10 (1/dil) and a \geq 4-fold increase in post-final vaccination titer

^a Post-final vaccination in each of the derived endpoints is defined as 28 (window, 28–35) days post-final vaccination for subjects 6 months to < 9 years of age, and 21 (window, 21–28) days post-vaccination for subjects \geq 18 years of age

9.3.2.2 Immunogenicity Assessment Methods

Anti-influenza antibodies will be measured by HAI assay performed by Sanofi Pasteur’s GCI department or an external testing laboratory under GCI’s supervision. Serum samples and quality control sera (sheep and/or human sera) will be incubated with Sigma Type III NA to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins will be performed by incubating the serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures will be centrifuged and the supernatants containing the treated sera

will be collected for testing. Ten 2-fold dilutions (starting at 1/10) of the treated serum samples and quality control sera will be incubated with a previously titrated influenza virus at a concentration of 4 hemagglutination unit/25 μ L. Influenza virus will not be added to the serum control wells containing only serum and RBCs. The mixture will be incubated and a RBC suspension will be added. Following incubation, the results will be read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample will be titrated in independent duplicates, and the 2 values, which do not differ by more than one 2-fold dilution, will be reported. The geometric mean titer between the 2 values will be calculated after the release of the data to the Clinical Data Management (CDM) platform. The lower limit of quantification (LLOQ) for HAI is set at 10, the lowest serum dilution used in the assay (i.e., 1/10). Titers below this level are reported as < 10. If the highest/last serum dilution used in the assay exhibits complete inhibition of hemagglutination, the serum antibody titer will be reported as \geq 10240 (1/dil).

9.3.3 Efficacy

No clinical efficacy will be obtained in the study.

9.3.4 Serum Collection

The observational objective for serum collection is presented in Section 2.1.3.

9.3.4.1 Serum Collection Endpoints and Assessment Methods

There are no observational endpoints for the serum collection objective.

10 Reporting of Serious Adverse Events

In order to comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs 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 product(s). 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 into the electronic SAE reporting form (eSAE form).

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 must be reported, even if the Investigator considers that it is not related to the vaccine. The eSAE form must be signed by a licensed physician (M.D. or D.O.) for whom the task is listed on the Study Task Delegation and Signature List after each update to the eSAE form.

The Investigator must complete the eSAE form in the EDC application. After validation, an e-mail alert will automatically be sent to the GPV mailbox, the CRA, and the RMOs. This message will include the country, the study code, the subject number, whether the report is an initial or a follow-up report, the diagnosis and/or symptoms, the seriousness criteria, the relationship, if related, and the outcome, if fatal.

If the EDC system is unavailable, the site must notify the Sponsor using the paper version of the SAE Reporting Form, as follows:

The Investigator must complete the SAE Reporting Form, check off the “Initial Reporting Form” box, and send it to the Sponsor by 1 of the following means:

- By fax, to the following number: [REDACTED]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [REDACTED]
- By express mail, to the following address:
Reception & Triage – Case Management
Global Pharmacovigilance Department, Sanofi Pasteur, Inc.
Discovery Drive, Swiftwater, PA 18370

When the system becomes available, the Investigator must transcribe the information from the paper version of the eSAE Form 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 eSAE Form completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). After validation, an e-mail alert will be sent automatically to the GPV Department and to the CRA. All relevant information must be included directly in the eSAE form. 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 that occurs after a subject has completed the study but that is likely to be related to the product 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 and the product will first be evaluated by the Investigator, using the following definitions:

0 - Not related: The AE 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 is incompatible with a causal relationship; or the SAE started before the first vaccination (screening phase, if applicable).

1 - Related: There is a “reasonable possibility” that the SAE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.

(ICH Guidelines, Clinical Safety Data Management E2A)

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

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 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. 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 eCRF 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 daily safety information as described in Section 9.3.1.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1, Table 9.2, Table 9.3, Table 9.4, and Table 9.5) as well as areas for free text to capture additional safety information or other relevant details. Subjects or subjects’ parent(s)/guardian(s) will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects or subjects’ parents/guardians on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the subjects or subjects’ parent(s)/guardian(s) 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 eCRF. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The eCRF 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 eCRFs, 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 guidelines 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 in order to track all modifications and to ensure database integrity.

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

11.2 Data Management

Management of Clinical Data

Data generated during the study will be managed following 2 different processes:

- Clinical data, defined as all data reported in the eCRF, and laboratory data will be handled by the Sponsor's CDM platform or authorized representative.
- Data pertaining to SAEs, which are reported by the Investigator on the eSAE forms or SAE reporting forms, will be handled by the Sponsor's GPV Department.

During the study, clinical data reported in the eCRFs 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 in order 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 before integration into the clinical database.

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

Serious Adverse Event Data Management

During the study, data pertaining to SAEs reported on eSAE forms will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an eSAE form, the data will be entered into the GPV database after a duplicate check. Each SAE case will be assigned a case identification number. Each case will be entered in the GPV database and assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. Assessment of related cases will be done in collaboration with the Product Safety Officer and the RMO. 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 pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

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 the recruitment and 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 violations.

12.1.1 Hypotheses and Statistical Methods for Primary Objectives

There are no primary objectives for this study.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

There are no secondary objectives for this study.

12.1.3 Statistical Methods for Observational Objectives

For the main safety and immunogenicity parameters, 95% CIs of point estimates of proportions will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions.

12.1.3.1 Safety

All analyses will be descriptive; no hypotheses will be tested.

12.1.3.2 Immunogenicity

All analyses will be descriptive; no hypotheses will be tested. Data will be summarized and presented for each age group.

The following immunogenicity parameters^a will be calculated for each influenza strain with 95% CIs:

- Geometric mean HAI assay titers at pre-vaccination and post-final vaccination
- Geometric means of titer ratios (post-final vaccination divided by pre-vaccination).
- Seroprotection rates: The percentages of subjects with a titer ≥ 40 (1/dil) at pre-vaccination and at post-final vaccination
- Seroconversion rates: The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-final vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4 -fold increase in post-final vaccination titer

^a Post-final vaccination in each of the immunogenicity parameters is defined as 28 (window, 28–35) days post-final vaccination for subjects 6 months to < 9 years of age, and 21 (window, 21–28) days post-vaccination for subjects ≥ 18 years of age.

12.2 Analysis Sets

Three main analysis sets will be used: the Safety Analysis Set, the Full Analysis Set (FAS), and the Per-Protocol Analysis Set (PPAS).

12.2.1 Safety Analysis Set

The Safety Analysis Set is defined as those subjects who have received at least 1 dose of the study vaccine.^a All subjects will have their safety analyzed after “any dose” according to the study vaccine they received as the first dose. Safety analysis after each dose will be assessed in the subset of the Safety Analysis Set having received that dose. All subjects will have their safety data analyzed after each vaccination according to the vaccine they actually received for this dose.

^a for which safety data are scheduled to be collected

Safety data recorded for a vaccine other than the assigned study vaccine will be excluded from the study statistical summaries and listed separately.

12.2.2 Full Analysis Set

The FAS is defined as those subjects who have received at least 1 dose of the study vaccine and have a valid post-vaccination blood sample result for at least 1 strain.

12.2.3 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least 1 of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine dose other than the one that he/she was assigned to receive
- Preparation and/or administration of vaccine was not done as per-protocol
- Subject did not provide a post-dose serology sample in the proper time window
- Subject received a protocol-prohibited therapy/medication/vaccine that might impact antibody response to the study vaccine
- Any other deviation identified during conduct of the study and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity

12.2.4 Populations Used in Analyses

Baseline and demographic analyses will be performed on all enrolled subjects.

The safety analyses will be performed on the Safety Analysis Set.

The immunogenicity analyses will be performed on both the FAS and PPAS.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No imputation of missing data will be conducted. All subjects with safety data and all safety data recorded in the eCRFs will be included in the safety analyses. No search for outliers will be performed.

12.3.2 Immunogenicity

For the computations, LLOQ and upper limit of quantification (ULOQ) will be managed as follows:

- If a titer is < LLOQ, then LLOQ/2 will be used
- If a titer is \geq LLOQ and < ULOQ, then the titer itself will be used
- If a titer is \geq ULOQ, then ULOQ will be used

Missing data will not be imputed. No search for outliers will be performed.

12.4 Interim/Preliminary Analysis

No interim analyses are planned.

12.5 Determination of Sample Size and Power Calculation

The study will enroll approximately 240 subjects: approximately 60 subjects 6 to < 36 months of age will be administered Fluzone Quadrivalent vaccine (Group 1), approximately 60 subjects 3 to < 9 years of age will be administered Fluzone Quadrivalent vaccine (Group 2), approximately 60 subjects 18 to < 65 years of age will be administered Fluzone Quadrivalent vaccine (Group 3), and approximately 60 subjects \geq 65 years of age will be administered Fluzone High-Dose vaccine (Group 4).

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 Trial/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 “Investigator’s Comment” page of the diary card, and transfer the information to the eCRF.

The subject pre-screening log should list all individuals contacted by the Investigators to 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 later 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.

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.

Sanofi Pasteur personnel (or designates), the IRB(s), and regulatory agencies, including the FDA, require direct access to all study records, and will treat these documents in a confidential manner.

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.

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, eCRF 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 eCRF Completion Guidelines for entering data into the eCRF, and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

^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.

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 eCRFs. 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, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed eCRFs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). 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 eCRF, 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 and Medical Quality Operations department 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 must keep all study documents after the completion or discontinuation of the study, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, study documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any study documents upon less than 90 days advance written notification to the Sponsor. In addition, study documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the study documents.

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, including certificates attesting that satisfactory audit and inspection procedures have been carried out, will be kept by the Sponsor in the Trial Master File. Data on AEs are included in the Trial Master File. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A CTA 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 References List

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