NCT05050318

Title Page

Protocol Title:

Collection of Serum Samples From Children 6 Months to < 9 Years of Age Who Received Fluzone® Quadrivalent and Adults ≥ 65 Years of Age Who Received Fluzone® High-Dose Quadrivalent, Influenza Vaccines, 2021–2022 Formulations

Study Code: GRC00102

Amendment Number: Not applicable

Compound: Fluzone® Quadrivalent and Fluzone® High-Dose Quadrivalent Influenza Vaccines (2021–2022 Formulations)

Brief Title:

Annual Study for Collection of Serum Samples in Children and Older Adults Receiving the 2021–2022 Formulations of Fluzone Quadrivalent Vaccine and Fluzone High-Dose Quadrivalent Vaccine, Respectively

Study Phase: IV

Sponsor Name and Legal Registered Address:

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

Manufacturer: Same as Sponsor

Regulatory Agency Identifier Numbers:

WHO UTN: U1111-1266-5255

Protocol Version Number: 1.0

Approval Date: 21 July 2021

Medical Monitor Name and Contact Information are provided in the Operating Guidelines.

The study sites, the Investigators at each site, and the Coordinating Investigator are listed in a separate document.

Table of Contents

Document History

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

List of Tables

List of Figures

Protocol Summary

1.1 Synopsis

Protocol Title:

Collection of Serum Samples From Children 6 Months to < 9 Years of Age Who Received Fluzone® Quadrivalent and Adults ≥ 65 Years of Age Who Received Fluzone® High-Dose Quadrivalent, Influenza Vaccines, 2021–2022 Formulations

Brief Title:

Annual Study for Collection of Serum Samples in Children and Older Adults Receiving the 2021–2022 Formulations of Fluzone Quadrivalent Vaccine and Fluzone High-Dose Quadrivalent Vaccine, Respectively

Rationale:

The aim of Study GRC00102 is to obtain serum samples for submission to the Center for Biologics Evaluation and Research (CBER) to aid in the influenza vaccine strain selection process. Children 6 months to < 9 years of age will receive the 2021–2022 formulation of Fluzone Quadrivalent vaccine and adults ≥ 65 years of age will receive the 2021–2022 formulation of Fluzone High-Dose Quadrivalent vaccine.

No early safety data review is planned for this study.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To provide serum samples (collected from participants before vaccination [Blood Sample 1] and after final vaccination [Blood Sample 2]) to CBER for further analysis by the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA) to support formulation recommendations for subsequent influenza vaccines. In addition, serum samples from adult participants may be further analyzed by the Sponsor to assess breadth of immune response induced by the study vaccines.	• There are no endpoints for this objective.

Overall Design

Type of design	Parallel, multi-site
Phase	IV
Control method	None
Study population	Children 6 months to < 9 years of age Adults ≥ 65 years of age
Countries	United States
Level and method of blinding	None (open-label)
Study intervention assignment method	Participants will not be randomized

Brief Summary:

This is a phase IV, multi-site, open-label study. The study will collect serum samples from children 6 months to < 9 years of age who received Fluzone Quadrivalent vaccine and adults ≥ 65 years of age who received Fluzone High-Dose Quadrivalent vaccine for submission to CBER to aid in the influenza vaccine strain selection process.

Study Duration:

Participants 6 months to < 9 years of age: 28 (window, 28–35) days following the last dose of influenza vaccine, including serious adverse event (SAE)/adverse event of special interest (AESI) follow-up).
No additional safety follow-up beyond Visit 2 (for participants receiving 1 dose) or Visit 3 (for participants receiving 2 doses) is planned.
Participants ≥ 65 years of age: 21 (window, 21–28) days after vaccination, including SAE/AESI follow-up. No additional safety follow-up beyond Visit 2 is planned.

Visit Frequency:

For Participants 6 Months to < 9 Years of Age: 2 or 3 visits, 1 or 2 vaccinations, 1 or 2 telephone calls, 2 blood samples

For Participants ≥ 65 Years of Age: 2 visits, 1 vaccination, 1 telephone call, 2 blood samples

Number of Participants:

A total of 90 participants are expected to be enrolled.

Intervention Groups and Duration:

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

- Group 1: Children 6 to < 36 months of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (30 participants planned)
- Group 2: Children 3 to < 9 years of age assigned to receive a 0.5-mL dose of Fluzone Quadrivalent vaccine (30 participants planned)
- Group 3: Adults ≥ 65 years of age assigned to receive a 0.7-mL dose of Fluzone High-Dose Quadrivalent vaccine (30 participants planned)

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

The duration of each subject's participation is as follows:

- Participants 6 months to < 9 years of age: 28 (window, 28–35) days following the last dose of influenza vaccine, including SAE/AESI follow-up. No additional safety follow-up beyond Visit 2 (for participants receiving 1 dose) or Visit 3 (for participants receiving 2 doses) is planned.
- Participants ≥ 65 years of age: 21 (window, 21–28) days after vaccination, including SAE/AESI follow-up. No additional safety follow-up beyond Visit 2 is planned.

Study interventions

Participants will receive an intramuscular (IM) injection at Visit 1. For participants 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 IM injection of Fluzone Quadrivalent vaccine will be administered at Visit 2 (28 [window, 28–35] days after Visit 1).

Study interventions are described in Table 1.1.

Table 1.1: Identity of study interventions

Intervention Name	Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2021–2022 formulation	Fluzone High-Dose Quadrivalent vaccine (0.7-mL dose), 2021–2022 formulation
Use	Other (as indicated in the prescribing material)	Other (as indicated in the prescribing material)
IMP and NIMP	IMP	IMP
Type	Vaccine	Vaccine
Dose Form	Suspension for injection in a pre-filled syringe	Suspension for injection in a pre-filled syringe
Unit Dose Strength(s)	15 µg of HA of each of the following strains per dose: • A/Victoria/2570/2019 (H1N1)pdm09-like virus • A/Cambodia/e0826360/2020 (H3N2)-like virus • B/Washington/02/2019 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B Yamagata lineage)-like virus	60 µg of HA of each of the following strains per dose: • A/Victoria/2570/2019 (H1N1)pdm09-like virus • A/Cambodia/e0826360/2020 (H3N2)-like virus • B/Washington/02/2019 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B Yamagata lineage)-like virus
Excipients/Diluent	Octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution	Octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution

Dosage Level	0.5 mL per dose	0.7 mL per dose
Number of Doses / Dosing Interval	1 or 2 doses 28 (window, 28–35) days apart for children aged 6 months to < 9 years (as per ACIP guidance)	1 dose
Route of Administration	IM injection	IM injection
Site of Administration	Anterolateral muscle of the thigh or the deltoid muscle	Deltoid muscle
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Fluzone Quadrivalent and Fluzone High-Dose Quadrivalent vaccines will be supplied with their manufacturer's commercial labeling and packaging.	
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable
Batch Number	TBD	TBD
Storage Conditions	Study interventions will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The study interventions must not be frozen.	

Note: Strains are based on WHO/FDA recommendations for the 2021-2022 NH influenza season

ACIP: Advisory Committee on Immunization Practices; FDA: Food and Drug Administration; HA: hemagglutinin; IM: intramuscular; IMP: Investigational Medicinal Product; NH: Northern Hemisphere; NIMP: Non Investigational Medicinal Product; TBD: to be determined; WHO: World Health Organization

Statistical considerations:

None

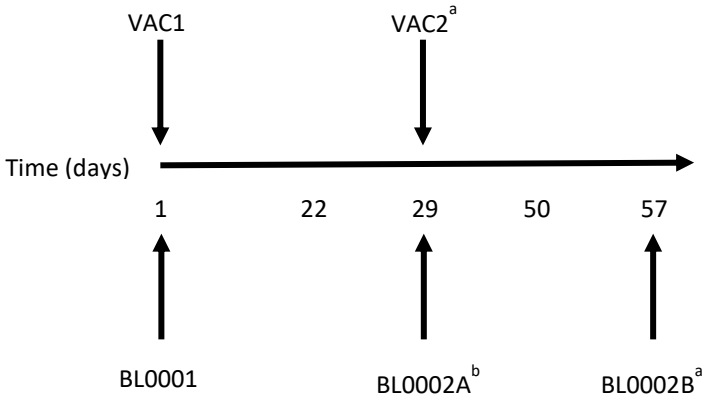
Data Monitoring/Other Committee:

None

Schema

The graphical design of GRC00102 study is presented in Figure 1.1 and Figure 1.2.

Figure 1.1 – Graphical study design for participants 6 months to < 9 years of age



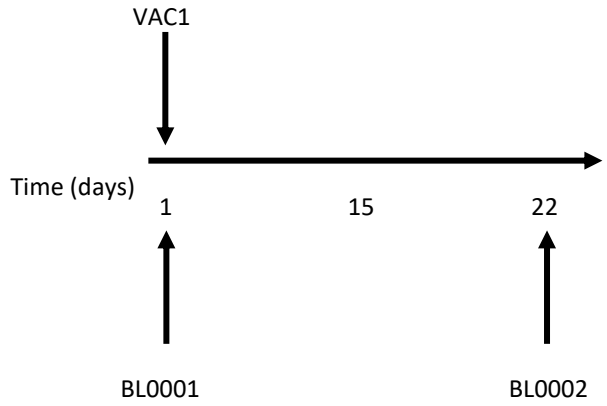
BL: blood sample

VAC: vaccination

[a] Participants receiving 2 doses of study vaccine, as per ACIP guidance

[b] Participants receiving 1 dose of study vaccine

Figure 1.2 – Graphical study design for participants ≥ 65 years of age.



BL: blood sample
VAC: vaccination

1.2 Schedule of Activities (SoA)

Visit procedures are detailed in the Operating Guidelines.

Table 1.2: Schedule of activities 1

For Participants 6 Months to < 9 Years of Age: Phase IV Study, 2 or 3 Visits, 1 or 2 Vaccinations, 1 or 2 Telephone Calls, 2 Blood Samples, 1 or 2 Months Duration Per Participant

	All Participants			Participants Receiving 1 Dose of Influenza Vaccine	Participants Receiving 2 Doses of Influenza Vaccine		
Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Telephone Contact**	**Visit 2**	**Visit 2**	**Telephone Contact**	**Visit 3**
Study timelines (days)		**Day 01**	**Visit 1 + 21 days**	**Visit 1 + 28 days**	**Visit 1 + 28 days**	**Visit 2 + 21 days**	**Visit 2 + 28 days**
Time windows (days)		-	**+ 19 to 23 days**	**+ 28 to 35 days**	**+ 28 to 35 days**	**+ 19 to 23 days**	**+ 28 to 35 days**
Visit procedures:							
Informed consent/assent[a]	X	X					
Inclusion/exclusion criteria	X	X					
Collection of demographic data	X	X					
Collection of medical history	X	X					
Influenza vaccination history	X	X					
History-directed physical examination		X			X		
Pre-vaccination temperature[b]	X	X			X		
Review contraindications for vaccination	X				X		
Allocation of participant number	X	X					
Blood sampling (BL)[c]	X	BL0001		BL0002A			BL0002B
Vaccination[d]	X	X			X		
Immediate surveillance (20 minutes)	X	X			X		
Diary card (DC) provided		DC1			DC2		
Telephone contact[e]			X			X	

	All Participants			Participants Receiving 1 Dose of Influenza Vaccine	Participants Receiving 2 Doses of Influenza Vaccine		
Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Telephone Contact**	**Visit 2**	**Visit 2**	**Telephone Contact**	**Visit 3**
Study timelines (days)		**Day 01**	**Visit 1 + 21 days**	**Visit 1 + 28 days**	**Visit 1 + 28 days**	**Visit 2 + 21 days**	**Visit 2 + 28 days**
Time windows (days)		-	**+ 19 to 23 days**	**+ 28 to 35 days**	**+ 28 to 35 days**	**+ 19 to 23 days**	**+ 28 to 35 days**
Diary card reviewed				DC1	DC1		DC2
Diary card collected				DC1	DC1		DC2
Interim history	X			X	X		X
Reporting medical events to allow for the collection of SAEs and AESIs	X	To be reported throughout the study period					
Collection of reportable concomitant medications	X	X		X	X		X
End of Active Phase participation record[f]	X			X			X

AESI: adverse event of special interest; CRF: case report form; SAE: serious adverse event

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

[b] The preferred route for this study is rectal for participants 6 to < 36 months of age, and oral for participants 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 participants at Visit 1, prior to vaccination, and at either Visit 2 (for participants receiving 1 influenza vaccine dose) or at Visit 3 (for participants receiving 2 influenza vaccine doses).

[d] One or 2 doses of influenza vaccine will be administered according to the 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 will be administered approximately 28 days later during Visit 2.

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

[f] The End of Active Phase participation record will be completed at Visit 2 for participants receiving 1 dose of influenza vaccine or at Visit 3 for participants receiving 2 doses of influenza vaccine. In case of participant discontinuation at a visit, the entire visit will be completed.

Table 1.3: Schedule of activities 2.

For Participants ≥ 65 Years of Age: 2 Visits, 1 Vaccination, 1 Telephone Call, 2 Blood Samples, 21 Days Duration Per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Telephone Contact[c]**	**Visit 2**
Study timelines (days)		**Day 01**	**Visit 1 + 14 days**	**Visit 1 + 21 days**
Time windows (days)		**-**	**+ 12 to 16 days**	**+ 21 to 28 days**
Visit procedures:				
Informed consent	X	X		
Inclusion/exclusion criteria	X	X		
Collection of demographic data	X	X		
Collection of medical history	X	X		
Influenza vaccination history (previous season)	X	X		
History-directed physical examination		X		
Pre-vaccination temperature[a]	X	X		
Allocation of participant number	X	X		
Blood sampling (BL)[b]	X	BL0001		BL0002
Vaccination	X	X		
Immediate surveillance (20 minutes)	X	X		
Diary card provided		X		
Telephone contact[c]			X	
Reporting of medical events to allow for the collection of SAEs, including AESIs	X	To be reported throughout the study period		
Diary card reviewed and collected				X
Collection of reportable concomitant medications	X	X		X
End of Active Phase participation record[d]	X			X

AESI: adverse event of special interest; CRF: case report form; SAE: serious adverse event

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

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

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

[d] In case of participant discontinuation at a visit, the entire visit will be completed.

2 Introduction

2.1 Study Rationale

The aim of Study GRC00102 is to obtain serum samples for submission to CBER to aid in the influenza vaccine strain selection process. Children 6 months to < 9 years of age will receive the 2021–2022 formulation of Fluzone Quadrivalent vaccine and adults ≥ 65 years of age will receive the 2021–2022 formulation of Fluzone High-Dose Quadrivalent vaccine.

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

No early safety data review is planned for this study.

2.2 Background

This is a study using the 2021–2022 formulations of quadrivalent inactivated influenza vaccine (Fluzone Quadrivalent, Influenza Vaccine) and high-dose quadrivalent inactivated influenza vaccine (Fluzone High-Dose Quadrivalent, Influenza Vaccine).

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

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

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

secondary bacterial pneumonia, and exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and congestive heart failure.

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

Antigenic variation is an important feature of the influenza virus. The viral HA and NA surface antigens are subject to continuous and sequential evolution within immune or partially immune populations. Antigenic drift results from mutation(s) affecting the RNA segment coding for either HA or NA, but more commonly HA. As a result, there is alteration in protein structure involving 1 or a few amino acids, resulting in minor changes in antigenicity. Antigenic variants within a subtype (e.g., H1 or H3) emerge and through natural selection gradually become the more predominant circulating virus strain, while the preceding antigenic variant is suppressed by specific immunity in the population. In contrast to antigenic drift, antigenic shift represents the emergence of completely new subtypes, typically through gene reassortment with other circulating strains and acquisition of antigenically different gene sequences. Antigenic shift occurs at irregular intervals and may lead to pandemics (1) (2). While influenza B appears to be more genetically stable than influenza A, the dominant circulating B strain typically varies from season to season. For over a decade, both Yamagata and Victoria lineages have co-circulated during each season with varying prevalence (4). The large antigenic divergence between the 2 influenza B lineages limits antigenic cross-reactivity; therefore, immunity to 1 B lineage may not provide adequate protection against the other. Accordingly, switching from a trivalent vaccine to a quadrivalent vaccine is expected to prevent additional morbidity and mortality associated with mismatched influenza B strains that may occur with trivalent vaccines (4). With this in mind, Fluzone Quadrivalent vaccine and Fluzone High-Dose Quadrivalent vaccine were developed.

Vaccination with influenza vaccine is the primary method for preventing influenza and its severe complications. It has been shown to be effective in reducing influenza-associated morbidity and mortality in groups at increased risk for influenza-related complications such as infants and young children and persons 50 years of age and older. Of note, immune responses to the vaccine are lower in seniors than those in young healthy adults (5). Strategies to improve immune responses to the vaccine in the elderly population could provide substantial additional reductions in influenza-associated morbidity and mortality. One approach is to increase the dose of HA in inactivated vaccines. Previous studies evaluating the immune responses in terms of hemagglutination inhibition (HAI) antibodies with higher doses of HA per strain in different influenza vaccines support a dose-response effect (6).

Fluzone High-Dose Quadrivalent vaccine contains 60 µg HA per virus strain per dose, which is 4 times the amount of HA per strain per dose in Fluzone Quadrivalent vaccine. It was developed for use in the elderly to elicit enhanced immune responses against influenza through the use of

higher antigen content, with the goal of providing older adults with improved protection against the disease.

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

The objective of this study is to provide serum samples collected from children 6 months to < 9 years of age who receive Fluzone Quadrivalent vaccine and adults ≥ 65 years of age who receive Fluzone High-Dose Quadrivalent vaccine to CBER. The serum samples are used for further analysis by the WHO, CDC, and FDA to support formulation recommendations for subsequent influenza vaccines. In addition, serum samples from adult participants may be further analyzed by the Sponsor to assess breadth of immune response induced by the study vaccines.

2.2.1 Epidemiology

Influenza is noted for occurring in epidemics. Typically, localized influenza epidemics begin abruptly, peak in 2 to 3 weeks, and last 5 to 6 weeks, although this can vary considerably by season (for example, the 2017–2018 season lasted 19 weeks (7)). The first sign of influenza in a community is usually reports of increased numbers of children with febrile respiratory illness, although a nursing home outbreak may be the first indication. Outbreaks in children are usually followed by the occurrence of influenza-like illness among adults. Following this is an increase in hospital admissions for pneumonia, exacerbation of chronic obstructive pulmonary disease, croup, and congestive heart failure. Increased absenteeism from school and the workplace occur as a late indicator. Finally, an increased number of deaths due to pneumonia and influenza are a highly specific indicator of influenza. However, due to the reporting delay and time course from infection to death, this indicator lags behind the others (2).

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

The public health impact of influenza is dramatic. Annually, from the 2010–2011 through 2017–2018 influenza season in the United States (US), the CDC estimated that influenza resulted in 9.3–49.0 million illnesses, 140,000–960,000 hospitalizations, and 12,000–79,000 deaths (8). Estimated annual overall hospitalizations and deaths attributable to influenza during this period in the United States were higher compared to historical data, with annual estimated hospitalizations ranging from approximately 55,000 to 431,000 per season (mean: 226,000) from 1979–1980 through 2000–2001 and deaths ranging from 3,000 to 49,000 each season from 1976–1977 through 2006–2007 (9) (10). During the 2010–2011 through 2017–2018 influenza seasons, annual estimates for influenza-related hospitalizations and deaths were highest (45%–72% and 69%–89% of overall estimates, respectively) among adults ≥ 65 years of age (11). During the 2017–2018 season, rates of hospitalization in all age groups were the highest seasonal rates seen since hospital-based surveillance was expanded in 2005 to include all ages, with an estimated 11.5 million cases of influenza in children, 30 million cases of influenza in adults 18–64 years of age, and more than 7.3 million cases in adults ≥ 65 years of age (12).

In the United States, death associated with laboratory-confirmed influenza virus infection among children < 18 years of age has been a nationally reportable condition since 2004. Since reporting began, the total number of influenza-associated deaths among children during 1 season has ranged from 37 (during the 2011–2012 season) to 186 (during the 2017–2018 season, as of April 19, 2019); this excludes the 2009 pandemic, when 358 pediatric deaths from 15 April 2009 through 2 October 2010 were reported to the CDC (13). During the 2009 pandemic, the majority of children who died had 1 or more underlying medical conditions previously associated with conferring a greater risk for influenza complications (14). During the 2017–2018 season, approximately 80% of the deaths occurred in children who had not received the 2017–2018 influenza vaccine (13).

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 (15) (16) (17). 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).

2.2.2 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 ACIP of the CDC recommends that all eligible persons 6 months of age and older receive annual vaccination against influenza (5).

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 (5).

Annually, from the 2011–2012 through 2018–2019[a] influenza seasons in the United States, overall vaccine effectiveness ranged from 19% to 52%, for children 6 months to < 9 years of age it ranged from 25% to 68%, and for adults ≥ 65 years of age it ranged from 17% to 50% (18). The CDC estimated that influenza vaccination prevented 11% of influenza-related hospitalizations

[a] Preliminary estimates for 2018–2019.

during the 2018–2019[a] season and averted 2625 influenza-associated deaths among adults ≥ 65 years of age. In this same period, for persons < 18 years of age, an estimated 144 influenza-associated deaths were averted (19).

2.2.3 The Advisory Committee on Immunization Practices Recommendations

Because children 6 to < 24 months of age are at substantially increased risk for influenza-related hospitalizations, and children 24 through 59 months of age are at increased risk for influenza-related clinic and emergency department visits, the ACIP recommends annual vaccination of all eligible children in these age groups. In recent years, the 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 (5). The ACIP continues to emphasize the importance of vaccinating persons ≥ 6 months of age who have high-risk medical conditions (5).

If a child 6 months to < 9 years of age is receiving influenza vaccine for the first time, based on ACIP recommendations, 2 doses of influenza vaccine should be administered 4 weeks apart during the current season. This recommendation is based on studies demonstrating that vaccine effectiveness is lower among children who have never received influenza vaccine previously or who received only 1 dose in their first year of vaccination than it is among those children who received 2 doses in their first year of being vaccinated. Children 6 months to < 9 years of age who are adequately primed, based on influenza vaccination history, should receive 1 dose during the current season as per ACIP recommendations (5).

2.2.4 Background of the Investigational Product

Vaccine Testing and Release

Before being released for clinical use, the 2021–2022 formulations of Fluzone Quadrivalent and Fluzone High-Dose Quadrivalent vaccines will have passed all approved release-testing requirements.

Previous Clinical Experience: Fluzone Vaccine

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

[a] Latest data available.

Accordingly, Fluzone Quadrivalent vaccine offers the possibility of protecting against both B lineages simultaneously, without compromising vaccine safety (20) (21).

Fluzone High-Dose Vaccine

Fluzone High-Dose vaccine, a trivalent formulation with 60 µg HA per viral strain, has been shown in pre-licensure studies to elicit a higher immune response in the elderly than does Fluzone vaccine (15 µg HA per viral strain) (22) (23) (24). 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 (25).

Fluzone High-Dose Quadrivalent Vaccine

In a pre-licensure study (26), Fluzone High-Dose 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 High-Dose vaccine with respect to the strains contained in each vaccine. The study also demonstrated that the safety profile of Fluzone High-Dose Quadrivalent vaccine was similar to that of Fluzone High-Dose vaccine.

The efficacy of Fluzone High-Dose is relevant to Fluzone High-Dose Quadrivalent since both vaccines are manufactured according to the same process and have overlapping compositions (27).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events (AEs), the potential risks, and uncertainties of Fluzone Quadrivalent vaccine and Fluzone High-Dose Quadrivalent vaccine may be found in the US Prescribing Information for the vaccine administered.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.1.

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: Fluzone Quadrivalent Vaccine		
Refer to the package insert for more information regarding potential risks	Identified and potential risks observed in clinical trials and/or post-marketing surveillance.	Exclusion/inclusion criteria take into account contraindications, warnings and precautions as defined in product label.
Injection site reactions	Most common injection site reactions in children 6 to < 36 months of age: pain or tenderness, erythema, and swelling Most common injection site reactions in children 3 to < 9 years of age: pain, erythema, and swelling	Injection site reactions are generally mild and usually resolve within 3 days.
Systemic reactions	Most common solicited systemic reactions in children 6 to < 36 months of age: irritability, abnormal crying, malaise, drowsiness, appetite loss, myalgia, vomiting, and fever Most common solicited systemic reactions in children 3 to < 9 years of age are: myalgia, malaise, and headache	Systemic findings most often affect persons who have had no prior exposure to the virus antigens in the vaccine (e.g., young children) (28). These reactions begin 6 to 12 hours after vaccination and usually resolve within 3 days.
Immediate allergic reactions	Immediate allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination. These reactions probably result from	These types of reactions are exceedingly rare and would most likely occur in persons with a severe reaction to influenza vaccine in the past. Vaccine should not be administered to anyone who has had a severe

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	hypersensitivity to some vaccine component (29) (30) (31).	allergic reaction to any component of the vaccine.
Guillain-Barré syndrome (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 (32). 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 (33).	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.
Febrile Seizures	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) (34). Using data collected through the	The maximum estimated absolute excess risk due to concomitant administration of IIV3, PCV, and diphtheria-tetanus-acellular-pertussis (DTaP)-containing vaccines compared with administration of these vaccines on separate days was 30 cases per 100,000 vaccinees. According to CDC,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	CDC-sponsored Vaccine Safety Datalink (VSD) project, Tse et al (35) 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 (36) 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 DTaP-containing vaccine.	the risk of febrile seizure following influenza vaccination is small (37).
Investigated Vaccine: Fluzone High-Dose Quadrivalent Vaccine		
Refer to the package insert for more information regarding potential risks	Identified and potential risks observed in clinical trials and/or post-marketing surveillance.	Exclusion/inclusion criteria take into account contraindications, warnings and precautions as defined in product label.
Injection site reactions	Most common injection site reactions in adults ≥ 65 years of age: pain	Injection site reactions are generally mild and usually resolve within 3 days. A Phase III study performed in persons ≥ 65 years of age

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
		demonstrated increased rates of solicited injection site reactions in participants receiving Fluzone High-Dose vaccine compared to persons receiving Fluzone vaccine but were typically mild and transient (24).
Systemic reactions	Most common solicited systemic reactions in adults ≥ 65 years of age: malaise, myalgia, and headache	A Phase III study performed in persons ≥ 65 years of age demonstrated increased rates of solicited systemic reactions in participants receiving Fluzone High-Dose vaccine compared to persons receiving Fluzone vaccine but were typically mild and transient (24). 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 (38). 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 (39).
Immediate allergic reactions	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 (29) (30) (31).	These types of reactions are exceedingly rare and would most likely occur in persons with a severe reaction to influenza vaccine in the past. Vaccine should not be administered to anyone who has had a severe

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
		allergic reaction to any component of the vaccine.
Guillain-Barré syndrome	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 (32). 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 (33).	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.
Study Procedures		
Vasovagal reactions (syncope), or psychogenic reactions to needle (vaccine injection or blood sampling)	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw, and may be accompanied by several neurological signs such as transient visual disturbance,	Observation period after vaccination for early detection and treatment.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	paresthesia or seizure-like activity.	

DTaP: diphtheria-tetanus-acellular-pertussis; GBS: Guillain-Barré syndrome; IIV3: trivalent inactivated influenza vaccine; PCV: pneumococcal conjugate vaccine; VSD: Vaccine Safety Datalink

2.3.2 Benefits from Study Participation

The benefit to subjects participating in this study is potential protection from influenza disease following the receipt of the 2021–2022 formulation of Fluzone Quadrivalent or Fluzone High-Dose Quadrivalent vaccine.

2.3.3 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, the potential risks that may result from study participation are balanced by the anticipated benefits that may be afforded to participants.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 3.1.

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To provide serum samples (collected from participants before vaccination [Blood Sample 1] and after final vaccination [Blood Sample 2]) to CBER for further analysis by the WHO, CDC, and FDA to support formulation recommendations for subsequent influenza vaccines. In addition, serum samples from adult participants may be further	• There are no endpoints for this objective.

Objectives	Endpoints
analyzed by the Sponsor to assess breadth of immune response induced by the study vaccines.	

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Parallel, multi-site
Phase	IV
Control method	None
Study population	Children 6 months to < 9 years of age Adults ≥ 65 years of age
Level and method of blinding	None (open-label)
Study intervention assignment method	Participants will not be randomized
Number of participants	90 participants (30 from 6 months to < 36 months of age, 30 from 3 years to < 9 years of age, and 30 from 65 years and older)
	Each participant will be assigned to a vaccine group based on the participant's age at the time of enrollment to receive either 1 or 2 doses of Fluzone Quadrivalent vaccine as per ACIP guidance (participants 6 months to < 9 years of age) or 1 dose of Fluzone High-Dose Quadrivalent vaccine (participants ≥ 65 years of age).
Total duration of study participation	• Participants 6 months to < 9 years of age: 28 (window, 28–35) days following the last dose of influenza vaccine (Visit 2 [for participants receiving 1 dose] or Visit 3 [for participants receiving 2 doses]).Participants ≥ 65 years of age: 21 (window, 21–28) days after vaccination.

Countries	United States
Use of Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

4.2 Scientific Rationale for Study Design

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

4.3 Justification for Dose

For participants 6 months to < 9 years of age: the vaccination schedule of 1 or 2 doses (as per ACIP guidance for children 6 months to < 9 years of age) for the influenza season is per standard practice for receipt of annual influenza vaccination.

For participants ≥ 65 years of age: The vaccination schedule of a single dose for the influenza season is per standard practice for receipt of annual influenza vaccination.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last visit planned in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the synoptic clinical study report is finalized.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Aged 6 months to < 9 years or ≥ 65 years of age on the day of inclusion [a].

Type of participant and disease characteristics

I02: Participants who are healthy as determined by medical evaluation, including medical history and physical examination.

I03: For infants and toddlers, born at full term of pregnancy (≥ 37 weeks) or born after a gestation period of 27 through 36 weeks and medically stable as assessed by the investigator, based on the following definition: "Medically stable" refers to the condition of premature infants who do not require significant medical support or ongoing management for debilitating disease and who have demonstrated a clinical course of sustained recovery by the time they receive the first dose of study intervention.

Weight

I04: For participants 6 to < 12 months of age, born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 5.5 lbs (2.5 kg).

Informed Consent

I05: Informed consent form (ICF) has been signed and dated by participants ≥ 65 years of age.

I06: Assent form has been signed and dated by participants 7 to < 9 years of age, and ICF has been signed and dated by parent(s) or another legally acceptable representative for participants 6 months to < 9 years of age.

Other Inclusions

I07: Participants or participant and parent/legally acceptable representative (of participants 6 months to < 9 years of age) are able to attend all scheduled visits and to comply with all study procedures.

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the 3 months preceding planned inclusion).

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

E02: Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[b].

E03: Thrombocytopenia, contraindicating IM injection, at the discretion of the Investigator.

E04: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination.

E05: Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion.[c]

E06: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of study intervention administration or febrile illness (temperature ≥ 100.4°F [38.0°C]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided.

E07: Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion.

E08: History of serious adverse reaction to any influenza vaccine.

E09: Personal history of Guillain-Barré syndrome (GBS).

E10: Any condition that in the opinion of the Investigator would pose a health risk to the participant if enrolled or could interfere with the evaluation of the vaccine.

E11: Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.

E12: Known seropositivity for human immunodeficiency virus, hepatitis B, or hepatitis C.

Prior/concomitant therapy

E13: Receipt of any vaccine in the 30 days preceding the first study intervention administration, or planned receipt of any vaccine before Visit 2 for participants receiving 1 dose of influenza vaccine or Visit 3 for participants receiving 2 doses of influenza vaccine.

E14: Previous vaccination against influenza (in the 2021-2022 influenza season) with an investigational or marketed vaccine.

E15: Receipt of blood-derived immune globulins, blood, or blood-derived products in the past 3 months.

Prior/concurrent clinical study experience

E16: 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: Participants may be considered eligible for enrollment if no intervention for the

[b] The components of study interventions are listed in the Prescribing Information for each study vaccine.

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

other study occurred within the 30 days prior to the first study vaccination and none are planned before the participant would complete safety surveillance for the present study.

Other exclusions

E17: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

E18: Identified as an Investigator or employee of the Investigator or study site with direct involvement in the proposed study or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) or in-law of the Investigator or employee with direct involvement in the proposed study.

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

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

6 Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the case report form (CRF) as reportable medications (see Section 6.8). Study procedures (e.g., blood sampling) are also not considered as study interventions.

6.1 Study Interventions Administered

Table 6.1: Identity of study interventions

Study interventions are described in Table 6.1.

Intervention Name	Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2021–2022 formulation	Fluzone High-Dose Quadrivalent vaccine (0.7-mL dose), 2021–2022 formulation
Use	Other (as indicated in the prescribing material)	Other (as indicated in the prescribing material)
IMP and NIMP	IMP	IMP
Type	Vaccine	Vaccine
Dose Form	Suspension for injection in a pre-filled syringe	Suspension for injection in a pre-filled syringe
Unit Dose Strength(s)	15 µg of HA of each of the following strains per dose: • A/Victoria/2570/2019 (H1N1)pdm09-like virus • A/Cambodia/e0826360/2020 (H3N2)-like virus • B/Washington/02/2019 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B Yamagata lineage)-like virus	60 µg of HA of each of the following strains per dose: • A/Victoria/2570/2019 (H1N1)pdm09-like virus • A/Cambodia/e0826360/2020 (H3N2)-like virus • B/Washington/02/2019 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B Yamagata lineage)-like virus
Excipients/Diluent	Octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution	Octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution
Dosage Level	0.5 mL per dose	0.7 mL per dose

Number of Doses / Dosing Interval	1 or 2 doses 28 (window, 28–35) days apart for children aged 6 months to < 9 years (as per ACIP guidance)	1 dose
Route of Administration	IM injection	IM injection
Site of Administration	Anterolateral muscle of the thigh or the deltoid muscle	Deltoid muscle
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Fluzone Quadrivalent and Fluzone High-Dose Quadrivalent vaccines will be supplied with their manufacturer's commercial labeling and packaging.	
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable
Batch Number	TBD	TBD
Storage Conditions	Study interventions will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The study interventions must not be frozen.	

Note: Strains are based on WHO/FDA recommendations for the 2021-2022 NH influenza season

ACIP: Advisory Committee on Immunization Practices; FDA: Food and Drug Administration; HA: hemagglutinin; IM: intramuscular; IMP: Investigational Medicinal Product; NH: Northern Hemisphere; NIMP: Non Investigational Medicinal Product; TBD: to be determined; WHO: World Health Organization

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the Operating Guidelines.

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4) Further guidance and information for the final disposition of unused study interventions are provided in the Operating Guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

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

Participant numbers will be 12 digits long, with a 3-digit country identifier, a 4-digit study site identifier, and a 5-digit participant identifier. The 5-digit participant identifier will correspond to the chronological order of enrollment in the site. For example, participant 840000100001 is the first participant enrolled in Site Number 1 (in the United States) and participant 840000200002 is the second participant enrolled in Site Number 2 (in the Unites States).

Participant number should not be reassigned for any reason.

6.3.2 Blinding and Code-breaking Procedures

This is an open-label study.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any non-compliance is documented so that it can be accounted for in the data analyses:

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

6.5 Dose Modification

Not applicable.

6.6 Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately.
2) Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted
3) Closely monitor the participant for any AE/SAE.
4) Document the quantity of the excess of the overdose in the source documents.

6.8 Concomitant Therapy

Reportable medications include medications that may affect the interpretation of safety data or may interfere with the development or measurement of the immune response (e.g., the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and / or immune assessment during study participation.

The following reportable medications are defined:

- Category 2: medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by Sanofi Pasteur laboratory or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

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

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

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

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

6.8.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available at the study site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications

Should a participant 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 SoA.

TCI01: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of study intervention administration or febrile illness (temperature ≥ 100.4°F [38.0°C]).

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the source documents.

7.1.2 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience at least one of the conditions listed below, the Investigator will discontinue vaccination:

DCI01: An anaphylactic or other significant allergic reaction to the previous dose of vaccine

DCI02: Receipt of any non-study vaccine (including a non-study dose of 2021–2022 influenza vaccine), blood-derived immune globulins, blood, or blood-derived products between Visit 1 and Visit 2.

DCI03: Bleeding disorder, receipt of anticoagulants, or thrombocytopenia, which may be a contraindication for IM vaccination, at the discretion of the Investigator.

DCI04: Development of any condition that in the opinion of the Investigator would pose a health risk to the participant 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).

DCI05: Development of immunodeficiency; or receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy; or receipt of long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks).

DCI06: Adverse events that are considered a contraindication for further participation in the study.

In the event of a local or national immunization program with a COVID-19 Vaccine, participants who receive the vaccine mentioned above at any time during the study will not be withdrawn from the study.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: Adverse Event, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant or Parent / Legally Acceptable Representative.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any biological samples taken (unless local law requires not to destroy them), and the investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact them and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of “lost to follow-up”.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Blood samples will be collected as described in the SoA table (Section 1.2).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL for participants 6 months to < 9 years of age or 40 mL for participants ≥ 65 years of age. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

No immunogenicity data will be obtained in the study.

8.2 Safety Assessments

This section presents safety assessments other than AEs, which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

8.2.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE/AESI or to a repetitive outpatient care will be collected in the CRF. Collected information will not be coded.

8.2.2 Physical Examinations

At Visit 01, the Investigator or a designee will perform a history-directed physical examination. Information will be recorded in the source document.

8.2.3 Vital Signs

Oral (participants 3 years to < 9 years and participants ≥ 65 years of age) or rectal (participants 6 months to < 36 months) pre-vaccination temperature will be assessed by the investigator prior to immunization. Tympanic, skin, and temporal artery thermometers must not be used.

8.2.4 Clinical Safety Laboratory Assessments

Not applicable.

8.3 Adverse Events (AEs), Serious Adverse Events, and Other Safety Reporting

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.2.

AEs will be reported by the participants or participants' parents/legally acceptable representatives to the investigator, then by the investigator to the Sponsor.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an SAE/AESI and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.2.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 20 minutes after each vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Adverse Events of Special Interest

Adverse events of special interest will be collected from Visit 1 to Visit 2 for participants receiving 1 dose of study vaccine, and from Visit 1 to Visit 3 for participants receiving 2 doses of study vaccine.

AESIs will be captured as SAEs. See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from Visit 1 to Visit 2 for participants receiving 1 dose of study vaccine, and from Visit 2 to Visit 3 for participants receiving 2 doses of study vaccine. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF (e.g., SAEs related to blood sampling).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.2. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting SAEs/AESIs

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. These diary cards will include areas for free text to capture additional safety information or other relevant details.

At specified intervals, the Investigator or a designee will interview the participants or participants' parents/legally acceptable representatives 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 designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

Care will be taken not to introduce bias when detecting SAEs/AESIs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about SAE occurrences.

8.3.3 Follow-up of SAEs and AESIs

After the initial SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant or participant's parents/legally acceptable representative(s) refuses further contact. All AEs that are considered by the Investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AESIs (as defined in Section 8.3.6)], will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). For related SAEs ongoing at last study visit, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.2.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

Not applicable as the study does not include women of childbearing potential.

8.3.6 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 participants receiving 1 dose of vaccine, or from Visit 1 through Visit 3 for participants receiving 2 doses of vaccine.

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

Biomarkers are not evaluated in this study.

8.7 Immunogenicity Assessments

See Section 8.1.2.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 Leftover Biological Samples and Use of Data

Any unused part of the biological samples collected for this study (serum samples) are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

In addition, participants or participants' parents/legally acceptable representatives will be asked to indicate in the ICF whether they will permit the future use of any unused stored biological samples for other tests, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of any unused biological samples will not be included in the site-specific ICF). If they refuse permission, the biological samples will not be used for any testing other than that directly related to this study. If they agree to this future use, they will not be paid for giving permission. 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 and their mechanism of action, the knowledge of infectious diseases, or to improve existing tests or develop new tests to assess vaccines, or to help identify new vaccine targets or biomarkers that predict participant response to the vaccine. Such research may also include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, a specific individual consent will be obtained.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research). In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to the use of their biological samples or data for those research projects.

All study participant data and biological samples will be coded such that no direct identifiers will be linked to participants. Coded data and biological samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The biological samples will be securely stored at the Sanofi Pasteur laboratory and/or other laboratories for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and sample related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

Note: The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health during the study are dedicated for immediate use. If any of these biological samples are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

9 Statistical Considerations

9.1 Statistical Hypotheses

No hypotheses will be tested. Only descriptive statistical analyses will be conducted in this study.

9.2 Sample Size Determination

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

No study power calculation will be done for this study.

9.3 Analysis Sets

For the purposes of analysis, the following analysis set is defined:

Participant Analysis Set	Description
All Vaccinated Participants Population	Participants who have received at least 1 dose of the study vaccine.

9.4 Statistical Analyses

No statistical analysis plan (SAP) will be written for this study. This section of the protocol will be followed to provide descriptive tables and listings of data.

9.4.1 General Considerations

Summaries of baseline demographic characteristics of the study participants will be presented. The number of participants enrolled and their age at enrollment (mean, median, and minimum and maximum), sex, race, and ethnic origin will be summarized, along with the number and description of protocol deviations. Listings of participants by age group, sex, vaccine received, and history of vaccination in the previous seasons will be provided.

9.4.2 Primary Endpoint(s)

There are no primary endpoints for this study.

9.4.3 Secondary Endpoint(s)

There are no secondary endpoints for this study.

9.4.4 Observational Endpoint(s)

There are no observational endpoints for this study.

9.4.5 Other Safety Analysis

Listings or tables of SAEs and AESIs will be provided.

9.5 Interim Analyses

No analyses are planned to be performed prior to the formal completion of the study.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "subject" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements. Similarly, "legally acceptable representative" is used in the protocol whereas "guardian" is used in the CRF.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, ICF, Investigator Brochure (IB), and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the Investigator's contract.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their parents/legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- In addition to the ICF that is signed by the participant or participant's parent/guardian, participants 7 to < 9 years of age will be asked to review and sign a study assent form.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The actual ICF used at each site may differ, depending on local regulations and IEC/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 IEC/IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's or participants' parents/legally acceptable representatives willingness to continue participation in the study, this will be communicated to him/her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s)/assent must be provided to the participant or their parents/legally acceptable representatives.

Recruitment Procedures

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

10.1.4 Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

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

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participants' race and ethnicity will be collected in this study because these data are required by regulatory agencies (e.g., on African-American population for the FDA in the United States or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by

the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects.
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
    - Personnel within Sanofi or partners or service providers involved in the study
    - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
    - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
    - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to object to the processing, to request for access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study.

10.1.6 Dissemination of Clinical Study Data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Instructions.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after the signature of the final synoptic study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 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.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the study site has all the documents necessary for archiving and a study site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- Information on the study intervention leads to doubt as to the benefit/risk ratio

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

- Total number of participants included earlier than expected

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

10.1.10 Publication Policy

Information related to publication policy is described in the Investigator's contract.

10.2 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" ARs (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an “expected” AR (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF.

By definition, solicited reactions are considered as being related to the corresponding IMP administered.

For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions

Injection / Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: « Administration site reaction » term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

Systemic ARs are all ARs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the injection or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

Unsolicited AE/AR

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to an IMP.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

All unsolicited AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

Adverse Event of Special Interest (AESI):

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

10.2.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is other medically important event

- The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment
- Medical or scientific judgment should be exercised by the investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new-onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorised medicinal product.

Note: *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 participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.2.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the injection site are considered to be related to the IMP (see definition in Section 6) and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of SAEs will be recorded as follows:
  - For SAEs/AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor (except for injection site reactions which will be related by default). Sponsor assessment is entered in the Global Pharmacovigilance Department (GPV) database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The Investigator will assess the ***causal relationship*** between each SAE/AESI and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:
  - Not related – The SAE/AESI is clearly/most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the SAE/AESI is incompatible with a causal relationship; or the SAE/AESI started before the first vaccination (screening phase, if applicable)

- Related – There is a "reasonable possibility" that the SAE/AESI was caused by the study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each SAE/AESI, the investigator **must** document in the medical notes that he/she has reviewed the SAE/AESI and has provided an assessment of causal relationship.
- There may be situations in which an SAE/AESI has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE/AESI data to the Sponsor.
- The investigator may change his/her opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of SAEs/AESIs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the SAE/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE/AESIs data to the Sponsor within 24 hours of receipt of the information.
- Serious adverse events/AESIs likely to be related to the study intervention, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.2.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Details regarding SAE reporting can be found in the Operating Guidelines.

SAE Reporting to the Sponsor via Paper CRF

- The SAE paper CRF can be sent to the Sponsor by 1 of the following means:
  - By fax, to the following number: 1-570-957-2782
  - In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
  - By express mail, to the following address:

    Sanofi Pasteur, Inc.
    Reception & Triage – Case Management
    Global Pharmacovigilance Department
    Discovery Drive, Swiftwater, PA 18370

Safety Emergency Call

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

This process does not replace the need to report an SAE/AESI. The Investigator is still required to follow the protocol-defined process for reporting SAEs/AESIs to the Global Pharmacovigilance Department (please refer to Section 10.2.4).

10.3 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.4 Appendix: Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
DTaP	Diphtheria-Tetanus-Acellular-Pertussis
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance Department
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product;
IRB	Institutional Review Board
IIV3	Trivalent Inactivated Influenza vaccine
NA	Neuraminidase
NIMP	Non Investigational Medicinal Product
PCV	Pneumococcal Conjugate Vaccine
RMO	Responsible Medical Officer
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SoA	Schedule of Activities
US	United States
VSD	Vaccine Safety Datalink
WHO	World Health Organization

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12 Sponsor Signature Page