Title Page

Protocol Title:

Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) in Children and Adolescents Aged 9 to 17 Years and Adults Aged 18 to 49 Years.

Study Code: VAP00027

Amendment Number: Amendment 1

Compound: Quadrivalent Recombinant Influenza Vaccine (RIV4)

Brief Title:

Study with Quadrivalent Recombinant Influenza Vaccine (RIV4) in Participants 9 through 49 Years of Age.

Study Phase: Phase III

Sponsor Name and Legal Registered Address:

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

Manufacturer:

Protein Sciences Corporation
Meriden, CT 06450, USA

Regulatory Agency Identifier Numbers:

BB-IND: 015784
EudraCT: 2022-000577-11
WHO UTN: U1111-1260-4678

Protocol Version Number: 2.0

Approval Date: 22 September 2022

Responsible medical officer (RMO) and pharmacovigilance (PV) representative names and contact information are provided in the Operating Guidelines.

The study centers, the investigators at each center, and the Coordinating Investigator(s) are listed in a separate document.

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Document History and Protocol Amendment Rationale

Previous Version(s)	Date	Comments
1.0	24 February 2022	Version submitted to the IECs/IRBs

IEC: Independent Ethics Committee; IRB: Institutional Review Board

Amendment 1

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment 1:

Change was implemented following request for clarification from the Food and Drug Administration (FDA) dated 13 July 2022, mainly the scheduled interim analysis.

Change was also implemented following request of the pediatric investigation plan (PIP) from the European Medicines Agency (EMA) dated 18 March 2022, mainly the addition of subgroup analyses by serostatus at baseline.

Additional information regarding influenza virus neutralization assay method is provided.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) in Children and Adolescents Aged 9 to 17 Years and Adults Aged 18 to 49 Years.

Brief Title:

Study with Quadrivalent Recombinant Influenza Vaccine (RIV4) in Participants 9 through 49 Years of Age.

Rationale:

The proposed study is a Phase III, non-randomized, open-label, uncontrolled, multi-center study to assess the immunogenicity and safety of the RIV4 in approximately 1334 participants 9 to 49 years of age (667 children and adolescents 9 to 17 years of age and 667 adults 18 to 49 years of age) in Europe and the United States (US). The goal of this study is to show that vaccination with RIV4 induces an immune response (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion [SC] rates) in children and adolescents 9 to 17 years of age that is non-inferior to responses induced by RIV4 in adults 18 to 49 years of age for the 4 virus strains at 28 days post-vaccination and to describe the HAI antibody response induced by RIV4 in all participants. In addition, the immunogenicity of RIV4 in terms of neutralization titer will be assessed in a subset of participants and the safety of RIV4 in all participants will be described.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the non-inferior hemagglutination inhibition (HAI) immune response of quadrivalent recombinant influenza vaccine (RIV4) for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years	• Individual HAI titer 28 days after vaccination (D29) • Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold rise in titer [1/dil] at D29)
Key Secondary	
Immunogenicity • To summarize the HAI immune response induced by RIV4 in all participants.	• Individual-HAI titer on D01 and 28 days after vaccination (D29) • Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 28 days after vaccination (D29) • Individual titer ratio: 28 days after vaccination (D29) /D01 • Participants with titer ≥ 40 (1/dil) on D01 and 28 days after vaccination (D29) • Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 (1/dil) at D29 or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold rise in titer (1/dil) at D29)
Safety • To describe the safety profile of RIV4 vaccine in all participants and by age group	• Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Occurrence of solicited (pre-listed in the participant's diary card [DC]/electronic diary card [eDC] and case report book [CRB]) injection site reactions and systemic reactions occurring up to 8 days after vaccination

	• Occurrence of unsolicited AEs up to 28 days after vaccination • Occurrence of medically attended adverse events (MAAEs) up to 28 days after vaccination • Occurrence of SAEs (including AESIs) throughout the study • Occurrence of AESIs throughout the study

Note: All AESIs will be collected in the pharmacovigilance database, regardless of seriousness

Overall Design

Type of design	Parallel, multi-center
Phase	Phase III
Control method	None
Study population	Healthy participants aged 9 to 49 years
Countries	US and Europe
Level and method of blinding	Open-label
Study intervention assignment method	Maximization of planned stratification of each age subgroup

Brief Summary:

The purpose of this study is to demonstrate the non-inferiority (NI) of the HAI immune response of RIV4 in participants aged 9 to 17 years vs participants aged 18 to 49 years and to describe the immunogenicity and safety profile of RIV4 in all participants.

Number of Participants:

Approximately 1334 participants 9 to 49 years of age (667 children and adolescents 9 to 17 years of age and 667 adults 18 to 49 years of age) will be enrolled.

This study is not randomized, so caution will be given on the recruitment of participant to limit bias and thus allow extrapolation of study results. In particular, at least 30% of children aged 9 to 11 years will be recruited among children and adolescents, and the proportion of adults aged above 35 years will be limited to 50%.

Intervention Groups and Duration:

Eligible participants 9 to 49 years of age will receive a single intramuscular (IM) injection of RIV4 at D01.

The participation duration will be approximately 6 months for each participant.

Study intervention

Investigational medicinal product: Quadrivalent Recombinant influenza vaccine (RIV4) season/2022-2023/NH

- Form: Solution for injection
- Composition: 45 µg of HA of each of the following strains per dose: A/H1N1 strain, A/H3N2 strain, B/Victoria lineage strain and B/Yamagata lineage strain
- Route of administration: IM

Statistical considerations:

The number of participants enrolled and their age at enrollment, sex, race, and ethnic origin will be summarized for each group, as well as the number and description of protocol deviations. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates will be calculated using the normal approximation of log-transformed titers.

Primary endpoints:

The primary objective includes 8 endpoints (GMTs and seroconversion (SC) rates for each of the 4 strains).

For each strain, the non-inferiority (NI) methodology will be applied to compare the post-vaccination GMTs and the SC rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis.

The primary analysis will be conducted in 2 steps, starting with testing for NI of GMTs between the study groups. If NI of GMTs based on the 4 strains is demonstrated, then NI for SC will also be tested.

Since all 8 hypotheses have to be rejected at 0.025 significance level, no formal adjustment for multiplicity is necessary.

To keep the study power of 80%, the sample size was increased accordingly, to have an overall Type II error <20% for the 8 NI tests.

Secondary endpoints (immunogenicity):

Immunogenicity parameters by HAI measurement method will be described by study group with 95% confidence intervals (CIs).

Reverse cumulative distribution curves (RCDCs) of pre-vaccination titer at D01 and post-vaccination titer at D29 will be generated for each study group.

Subgroup analyses will be performed; in particular, immunogenicity will be described according to age subgroups, sex, race, previous influenza vaccination status, and baseline seropositivity status, as appropriate according to number of participants in the respective subgroups.

Secondary endpoints (safety):

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

Analysis will be conducted for each study group.

Data Monitoring/Other Committee:

No independent Data Monitoring Committee (DMC) is planned.

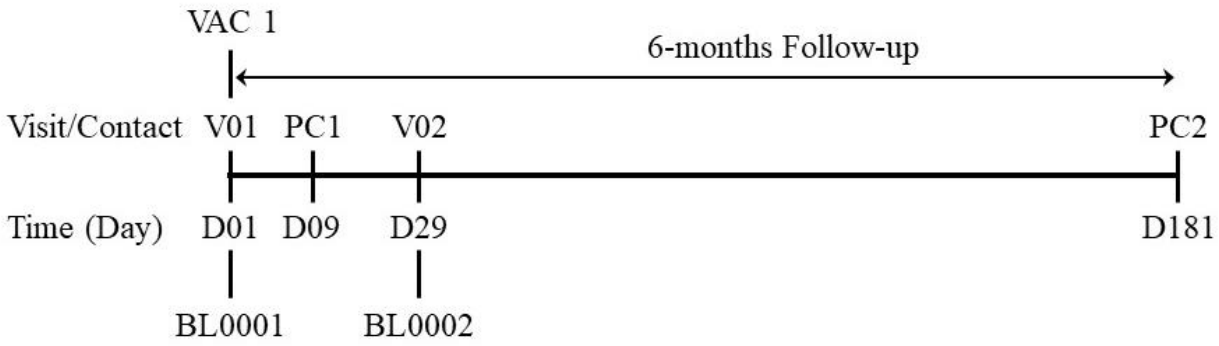
Participant safety data will be continuously monitored by the Sponsor's internal safety management team (SMT), led by the Global Safety Officer, to detect any safety signals during the study period.

In addition, this study will include an early safety data review (ESDR).

1.2 Schema

The graphical design of VAP00027 study is presented in Figure 1.1.

Figure 1.1 – Graphical study design



BL: Blood sample
VAC: vaccination
PC: Phone Call

1.3 Schedule of Activities (SoA)

Visit procedures are detailed in the Operating Guidelines.

Table 1.1: Schedule of activities

Phase III Study, 2 Visits, 2 Phone calls, 1 Vaccination, 2 Blood Samples, 6 Months' Duration Per Participant

Visit/Contact	*Collection of information in the case report form (CRF)*	Visit 1	Phone Call (PC) 1*	Visit 2	PC2 6-month safety follow-up†
Study timelines (Days)		D01	D09	D29	D181
Time interval (Days)			V01 + 8D	V01 + 28D	V01 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:					
Informed consent	X	X			
Inclusion/exclusion criteria	X	X			
Collection of demographic data§§	X	X			
Urine pregnancy test (if applicable) ‡		X			
Collection of Medical history (Significant medical history)***	X	X			
Collection of concomitant medications	X Reportable concomitant medication	28 days after vaccination			
History of seasonal influenza vaccination	X	X			
Physical examination§		X		X	
Pre-vaccination temperature		X			

Visit/Contact	*Collection of information in the case report form (CRF)*	Visit 1	Phone Call (PC) 1*	Visit 2	PC2 6-month safety follow-up†
Study timelines (Days)		D01	D09	D29	D181
Time interval (Days)			V01 + 8D	V01 + 28D	V01 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:					
Contact Interactive Response Technology (IRT) system for participant number, dose number and randomization to the SN subset	X	X			
Blood sampling (BL) (5 mL)	X	BL0001**		BL0002	
Vaccination (VAC)	X	X			
Immediate surveillance (30 min)	X	X			
Diary card (DC) / electronic DC [eDC] / Memory Aid (MA) provided		DC/eDC		MA	
DC/eDC collected and reviewed				DC/eDC ††	
MA reviewed					MA
Collection of solicited injection site and systemic reactions	X	7 days after vaccination			
Collection of unsolicited adverse events (AEs)	X	28 days after vaccination			
Collection of medically attended AEs (MAAEs)	X	28 days after vaccination			
Collection of information on serious adverse events (SAEs), including adverse events of special interest (AESIs)	X	To be reported at any time during the study			
Collection of pregnancy	X	To be reported at any time during the study			

Visit/Contact	*Collection of information in the case report form (CRF)*	Visit 1	Phone Call (PC) 1*	Visit 2	PC2 6-month safety follow-up†
Study timelines (Days)		D01	D09	D29	D181
Time interval (Days)			V01 + 8D	V01 + 28D	V01 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:					
End of Active Phase participation record	X			X	
Six months follow-up participant record	X				X

* The investigator or an authorized designee will remind the participant or participant's parent(s)/legally acceptable representative(s) to bring back the DC/eDC at the next visit and will answer any questions.
† The investigator or an authorized designee will interview the participant or participant's parent(s)/legally acceptable representative(s) to collect the information recorded in the MA, and will attempt to clarify anything that is unclear
‡To be performed in menarche participants
§ Complete physical examination to be performed at Visit 1 and symptom directed examination to be performed at Visit 2
** Blood sample to be drawn before vaccination
†† The investigator or an authorized designee will interview the participant or participant's parent(s)/legally acceptable representative(s) to collect the information recorded in the DC/eDC, and will attempt to clarify anything that is incomplete or unclear.
§§ To comply with US Food and Drug Administration (FDA) expectations, Sponsors are to enroll participants who reflect the demographic for clinically relevant populations with regards to age, gender, race, and ethnicity (FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and Food and Drug Administration staff [Internet]. 2016. Available from: https://www.fda.gov/media/75453/download)
***Including history of laboratory-confirmed influenza illness over the previous 3 influenza seasons.

2 Introduction

Sanofi Pasteur's RIV4 vaccine is a vaccine that is being developed for protection against influenza.

2.1 Study Rationale

The proposed study is a Phase III, non-randomized, open-label, uncontrolled, multi-center study to assess the immunogenicity and safety of the RIV4 in approximately 1334 participants 9 to 49 years of age (667 children and adolescents 9 to 17 years of age and 667 adults 18 to 49 years of age) in Europe and the US. The goal of this study is to show that vaccination with RIV4 induces an immune response (as assessed by HAI, GMTs and SC rates) in children and adolescents 9 to 17 years of age that is non-inferior to responses induced by RIV4 in adults 18 to 49 years of age for the 4 virus strains at 28 days post-vaccination and to describe the HAI antibody response induced by RIV4 in all participants. In addition, the immunogenicity of RIV4 in terms of neutralization titer will be assessed in a subset of participants and the safety of RIV4 in all participants will be described.

2.2 Background

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. The virus is transmitted easily from person to person via droplets and small particles produced when infected people cough or sneeze. Members of high-risk groups, such as infants and younger children as well as children with underlying medical conditions, are at increased risk of influenza and its complications. Complications in the pediatric population include secondary bacterial pneumonia, acute otitis media, bronchitis, febrile seizures, Reye's syndrome, myositis, neurologic conditions, and exacerbations of underlying conditions (1) (2) (3). One study assessing the impact of influenza infection on young children, their family, and the health care system found that 28.6% of children with influenza had a secondary complication (pneumonia/chest infection, febrile convulsion, otitis media, croup), 40.9% were prescribed antibiotics, 65.4% of children missed school/day care, and 53.4% of parents missed work (4)

In adults, influenza is typically characterized by the rapid onset of fever, myalgia, sore throat, and non-productive cough, and can also cause severe malaise lasting for several days. The clinical manifestations in children, especially in young children less than 5 years of age, are less characteristic and may be more diverse than the clinical symptoms seen in adults (2). Besides symptoms of non-productive cough, nasal congestion, rhinitis, and sore throat, gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain can occur for 10–30% of children with influenza (5) (6).

The burden of influenza disease has been estimated in several modeling studies. In a 2018 study, Iuliano et al. estimated the number of global annual influenza-associated respiratory deaths using country-specific influenza-associated excess respiratory mortality estimates from 1999–2015 and reported that 9 243 to 105 690 influenza-associated respiratory deaths occur in children younger

than 5 years each year (7). Matias et al. investigated the average seasonal burden of influenza-attributable hospitalizations in the US from 1997 to 2009 and found that children 0-4 and 5-17 years of age were estimated to have an annual mean rate of 128 and 20 per 100 000 population respectively (8). About half of the cases in children were due to influenza A infections and the other half were due to influenza B infections.

Vaccination currently represents the most effective medical intervention against influenza and its severe complications. Thus, the World Health Organization (WHO) recommends that people who are most at risk for severe seasonal influenza, including children less than 5 years of age (9) (10) should receive an annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (11) (12). The effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age and immune competence of the vaccine recipient. Infants and young children remain at increased risk for influenza because of their maturing immune system and lack of prior exposure and thus lack of immunity. Furthermore, during 3 recent influenza seasons in the US (US 2015-2016, 2016-2017, 2017-2018 seasons), vaccine effectiveness in children 6 months to 8 years of age was 51%, 57%, and 68% respectively (13).

Background of the Study Intervention

Protein Sciences Corporation (PSC), now a Sanofi Company, has initially developed a trivalent recombinant influenza vaccine (RIV3) consisting of purified recombinant hemagglutinin (rHA) produced from a proprietary technology that is based on the insect cell – baculovirus system referred to as the Baculovirus Expression Vector System.

This RIV3 contains 135 µg of rHA derived from the 3 influenza strains (2 A subtypes and 1 B lineage) 45 µg of each of A strains (A/H1N1 and A/H3N2) and 45 µg of B strain (from Victoria or Yamagata lineages). The vaccine contains no egg proteins, preservatives, antibiotics or adjuvant.

Data from multiple Phase II and Phase III studies with RIV3 showed the vaccine was well tolerated, immunogenic, and 44.6% (95% CI, 18.8% - 62.6%) effective in preventing culture-confirmed influenza in adults from 18 to 49 years of age (14). Furthermore, studies in adults 50 – 64 years of age (15) and in adults 65 years of age and older (16) showed HAI antibody responses induced by RIV3 met the pre-specified SC criterion of the lower bound of the 95% CI ≥ 40% for adults < 65 years and ≥ 30% for adults ≥ 65 years of age for all three vaccine strains. The pre-specified criterion for the proportion of participants with post-vaccination HAI titers of ≥ 1:40 (“seroprotection”) with the lower bound of the 95% CI ≥ 70% for adults < 65 years and ≥ 60% for adults ≥ 65 years of age was also met for both influenza A antigens. Responses to the B antigen were commonly less robust among recipients of RIV3 and the comparator trivalent influenza vaccine but were of similar magnitude in recipients of both vaccines (15) (16).

RIV3 was licensed under trade name Flublok® in the US for active immunization for the prevention of influenza disease for adults 18-49 years of age in 2013, followed by approval for adults 50 years of age and older in 2014.

To mitigate the risk posed by the potential widespread circulation of a strain from the alternate B lineage not contained in the trivalent formulation, RIV4 containing 45 µg of each of A strains

(A/H1N1 and A/H3N2) and B strains (from Victoria and Yamagata lineages) has been developed based on the same manufacturing process used for RIV3.

Clinical data generated with RIV4 in 2 subsequent Phase III studies showed RIV4 provided 30% to 43% better protection against influenza disease compared to a quadrivalent inactivated influenza vaccine (IIV4) in adults 50 years of age and older (17) during a season characterized by predominantly antigenically drifted strains of influenza A (H3N2) and was non-inferior to the same IIV4 comparator vaccine for 3 of 4 influenza vaccine strains as assessed by seroconversion rates and GMTs in adults 18 to 49 years of age (18).

Vaccination with RIV4 was found to be safe and well tolerated among 5326 adults ≥ 18 years participating in these 2 studies, with no safety concerns identified. The safety profile of RIV4 showed comparable reactogenicity (solicited injection site reactions and solicited systemic reactions) to IIV4 and no notable difference in the occurrence of unsolicited adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and deaths.

RIV4 was licensed in the US in 2016 under the trade name Flublok® Quadrivalent and in Mexico in March 2018 under the trade name Flublok Tetravalente. In November 2020, marketing authorization was granted for RIV4 in the European Union (EU) under the trade name Supemtek®. Marketing authorization has also been approved in Brazil (May 2019, trade name Flublok Quadrivalent), Argentina (January 2020, trade name Virublok®), Canada (January 2021, trade name Supemtek), Hong Kong (April 2021, trade name Flublok Quadrivalent), Australia (May 2021, trade name Flublok Quadrivalent), and Switzerland (October 2021, trade name Supemtek).

With approximately 21 334 843 doses of RIV4 and RIV3 distributed cumulatively and after post-marketing surveillance data collected up to August 2021, the safety profile of the recombinant influenza vaccine in humans is consistent with the established clinical safety profile and has been confirmed to be well tolerated with no safety concerns.

After registration of RIV4 for an indication in adults aged 18 years and older, Sanofi Pasteur plans to extend the indication to the pediatric population.

Two randomized, active-controlled trials of recombinant influenza vaccine were conducted by PSC in the pediatric age group in the US. The clinical data from pediatric studies utilizing either RIV3 or RIV4 demonstrated very satisfactory safety and reactogenicity profiles.

A Phase I clinical trial (19) was conducted with RIV3 in 156 children aged 6 months – 5 years (98 participants received RIV3 [among them 61 received the full-dose of 45 µg per antigen] and 58 received a licensed trivalent influenza vaccine [IIV3 - Fluzone]).

A Phase II clinical trial (20) was conducted in 219 children and adolescents 6 – 17 years of age who received either RIV4 or a licensed quadrivalent inactivated influenza vaccine (IIV4 - Fluarix Quadrivalent).

The clinical data from pediatric studies showed acceptable safety and reactogenicity profiles of RIV3 or RIV4.

By evaluating a series of age cohorts ranging from 6 months to 17 years, it was shown that HAI immunity appears to be induced to a greater degree as the participants become older. Some of this

apparent diminished immune response in younger children may have been reflective of the relatively small sample sizes.

Therefore, Sanofi Pasteur proposes to conduct a Phase III study (VAP00027) to evaluate the immunogenicity and safety of RIV4 in participants aged 9 to 17 years and in participants 18 to 49 years. The goal of this study is to demonstrate that RIV4 immunogenicity in participants aged 9 to 17 years is non-inferior to participants aged 18 to 49 years and to support the immuno-bridging of efficacy in adults to children/adolescents aged 9 to 17 years.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events, the potential risks, and uncertainties of RIV4 may be found in the Investigator's Brochure (IB).

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: Quadrivalent Recombinant Influenza Vaccine (RIV4)		
Anaphylaxis	Anaphylaxis is an identified risk for RIV4 (see Investigator's Brochure [IB] (21) for more information regarding the data from previous experience with RIV4). No case of anaphylaxis was reported as related to trivalent recombinant influenza vaccine (RIV3) or RIV4 during the clinical development. Adverse events (immune system disorders) have been spontaneously reported during post-approval use of RIV3 or RIV4. Post-marketing observational study of safety comparing RIV3 with licensed inactivated influenza vaccine (IIV) in adults using adjusted logistic regression	Exclusion criterion E02 for those at increased risk. Observation period after vaccination for early detection and treatment. Addressed in IB (21) (administration precautions, potential adverse events). Each site must have measures to treat anaphylaxis available at the time of vaccination

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	analyses, showed that there was no significant difference in acute hypersensitivity reactions and fever during post-vaccination days 0-2 in the outpatient, emergency department and inpatient settings (22). Background incidence rate: Using health care data from the Vaccine Safety Datalink, the rate of anaphylaxis was estimated to 1.31 (95% confidence interval [CI]: 0.90-1.84) per million vaccine doses (23).	
Guillain-Barré Syndrome (GBS)	No cases of GBS were reported as related to RIV3 or RIV4 during the vaccine's clinical development. Two cases of GBS were reported during the post-marketing experience for RIV4. A causal association between these cases of GBS and RIV4 has not been established.	Exclusion criterion E07 for those at increased risk. During the informed consent process, the participants and/or their parent(s)/legally acceptable representative(s) will be informed of this potential risk and the need to attend the clinic if they are unwell. GBS is an AESI and will be collected until study end. Addressed in IB (21) (administration precautions, potential adverse events)
Injection site reactions and systemic reactions	The most commonly reported solicited adverse reactions in adults 18 through 49 years of age during the clinical trial PSC16 were tenderness (48%) and pain (37%) at the injection site; the most commonly reported solicited systemic adverse reactions were headache (20%), fatigue (17%), myalgia (13%) and arthralgia (10%). Most reactions were of mild grade, occurred within the first 3 days following vaccination and resolved spontaneously within 1	During the informed consent process, the participants and/or their parent(s)/legally acceptable representative(s) will be informed of these potential reactions, the need to attend the clinic if the participants are unwell, and the possibility to take antalgic/antipyretic drug.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	to 3 days after onset (see IB for more information regarding the data from previous experience with RIV4).	
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, paresthesia or seizure-like activity, vasovagal syncope etc.	Observation period after vaccination for early detection and treatment.
Infection in rare instances at the injection site		Early detection, observation, and appropriate treatment.
Other		
Not applicable		

2.3.2 Benefits from Study Participation

All participants in the present study will receive an influenza vaccination with the investigational vaccine RIV4. These participants will benefit from coverage against influenza and may be less likely to catch influenza or develop complications.

However, as with all vaccines, vaccination with the study intervention may not protect individuals 100%. Protection generally lasts 6 to 12 months after vaccination, depending on the participant's response to the study intervention.

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 demonstrate the non-inferior hemagglutination inhibition (HAI) immune response of quadrivalent recombinant influenza vaccine (RIV4) for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years	• Individual HAI titer 28 days after vaccination (D29) • Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold rise in titer [1/dil] at D29)
Key Secondary	
Immunogenicity • To summarize the HAI immune response induced by RIV4 in all participants.	• Individual-HAI titer on D01 and 28 days after vaccination (D29) • Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 28 days after vaccination (D29) • Individual titer ratio: 28 days after vaccination (D29) /D01 • Participants with titer ≥ 40 (1/dil) on D01 and 28 days after vaccination (D29) • Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 (1/dil) at D29 or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold rise in titer (1/dil) at D29)
Safety • To describe the safety profile of RIV4 vaccine in all participants and by age group	• Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Occurrence of solicited (pre-listed in the participant's diary card [DC]/electronic diary card [eDC] and case report book [CRB]) injection site reactions and systemic reactions occurring up to 8 days after vaccination

	• Occurrence of unsolicited AEs up to 28 days after vaccination • Occurrence of medically attended adverse events (MAAEs) up to 28 days after vaccination • Occurrence of SAEs (including AESIs) throughout the study • Occurrence of AESIs throughout the study
Exploratory	
• To describe the neutralizing antibody immune response in a subset of participants[a].	• Individual seroneutralization (SN) antibody (Ab) titer on D01 and 28 days after vaccination (D29) • Individual SN Ab titer ratio (fold increase in post-vaccination titer relative to D01) at 28 days after vaccination (D29) • Participants with SN Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at 28 days after vaccination (D29) • Fold-increase in SN Ab titer (post/pre) ≥ 2 and ≥ 4 at 28 days after vaccination (D29) • Detectable SN Ab titer (SN Ab titer ≥ 10 [1/dil]) at D01 and 28 days after vaccination (D29)

[a] At least 400 participants will be randomized to be included in the subset. The randomization of participants in the subset will be stratified to include at least 30% of children aged 9 to 11 years among children and adolescents 9 to 17 years old; and the proportion of adults aged above 35 years will be limited to 50% in the study group 18 to 49 years.

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design cc

Type of design	Parallel, multi-center
Phase	III
Control method	None
Study population	Healthy participants aged 9 to 49 years
Level and method of blinding	Open-label
Study intervention assignment method	Maximization of planned stratification of each age subgroup
Number of participants	Approximately 1334 participants (667 children and adolescents 9 to 17 years of age, and 667 adults18 to 49 years of age)
Intervention groups	Eligible participants will receive a single injection of RIV4 at D01
Total duration of study participation	Approximately 6 months
Countries	US and Europe
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	Safety Management Team (SMT)

4.2 Scientific Rationale for Study Design

RIV4 is already marketed in several countries for use in adult population. The current study aims to show that RIV4 elicits a non-inferior immune response in children and adolescents 9 to 17 years of age as compared to adults 18 to 49 years of age, in order to extend marketing authorization to the pediatric population.

4.3 Justification for Dose

The dose (45 µg of HA for each strain), and the administration schedule of RIV4 have been established previously (Studies PSC12 and PSC16).

4.4 End of Study Definition

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

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

However, for periodic safety reports, the study is considered completed when the 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 9 to 49 years on the day of inclusion[b]

Sex, contraceptive/barrier method and pregnancy testing requirements

I02. A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be pre-menarche[c], post-menopausal for at least 1 year, or surgically sterile.

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to the first study intervention administration until at least 4 weeks after the last study intervention administration.

  A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) the day of study intervention

  Refer to Appendix 10.3 (Contraceptive and Barrier Guidance) for further information.

Informed consent

[b] "9 to 49 years" means from the day of the 9th year after birth to the day before the 50th year after birth

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

I03. Assent form or informed consent form has been signed and dated by the participant (based on local regulations), and if applicable informed consent form has been signed and dated by the parent(s) or another legally acceptable representative

Other inclusions

I04. Participant or participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

I05. Covered by health insurance if required by local regulations

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 (eg, HIV); 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 past 3 months)

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

E03. Thrombocytopenia, or known thrombocytopenia, as reported by the participant or by the parent(s)/legally acceptable representative, contraindicating intramuscular vaccination based on the investigator's judgment

E04. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination based on the investigator's judgment

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

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

E07. Personal or family history of Guillain-Barré Syndrome (GBS)

E08. 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 study intervention

E09. Personal history of clinically significant development delay (at the discretion of the investigator), neurologic disorder, or seizure disorder

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[d] The components of study intervention are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[e] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders or chronic infection

E10. For participants 12 to 49 years of age: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E11. Receipt of any vaccine in the 4 weeks preceding the study intervention administration or planned receipt of any vaccine in the 4 weeks following the study intervention administration except for COVID-19 vaccination, which may be received at least 2 weeks before study intervention[f].

E12. Previous vaccination against influenza (in the 6 months prior to study intervention administration) with an investigational or marketed vaccine

E13. Receipt of immune globulins, blood or blood-derived products in the past 3 months

Prior/concurrent clinical study experience

E14. Participation at the time of study enrollment (or in the 4 weeks preceding the study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15. Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study before the end of the study

E16. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E17. For participants 12 to 49 years of age: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

E18. For participants 9 to 11 years of age: Identified as a natural or adopted child of the investigator or employee with direct involvement in the proposed study

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

[f] If the participant is enrolled and seeks vaccination of COVID-19 vaccine outside of the study, he/she and/or the parent(s)/legally acceptable representative will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. If the participant receives the authorized influenza or COVID 19 vaccine, this information will be collected.

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 randomly assigned to study intervention. Screening information is recorded in the source documents.

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

5.5 Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 10.4: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for enrollment/administration of study intervention.

6 Study Intervention 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 (eg, blood sampling) are also not considered as study interventions.

6.1 Study Intervention Administered

Study intervention is described in Table 6.1.

Table 6.1: Identity of study intervention

Intervention Name	RIV4 season/2022-2023/NH
Use	Experimental
IMP and NIMP	IMP
Type	Vaccine
Dose Formulation	Solution for injection in a pre-filled syringe
Unit Dose Strength(s)	45 µg of HA of each of the following strains per dose: • A/H1N1 strain • A/H3N2 strain • B/Victoria lineage strain • B/Yamagata lineage strain
Excipients/Diluent	Each 0.5 mL dose of RIV4 will contain: Sodium chloride 4.4 mg Monobasic sodium phosphate 0.2 mg* Dibasic sodium phosphate 0.5 mg* Polysorbate 20 (Tween® 20) 27.5 µg Octylphenol ethoxylate (Triton X-100®) ≤ 100 µg Water for injection Preservative is not used in the manufacture or formulation of RIV4.
Dosage Level(s)	0.5 mL per dose
Number of Doses / Dosing Interval	1 dose
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	Provided by the Sponsor

Packaging and Labeling	Each study intervention will be packaged in an individual box. Each pre-filled syringe will bear one fixed label and each box will bear detachable labels and one fixed label containing the sequential dose number. All will be labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	Supemtek/Flublok Quadrivalent
Batch Number	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.

IMP: Investigational Medicinal Product; NIMP: Non-Investigational Medicinal Product; TBD: to be determined
*: calculated from the anhydrous form.

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

At least 400 participants will be randomized to be part of the subset population to assess the exploratory objective. The randomization of the subset will be performed to reflect the age distribution of the whole population. Thus, the randomization of participants will be stratified to include at least 30% of children aged 9 to 11 years among children and adolescents 9 to 17 years

old; and the proportion of adults aged above 35 years will be limited to 50% in the study group 18 to 49 years.

Site staff will connect to the Interactive Response Technology (IRT), enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). The first of the 5-digit participant identifier will identify the participants as being part of the subset for exploratory objective (number 1) or not (number 2). For example, Participant 840000120005 is the fifth participant enrolled in Center Number 1 in the US (840 being the US country code), and is not part of the subset for exploratory objective.

Participant numbers should not be reassigned for any reason. The study groups are not randomized; they are based on age (9 to 17 years versus 18 to 49 years) and only one vaccine (RIV4) will be administered in this study. Only the subset of participants for each age group to be tested by the seroneutralization (SN) method will be randomized within each study group.

6.3.2 Blinding and Code-breaking Procedures

The study will be open-labeled.

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 given to each participant, and unused or wasted doses

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 10.4: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

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 RMO immediately.
2) Evaluate the participant to determine, in consultation with the RMO, 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 (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, 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:

- Medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs, systemic steroids/corticosteroids)
  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.
- 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)
- 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 until the end of the solicited and unsolicited follow-up period.

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention).

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 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

Not applicable as there is only one vaccination.

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.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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 1.3). At Visit 1 (BL0001) and Visit 2 (BL0002), blood (5 mL) will be collected in tubes provided by or recommended by the Sponsor.

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.4: Contingency Measures for a regional or national emergency that is declared by a governmental agency).

8.1 Efficacy and Immunogenicity Assessments

Planned time points for all immunogenicity assessments are provided in the SoA.

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

HAI assay:

The HAI assay is the main test that detects Ab directed against the HA antigen and is commonly used to assess the immunogenicity of influenza vaccines. HAI Ab titers to each virus strain represented in the vaccine will be measured in sera obtained at baseline (D01) and 28 days after immunization (D29). Test serum samples and quality control sera (sheep, ferret, and/or human sera) will be incubated with Sigma Type III neuraminidase (NA) from *Vibrio cholerae* to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins will then be performed by incubating the test serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures will be centrifugated and the supernatants containing the treated sera will be collected for testing. Ten 2-fold dilutions (starting at 1:10) of the treated test serum samples and quality control sera will be incubated with a previously titrated influenza antigen at a concentration of 4 hemagglutination units (HAU)/25 µL. Influenza antigens will not be added to the serum control wells containing only serum and RBCs. The mixture will be then incubated and an RBC suspension added. Following incubation, the results will be read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. [redacted]

Influenza virus SN assay:

The SN assay measures Abs directed against the viral neutralization epitopes of the influenza virus, which may be different from the hemagglutination epitopes; therefore, the SN titers may be different from the HAI titers.

To measure SN, serially diluted, heat-inactivated human serum samples are pre-incubated with a fixed amount of challenge virus prior to the addition of Madin-Darby canine kidney (MDCK) cells. After overnight incubation, the viral nucleoprotein production in infected MDCK cells is measured by enzyme-linked immunosorbent assay (ELISA), using monoclonal Ab specific to either influenza A nucleoprotein or influenza B nucleoprotein. Since serum neutralizing Abs to the influenza virus inhibit the viral infection of MDCK cells, the ELISA optical density results are inversely proportional to the titers of neutralizing Ab present in the serum. The LLOQ is set at the reciprocal of the lowest dilution used in the assay (ie, 10 [1/dil]). [redacted]

Assays will be performed by Sanofi Pasteur laboratory (Swiftwater, PA, USA) or an external testing laboratory under Sanofi Pasteur laboratory responsibility. The address is provided in the Operating Guidelines.

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 1.3).

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 or to a repetitive outpatient care will be collected in the CRF. Collected information will be coded.

8.2.2 Influenza Vaccination History

Participants and/or their parent(s)/legally acceptable representative will be questioned regarding previous influenza vaccination over the 3 previous influenza seasons. Information will be recorded in the source document.

8.2.3 Physical Examinations

At each visit, the investigator or a designee will perform a clinical or medically-driven physical examination. Information will be recorded in the source document.

8.2.4 Vital Signs

Oral pre-vaccination temperature will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.2.5 Clinical Safety Laboratory Assessments

Not applicable.

8.2.6 Pregnancy Testing

Urine pregnancy testing will be performed in women of childbearing potential (WOCBP) before vaccination.

8.2.7 Viremia/Vaccinemia

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 / 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 AE or SAE 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 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

Solicited injection site reactions will be collected from the day of vaccination (D01) until 7 days after vaccination (D08).

Solicited systemic reactions will be collected from the day of vaccination (D01) until 7 days after vaccination (D08).

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards (DCs)/electronic DCs (eDCs) and CRF, together with the intensity scales, are presented in Appendix 10.2.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious adverse events will be collected from the day of vaccination (D01) until 28 days after vaccination (D29).

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.2.5.1.2.

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected from the day of vaccination (D01) until 28 days after vaccination (D29).

Adverse Events of Special Interest (AESIs)

AESIs are considered as serious and will be collected from D01 to D181 (6 months).

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from D01 until D181 (6 months after vaccination). However, before the study intervention administration, only SAEs related to study procedures are to be collected in the CRF (eg, 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 AEs and SAEs

Individual DCs/eDCs, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants / parents / legally acceptable representatives for the recording of daily safety information. These DCs/eDCs will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants / parents / legally acceptable representatives will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants / parents / legally acceptable representatives on how to correctly use these tools.

At specified intervals, the investigator or a designee will interview the participants / parents / legally acceptable representatives to collect the information recorded in the DC/eDC, 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 DC/eDC will first be captured in the source document and then reported electronically.

The 6-month follow-up will be done by interviewing participants or parents/legally acceptable representative either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable.

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant or parents / legally acceptable representatives 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

Pregnant women are not eligible to participate in the study and WOCBP agree to use an effective contraceptive method, as defined in the inclusion criteria. However, a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 4 weeks after study intervention administration.
- If a pregnancy is reported, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 1 month beyond the estimated delivery date, but will be in accordance with local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.3.6 Adverse Events of Special Interest

AESIs will be captured as SAEs. These include new onset of GBS, encephalitis/myelitis, including transverse myelitis, Bell's palsy, optic neuritis, brachial neuritis, thrombocytopenia, vasculitis, and anaphylaxis.

8.3.7 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs. See Appendix 10.2.1 for definition of MAAEs.

8.3.8 Early Safety Data Review

- An ESDR conducted by the Safety Management Team (SMT) will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration. An initial safety review for this study is planned when approximately 10% of participants aged 9 to 17 years are vaccinated and have provided safety data for 7 days after administration of the study intervention.

- The safety data collected will be entered into the case report book (CRB) and will be summarized and reviewed by the Sponsor. It is understood that this review will be based on preliminary data that would not have been subject to validation and database lock.
- The following safety parameters collected from D01 to D08 will be assessed as part of the ESDR review by the Sponsor:
  - Immediate reactions
  - Solicited injection site and systemic reactions
  - Unsolicited AEs reported as related by the investigator
  - SAEs (including AESIs)
- Enrollment will not be paused during the Sponsor review.
- If any of the following criteria are met, a decision will be made by the Sponsor as to whether enrollment in the study will be paused and will be allowed to resume later:
  - An SAE (including AESI) considered as related to the vaccination by the investigator and Sponsor
  - > 10% of participants experiencing any Grade 3 AEs within 7 days after vaccination
- After the ESDR is conducted, the team will continue to monitor the safety of all participants via SMT and/or data review meetings during the conduct of the study. SMT periodicity will be detailed in the SMT charter.

8.4 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are 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 (blood 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 / 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 and the corresponding data, 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. Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research). 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.

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 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

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above.

The core SAP will be written and peer reviewed before the initiation of the study. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

For descriptive purposes, the following statistics will be presented:

Table 9.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number and percentage of participants
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum
Safety results	**Categorical data**	Solicited and biological safety: Number and percentage (95% CIs) of participants Unsolicited: Number and percentage (95% CIs) of participants, and number of events
	Continuous data	At least mean, standard deviation, minimum, and maximum
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs) of participants
	Continuous data (titer / data)	Log_{10}: Mean and standard deviation Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum Graphical representation by RCDC

9.1 Statistical Hypotheses

Primary Objective:

Statistical methodology for analyzing the 8 primary endpoints (GMTs and SC rates).

Non-inferiority of the age group 9-17 years as compared to 18-49 years after vaccination of both age groups with RIV4, will be conducted for GMTs and SC rates.

The primary analysis will be conducted in 2 steps starting with testing for NI of GMTs between the age group 9-17 years and the age group 18-49 years. If NI of GMTs based on the 4 strains is demonstrated, then NI of the SC rates will be also tested.

Step1: Geometric Mean Titers

For each virus strain, the null hypothesis and the alternative hypothesis are:

H_0: $GMT_{RIV4(9\text{-}17y)} / GMT_{RIV4(18\text{-}49y)} \leq 0.667$

H_A: $GMT_{RIV4(9\text{-}17y)} / GMT_{RIV4(18\text{-}49y)} > 0.667$

or equivalently,

$$H_0: \log_{10}(GMT_{RIV4(9\text{-}17y)}) - \log_{10}(GMT_{RIV4(18\text{-}49y)}) \leq \log_{10}(0.667)$$

$$H_A: \log_{10}(GMT_{RIV4(9\text{-}17y)}) - \log_{10}(GMT_{RIV4(18\text{-}49y)}) > \log_{10}(0.667)$$

For the separately considered GMT hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of NI is supported.

All 4 strains must show NI of GMTs to consider that GMTs have demonstrated NI.

Step 2: Seroconversion Rates

For each virus strain, the null hypothesis and the alternative hypothesis are:

H_0: $P_{RIV4(9\text{-}17y)} - P_{RIV4(18\text{-}49y)} \leq -10\%$

H_A: $P_{RIV4(9\text{-}17y)} - P_{RIV4(18\text{-}49y)} > -10\%$

For the separately considered seroconversion hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of NI is supported.

All 4 strains must demonstrate NI of the SC rates to consider that SC rates have demonstrated NI.

Secondary Objectives:

There are no statistical hypotheses to be tested in the secondary objectives.

9.2 Sample Size Determination

A total of approximately 1200 evaluable participants 9 to 49 years of age (600 children and adolescents 9 to 17 years of age [approximately 30% children 9 to 11 years of age] and 600 adults 18 to 49 years of age) will be assessed.

Assuming the same GMT for each strain in the age groups (9 to 17 years vs. 18 to 49 years) compared, and a standard deviation of $\log_{10}$ titers of 0.6 with a NI margin of 1.5; NI for GMTs would be demonstrated with a power of at least 99.6%.

Assuming in each vaccine group the same expected SC rates (0.7, 0.5, 0.6, 0.5) for each of the 4 strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria), based on conservative estimates from historical data, and a NI margin of 10%, the NI for SC rate can be demonstrated with a study power of approximately 80.10% (96.66%, 93.70%, 94.38% and 93.70% for each strain, respectively).

Hence, the overall study power is estimated to be 80.0% (80.0% = 99.6%[GMTs] x 80.10%[SC rate]).

As shown above, to keep the overall study power of 80%, the sample size was increased accordingly, to have an overall type II error <20% for the 8 NI tests.

Assuming an attrition rate of approximately 10% in this age group, a total of approximately 1334 participants 9 to 49 years of age will be enrolled.

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	All participants with data in the CRF. Note: the study groups are not randomized. The study groups are determined based on age. However, a subset of participants from each age group will be randomly selected in order for their blood to be tested using the SN method.
Safety Analysis Set (SafAS)	Participants who have received one dose of the study vaccine. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of participants who received one dose of the study vaccine and had a post-vaccination blood sample. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from FAS who were randomized in the exploratory subset (FAS-SN).
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following criteria will be excluded from the PPAS: · Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria · Participant did not receive vaccine in the proper time window · Preparation and / or administration of vaccine was not done as per-protocol · Participant did not provide the post-dose serology sample at V02 in the proper time window or a post-dose serology sample was not drawn · Participant received a protocol-prohibited medications impacting or that may have an impact on the immune response as described in Section 6.8. The above criteria leading to exclusion from PPAS may be detailed and completed if necessary in the SAP, following the review of protocol deviations during the study conduct. PPAS(s) definition(s) will be finalized before the first database lock. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from PPAS who were randomized in the exploratory subset (PPAS-SN).

9.4 Statistical Analyses

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

The statistical analysis will be conducted as follows:

- The database will be cleaned and locked to analyze primary immunogenicity data and safety data collected up to 28 days after vaccination.
- The final database lock will occur after the 6-month follow-up.

The number of participants enrolled and their age at enrollment, sex, race, and ethnic origin will be summarized for each group, as well as the number and description of protocol deviations. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates will be calculated using the normal approximation of log-transformed titers.

Details will be provided in the SAP.

9.4.2 Primary Endpoints

The immunogenicity parameters will be calculated in each study group with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs and GMTs ratio.

Statistical methodology for analyzing the 8 primary endpoints (GMTs and SC rates).

Non-inferiority of RIV4 in participants aged 9 to 17 years vs participants aged 18 to 49 years will be conducted for GMTs and SC rates.

For each strain, the NI methodology will be applied to compare the post-vaccination GMTs and the SC rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis.

The primary analysis will be conducted in 2 steps starting with testing for NI of GMTs between the age group 9-17 years and the age group 18-49 years. If NI of GMTs based on the 4 strains is demonstrated, then NI of the SC rates will be also tested.

Step 1: Geometric Mean Titers

Assuming that $\log_{10}$ transformation of the data follows a normal distribution, the $\log_{10}$ (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of geometric means (GMs).

The statistical methodology is based on a 2-sided 95% CI of the ratio of the GMTs (RIV4(9-17y) divided by RIV4(18-49y)) at 28 days after vaccination. Non inferiority for GMTs is demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio is > 0.667 for each of the 4 virus strains. The 95% CI will be calculated using normal approximation of log-transformed titers.

Step 2: Seroconversion Rates

The statistical methodology is based on a 2-sided 95% CI of the difference in SC rates (RIV4 [9-17years] minus RIV4 [18-49years]) at 28 days after vaccination. Non-inferiority for SC rates is

demonstrated if the lower limit of the 2-sided 95% CI is >-10% for the 4 strains. The 95% CI of the rate difference is computed using the Wilson Score method without continuity correction.

The CI of the difference in proportions $P_{RIV4(9\text{-}17y)}$ - $P_{RIV4(18\text{-}49y)}$ is computed using the Wilson Score method without continuity correction, quoted by Newcombe.

All 4 strains must demonstrate NI of the SC rate in order for study seroconversion rates to demonstrate NI success.

The PPAS will be used as the primary analysis set for this objective (GMTs and SC rates).

The primary objective is successful if NI for GMTs and NI for SC rates are successful.

9.4.3 Secondary Endpoints

Immunogenicity

The immunogenicity parameters will be calculated with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs and GMTs ratio. The 95% CI of proportions difference (ie, difference between vaccine groups in SC) will be calculated using Wilson Score method without continuity correction. All analyses will be conducted by study group. The main parameters will also be described by age subgroup.

The RCDCs of pre-vaccination titer (D01), and post-vaccination titer (D29) will be generated for each study group. The RCDCs will include the plots of the 2 study groups in the same figure.

The analysis will be conducted for each immunogenicity variable on the PPAS and on FAS.

In addition, subgroup analyses will be performed; in particular, immunogenicity will be described according to age subgroups (9-11 years, 12-17 years, 18-34 years and 35-49 years), sex, race, previous influenza vaccination status (received a seasonal influenza vaccine in the last past influenza season or not) and, baseline seropositivity status (seropositive and seronegative are defined as baseline antibody titer ≥ 1:10 or < 1:10), as appropriate according to number of participants in the respective subgroups.

Safety

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

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

The number of participants with documented safety will be used as denominator of the frequencies.

For solicited reactions, the denominator will be the total number of participants who have non-missing data for the endpoint considered

For unsolicited AEs, the denominator will be the total number of participants who were vaccinated.

SafAS will be the analysis population of safety data.

9.4.4 Exploratory Endpoints

The immunogenicity parameters will be calculated with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs. All analyses will be conducted by study group. The main parameters will also de described by age subgroup. For some parameters (eg. GMTs, 4-fold rise) difference or ratio between groups may be calculated with 95%CI. The 95% CI of ratios of GMTs will be calculated using normal approximation of log-transformed titers and those for proportions difference (ie, difference between vaccine groups in SC) will be calculated using Wilson Score method without continuity correction.

The RCDCs of pre-vaccination titer (D01) and post-vaccination titer (D29) will be generated for each study group. The RCDCs will include the plots of the 2 groups on the same figure.

The analysis will be conducted for each immunogenicity variable on the PPAS subset (PPAS-SN) and on the FAS subset (FAS-SN).

9.5 Interim Analyses

Not applicable.

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, IB, and other relevant documents (eg, 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 (in addition to summaries required from the Sponsor)
  - 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 and/or their parents/legally acceptable representatives 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 center.
- Depending on local regulations, a separate Assent Form (AF) may be required to be signed by minor participants. The AF is in addition to, not in place of, an ICF that is signed by the parents/legally acceptable representative.

- 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 AF and ICF used at each center may differ, depending on local regulations and IEC/IRB requirements. However, all versions must contain the standard information found in the sample AF and ICF provided by the Sponsor. Any change to the content of the AF and 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 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 AF and ICF or an addendum to the original AF and ICF.
- Participants and/or their parents/legally acceptable representative must be re-consented to the most current version of the AF(s) and/or ICF(s) during their participation in the study.
- A copy of the AF(s) and/or ICF(s) must be provided to the participant and/or their parents/legally acceptable representatives.

Rationale for Including Participants Unable to Give Consent:

Some participants in the VAP00027 study will be in the pediatric population. Depending on local regulations, some participants will not be of age to give consent and participant's parent(s)/legally acceptable representative consent will be collected instead.

The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research, unless prohibited by local laws or IRBs/IECs. The investigator or designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

Participants will be recruited from the general population. The sites will ensure that any advertisements used to recruit participants (letters, pamphlets, posters, etc.) are submitted to Sanofi Pasteur prior to submission to the IEC / IRB for approval. Detailed guidance and information are provided in the Operating Guidelines.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their parent / legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension, use of local labs).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.4: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

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 (eg, on African-American population for the Food and Drug Administration [FDA]).

- 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" 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 and in the Transcelerate Investigator Registry 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

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. The Sponsor's internal safety review committee, led by the PV representative and the RMO, will be responsible for the review, assessment, and evaluation of safety data generated from this study. This committee is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

In addition, this study will include an ESDR (see Section 8.3.8).

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 (eg, 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 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.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, 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 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, DCs, medical and hospital records, screening logs, ICFs / AFs, 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 center study-site has all the documents necessary for archiving and a study-site closure visit has been performed along with a termination report.

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" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an "expected" adverse reaction (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 adverse event of special interest (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.

Medically Attended AE (MAAE):

An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent/legally acceptable representative to seek unplanned medical advice at a physician's office or Emergency Department. Physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This includes medical advice seeking during the study visit or routine medical care. This definition excludes pediatric check-ups, follow-up visits of chronic conditions with an onset prior to entry in the study, and solicited reactions.

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 (either solicited or unsolicited) and all solicited systemic AEs 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 unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the investigator only.
  - For SAEs and non-serious 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 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 unsolicited systemic AE and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:
  - Not related – The AE 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 AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)
  - Related – There is a "reasonable possibility" that the AE 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 AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE 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 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 AEs and SAEs

- 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 AE or SAE 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 data to the Sponsor within 24 hours of receipt of the information.
- Serious adverse events 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 one of the following means:
  - By fax, to the following number: +1-570-895-2782
  - 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: Global Pharmacovigilance and Epidemiology, Sanofi Pasteur Inc. 1 Discovery Drive, Swiftwater, PA, 18370-0187, US

Using a Verbal Autopsy Questionnaire to Aid in Determining the Cause of Death

- In case of the absence or inadequacy of health information that would allow a thorough evaluation of the causes of the death of a study participant, the verbal autopsy procedure may be triggered by either the investigator or the Sponsor. Detailed instructions on the use of the verbal autopsy questionnaire, as well as the questionnaire itself, are provided in the Operating Guidelines.

Safety Emergency Call
If, as per the investigator's judgment, a participant experiences a medical emergency, the investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines. This process does not replace the need to report an SAE. The investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

10.2.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.2.5.1 Tables for Clinical Abnormalities

10.2.5.1.1 Solicited AR Intensity Grading Scale

Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales – Children aged 2 through 11 years

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.
Intensity scale*	**CRF:** Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

	Diary card: Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity				

MedDRA: Medical Dictionary for Regulatory Activities

* For pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 10.2: Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents and adults aged≥ 12 years

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.

Intensity scale*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

MedDRA: Medical Dictionary for Regulatory Activities

* For pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 10.3: Solicited systemic reactions: terminology, definitions, and intensity scales – Children aged 2 through 11 years, adolescents or adults aged ≥ 12 years

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Chills
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Participants or parents / legally acceptable representatives are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC / eDC / MA, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is oral.

10.2.5.1.2 Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.2.5.1.1).

All other unsolicited AEs will be classified according to the following intensity scale:

- Grade 1
  - CRF: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - DC: No interference with activity.
- Grade 2
  - CRF: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - DC: Some interference with activity.
- Grade 3
  - CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - DC: Significant; prevents daily activity.

10.3 Appendix: Contraceptive and Barrier Guidance

10.3.1 Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1) Premenarchal
2) Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3) Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2 Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device
• Intrauterine hormone-releasing system [b]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **Effective Methods[d] That Are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[e]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. e) Male condom and female condom should not be used together (due to risk of failure from friction).

10.4 Appendix: Contingency measures for a regional or national emergency that is declared by a governmental agency

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in Section 5.5, Section 6.4, Section 8, and Section 10.1.3 for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and enrollment/administration of study intervention may be temporarily delayed/halted (see also Section 5.5).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely
- Use of local clinic or laboratory locations may be allowed.

Contingencies implemented due to emergency will be documented.

10.5 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.

10.6 Appendix: Abbreviations

Ab	antibody
AE	Adverse Events
AESI	Adverse events of special interest
AF	assent form
AR	Adverse reactions
BL	blood sampling
CI	confidence interval
CRF	Case report form
DC	diary card
DMC	Data Monitoring Committee
eDC	electronic diary card
ELISA	enzyme-linked immunosorbent assay
ESDR	early safety data review
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMT	geometric mean titer
GPV	Global Pharmacovigilance
HAI	hemagglutination inhibition
HAU	hemagglutination units
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IIV3	Trivalent inactivated influenza vaccine
IIV4	quadrivalent inactivated influenza vaccine
IM	intramuscular

IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IRT	interactive response technology
LLOQ	lower limit of quantitation
MA	memory aid
MAAE	medically attended adverse event
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NI	non-inferiority
NIMP	Non- Investigational Medicinal Product;
PPAS	Per-protocol analysis set
PSC	Protein Sciences Corporation
PV	pharmacovigilance
PY	Person Year
QTL	quality tolerance limit
RBC	red blood cell
RCDC	reverse cumulative distribution curve
rHA	recombinant hemagglutinin
RIV3	Trivalent Recombinant Influenza Vaccine
RIV4	Quadrivalent Recombinant Influenza Vaccine
RMO	Responsible Medical Officer
SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SC	seroconversion
SD-IIV4	standard-dose quadrivalent inactivated influenza vaccine
SMT	Safety Management Team
SN	seroneutralization
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined

USA	United States of America
VAC	vaccination
WHO	World Health Organization

10.7 References

1. Munoz FM. The impact of influenza in children. Seminars Pediatric Infect Dis. 2002;13(2):72–8.

2. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B Virus Infections in Children. Clin Infect Dis. 2003;36(3):299–305.

3. Antonova EN, Rycroft CE, Ambrose CS, Heikkinen T, Principi N. Burden of paediatric influenza in Western Europe: a systematic review. Bmc Public Health. 2012;12(1):968.

4. Willis GA, Preen DB, Richmond PC, Jacoby P, Effler PV, Smith DW, et al. The impact of influenza infection on young children, their family and the health care system. Influenza Other Resp. 2019;13(1):18–27.

5. Kondrich J, Rosenthal M. Influenza in children. Curr Opin Pediatr. 2017;29(3):297–302.

6. Kumar V. Influenza in Children. Indian J Pediatrics. 2017;84(2):139–43.

7. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285–300.

8. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of hospitalization attributable to influenza and RSV in the US during 1997–2009, by age and risk status. Bmc Public Health. 2017;17(1):271.

9. World Health Organization. Vaccines against influenza - WHO position paper - November 2012 - Weekly epidemiological record 2012 [461-76]. ://www.who.int/wer/2012/wer8747/en/ [Internet]. Weekly epidemiological record. Available from: https://www.who.int/wer/2012/wer8747/en/

10. World Health Organization. Global influenza strategy 2019-2030 [Internet]. [cited 2022 Feb 10]. Available from: https://apps.who.int/iris/handle/10665/311184

11. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Pietrantonj CD. Vaccines for preventing influenza in healthy adults. Cochrane Db Syst Rev. 2018;2020(2):CD001269.

12. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States. Jama. 2003;289(2):179–86.

13. Center for Disease Control and Prevention. National Center for Immunization and Respiratory Diseases. Past Seasons Vaccine Effectiveness Estimates 2019 [Internet]. [cited 2022 Feb 10]. Available from: https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html

14. Treanor JJ, Sahly HE, King J, Graham I, Izikson R, Kohberger R, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: A randomized, placebo-controlled trial. Vaccine. 2011;29(44):7733–9.

15. Baxter R, Patriarca PA, Ensor K, Izikson R, Goldenthal KL, Cox MM. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50–64 years of age. Vaccine. 2011;29(12):2272–8.

16. Keitel WA, Treanor JJ, Sahly HME, Gilbert A, Meyer AL, Patriarca PA, et al. Comparative immunogenicity of recombinant influenza hemagglutinin (rHA) and trivalent inactivated vaccine (TIV) among persons ≥65 years old. Vaccine. 2009;28(2):379–85.

17. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. New Engl J Medicine. 2017;376(25):2427–36.

18. Dunkle LM, Izikson R, Patriarca PA, Goldenthal KL, Muse D, Cox MMJ. Randomized Comparison of Immunogenicity and Safety of Quadrivalent Recombinant Versus Inactivated Influenza Vaccine in Healthy Adults 18–49 Years of Age. J Infect Dis. 2017;216(10):1219–26.

19. King JC, Cox MM, Reisinger K, Hedrick J, Graham I, Patriarca P. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy children aged 6–59 months. Vaccine. 2009;27(47):6589–94.

20. Dunkle LM, Izikson R, Patriarca PA, Goldenthal KL, Cox M, Treanor JJ. Safety and Immunogenicity of a Recombinant Influenza Vaccine: A Randomized Trial. Pediatrics. 2018;141(5):e20173021.

21. Quadrivalent Recombinant Influenza Vaccine. Investigator's Brochure. Version 8.0 dated 16 December 2021.

22. Hansen J, Goddard K, Timbol J, Zhang L, Lewis N, Dunkle L, et al. Safety of Recombinant Influenza Vaccine Compared to Inactivated Influenza Vaccine in Adults: An Observational Study. Open Forum Infect Dis. 2020;7(6):ofaa179.

23. McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immun. 2016;137(3):868–78.

11 Sponsor Signature Page

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