Title Page

Protocol Title: A Phase III Randomized, Modified Double-blind, Active-controlled, Multi-center Study to Describe the Immunogenicity and Safety of the Quadrivalent Recombinant Influenza Vaccine (RIV4) versus a Quadrivalent-inactivated Influenza Vaccine (IIV4) (Fluarix® quadrivalent) in Participants 18 Years of Age and Older in South Korea

Study Code: VAP00016

Protocol Version Number: 5.0

Amendment Number: 4

Compound: Quadrivalent Recombinant Influenza Vaccine

Study Phase: III

Short Title: Study Describing the Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) versus a licensed Quadrivalent-inactivated Influenza Vaccine (IIV4) (Fluarix® quadrivalent) in Participants 18 Years of Age and Older in South Korea.

Sponsor Name and Legal Registered Address:
Sanofi Pasteur
14 Espace Henry Vallée, 69 007 Lyon, France

Manufacturer: Same as Sponsor

Regulatory Agency Identifier Number(s):

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Medical Monitor Name and Contact Information Are Provided in the Operating Guidelines.

The study centers, the Investigators at each center are listed in a separate document.

Document History

Previous Versions	Date	Comments
1.0	10 November 2020	Version submitted to the IEC/IRB
2.0	07 April 2021	Version submitted to South Korean Health Authority
3.0	03 August 2021	Version submitted to South Korean Health Authority
4.0	21 October 2021	Version submitted to South Korean Health Authority

Overall Rationale for Amendment 2:

Changes were implemented following requests of the South Korean Health Authority (MFDS), mainly:

- Detailed Title
- Increased participant safety follow-up from 1 to 6 months
- Exclusion of pregnant women from participation

Overall Rationale for Amendment 3:

Changes were implemented following requests of the South Korean Health Authority (MFDS), mainly:

- Addition of D08 phone call to participants
- All medications from D08 to D181 will be collected
- For the solicited safety term “Injection site induration”, the Diary Card definition was modified to “Hardening/Firmness” from “Hardening”
- Additional solicited safety terms were included: “tenderness” was included in solicited injection site reactions; and “fatigue,” “nausea” and “arthralgia” were included in solicited systemic reactions.
- Update of Appendix 10.4 “Collection of pregnancy information” with the description of effective contraceptive methods
- To maintain the blind during the study period, only the independent statistician(s) will be unblinded at the time of the interim analysis

Overall Rationale for Amendment 4:

- Sanofi Pasteur decision to delete the interim analysis

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase III Randomized, Modified Double-blind, Active-controlled, Multi-center Study to Describe the Immunogenicity and Safety of the Quadrivalent Recombinant Influenza Vaccine (RIV4) versus a Quadrivalent-inactivated influenza vaccine (IIV4) (Fluarix® quadrivalent) in Participants 18 Years of Age and Older in South Korea

Short Title:

Study Describing the Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) versus a licensed Quadrivalent-inactivated Influenza Vaccine (IIV4) (Fluarix® quadrivalent) in Participants 18 Years of Age and Older in South Korea.

Rationale:

VAP00016 study is being proposed to collect and analyze the immunogenicity and safety of the Quadrivalent Recombinant Influenza Vaccine (RIV4) versus a locally licensed quadrivalent-inactivated influenza vaccine (IIV4) (Fluarix® quadrivalent) that will serve as a control.

Clinical data generated with RIV4 support an indication in persons starting at 18 years of age and older. VAP00016 study will be conducted during the 2021-2022 Northern Hemisphere (NH) influenza season in 300 participants 18 years of age and older in South Korea.

Objectives and Endpoints:

Primary* Objectives	Primary Endpoints
Immunogenicity	
• To describe the immune response induced by RIV4 and IIV4 in 18-49 and ≥ 50 years of age participants by hemagglutination inhibition (HAI) measurement method	• HAI antibody (Ab) titers obtained on Day (D) 01 and D29 • Individual HAI titers ratio D29/D01 • Seroconversion: titer < 10 (1/dilution [1/dil]) at D01 and post-injection titer ≥ 40 (1/dil) at D29, or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold increase in titer (1/dil) at D29 • Titer ≥ 40 (1/dil) at D01 and D29 • Detectable titer ≥ 10 (1/dil) on D01 and D29
Safety †	
• To describe the safety profile of all participants in RIV4 and IIV4 groups	• Presence of any unsolicited systemic adverse event (AE) reported in the 30 minutes after vaccination • Presence of solicited injection site, and systemic reactions occurring up to 7 days after

	vaccination, (ie, pre-listed in the participant's diary and case report form [CRF]) • Presence of unsolicited (spontaneously reported) AEs up to 28 days after vaccination • Presence of serious adverse events (SAEs), including adverse events of special interest (AESIs), throughout the trial period Other endpoints recorded or derived as described in the Statistical Analysis Plan (SAP). Depending on the item, these could include nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), time of onset, duration, number of days of occurrence, grade of severity, relationship to the vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

*This study has no secondary or exploratory objectives
† Details on safety endpoints (terminology, definitions, and intensity scales) are presented in Table 10.1 and Table 10.2.

Overall Design

Type of design	Parallel, multi-center
Phase	III
Control method	Active-controlled (control=IIV4)
Study population	Participants 18 years of age and older (2 age groups: participants 18-49 years of age and participants ≥ 50 years of age)
Country	South Korea
Level and method of blinding	Modified double-blind
Study intervention assignment method	Randomization

Disclosure Statement:

This is a parallel-group prevention study with 2 arms that is participant and Investigator blinded.

A designated unblinded administrator at each study site knows which vaccine has been administered. The Investigator/sub-Investigator/staff involved in the sampling and safety assessment are blinded. The staff in charge of the immunogenicity assays is blinded.

Number of Participants:

A total of 300 participants are planned to be randomized.

Intervention Groups and Duration:

In each age group (18-49 years of age and ≥ 50 years of age), eligible participants will be randomized in a 1:1 ratio to receive a single intramuscular (IM) injection of either RIV4 or IIV4 at D01.

The duration of each participant's participation will be approximately 6 months (180 days).

Data Monitoring Committee:

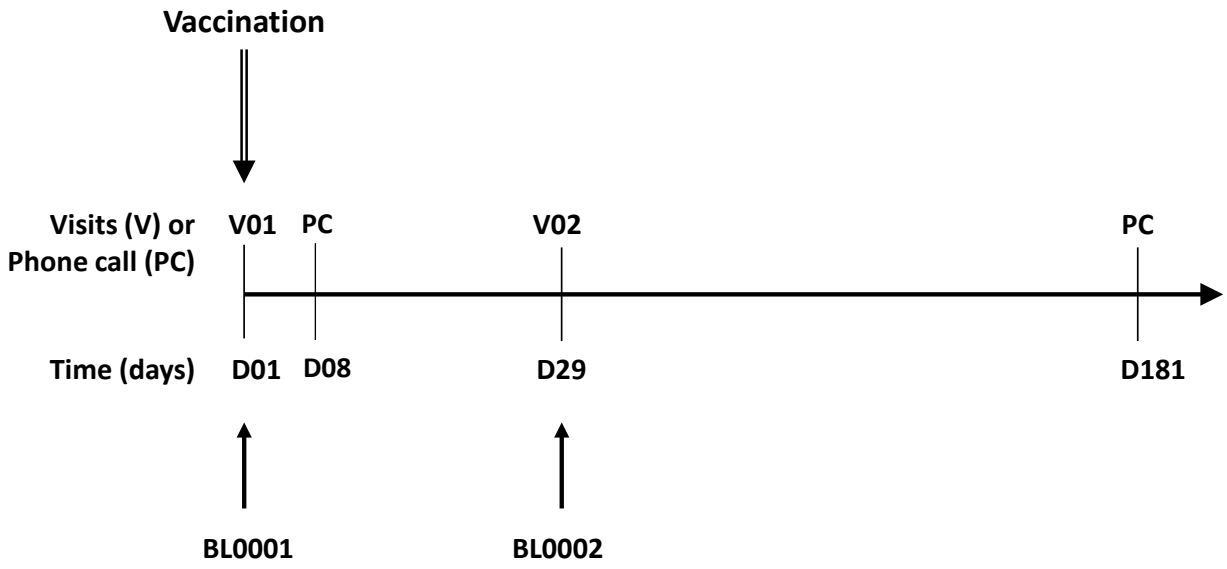
None.

For further details regarding the safety data collection, see Section 8 (Study Assessments and Procedures) and Section 10 (Supporting Documentation and Operational Considerations).

1.2 Schema

The graphical design of **VAP00016** study is presented in Figure 1.1.

Figure 1.1 – Graphical study design



Abbreviations: BL, Blood sampling; V, Visit; 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 and 2 Phone Calls, 1 Vaccination, 2 Blood Samples, 6 Months Duration Per Participant

Visit/Contact	***Information to be collected in the CRF***	**Visit 1**	**Phone call 1**	**Visit 2‡**	**Phone call 2 (6 Months Follow-up)**
Study timelines (days)		D01	D08	D29	D181
Time windows (days)		NA	[+2 D]	[+7 D]	[+14 D]
Visit procedures:					
Assent form/ Informed consent	X	X			
Inclusion/exclusion criteria	X	X			
Collection of demographic data	X	X			
Collection of Medical history†	X Significant Medical History	X			
Urine pregnancy test (if applicable) §		X			
Physical examination §§		X		X	
Pre-vaccination temperature		X			
Randomization/allocation of participant number	X	X			
Blood sampling (BL) [10 mL]	X	BL0001 Pre-vac		BL0002	
Vaccination (vac)	X	X			
Immediate surveillance (30 min)	X	X			
Diary card (DC) provided		X			
Collection of solicited injection site and systemic reactions*	X	Up to 7 days after vaccination (D01 to D08)			
Collection of unsolicited AEs	X	Up to 28 days after vaccination (D01 to D29)			
DC collected				X	
Memory Aid (MA) provided				X	
MA checked					X
Collection of concomitant medications	X	X	X	X	X

Visit/Contact	***Information to be collected in the CRF***	**Visit 1**	**Phone call 1**	**Visit 2‡**	**Phone call 2 (6 Months Follow-up)**
Study timelines (days)		D01	D08	D29	D181
Time windows (days)		NA	[+2 D]	[+7 D]	[+14 D]
Collection of SAEs, including AESIs	X	To be reported at any time during the study			
Collection of pregnancies	X	To be reported at any time during the study			
Check participant status, remind participant to collect AEs and of planned next visit			X		
End of active phase participation record ††	X			X	
End of 6-month safety follow-up participation record††	X				X

Abbreviations: DC, diary card; mL, milliliter; NA, not applicable; Pre-vac, pre-vaccination; AE, adverse event; SAE, serious adverse event; AESI, adverse event of special interest; CRF, case report form; BL, blood sampling; MA, Memory Aid

† Including collection of the history of seasonal influenza vaccination.

§ Female participants of childbearing potential must have a negative urine pregnancy test prior to vaccination. Urine pregnancy test is applicable to childbearing potential female participant (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile).

§§ Targeted physical examination based on medical history will be performed at Visit 1. Targeted physical examination may also be performed at Visit 2, as necessary.

‡ The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything incomplete or unclear.

* Solicited injection site and systemic reactions will be collected from D01 to D08 by the participant using the DC provided. The DC is collected at D29.

†† Participants will be in the active phase from enrollment (D01) until completion of V02 (D29) and in the 6-Month safety follow-up from completion of V02 until approximately 6 months after V01.

2 Introduction

2.1 Study Rationale

VAP00016 study is being proposed to collect and analyze the immunogenicity and safety of the RIV4 versus a locally licensed IIV4 (Fluarix® quadrivalent) that will serve as a control arm.

RIV4 is a next-generation formulation that does not contain preservatives, antibiotics, egg protein, or latex, any of which may produce hypersensitivity reactions in some individuals. The rationale for and the advantages of the recombinant platform technology for the manufacturing of influenza vaccine have been well described in the medical literature (1-3). Clinical data generated with RIV4 support an indication for active immunization in persons 18 years of age and older for the prevention of influenza disease.

This Phase III, parallel, randomized, active-controlled, multi-centered, modified double-blinded, VAP00016 study will be conducted during the 2021-2022 Northern Hemisphere (NH) influenza season in 300 participants 18 years of age and older in South Korea.

2.2 Background

Influenza is a highly contagious, acute viral respiratory disease caused by infection with influenza viruses (4). Influenza causes recurrent epidemics of acute disease in persons of all ages and is currently estimated to account for 290 000 to 650 000 excess deaths annually worldwide, most of which occur in older adults (5).

The incubation period of influenza ranges from 1 to 4 days and peak virus shedding usually occurs from 1 day before the onset of symptoms to 3 days after. Typical features of influenza include abrupt onset of fever and respiratory symptoms such as cough (usually nonproductive), sore throat, and coryza, as well as systemic symptoms such as headache, muscle aches, and fatigue. Complications of influenza include primary viral pneumonia, secondary bacterial pneumonia, and exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and cardiovascular diseases (4).

Annual influenza vaccination is the best means for preventing influenza illness and its complications. It has been shown to be effective in reducing influenza-associated morbidity and mortality. Health care providers should recommend vaccination for all persons ≥ 6 months of age who do not have contraindications to vaccination (6).

Influenza control depends upon epidemiological data of influenza virus circulation to ensure that vaccination is timed ahead of peak transmission. For most countries, the World Health Organization (WHO) recommended timing of vaccination was appropriate for (ie, within 4 months before) the timing of the influenza peak activity (7).

Each year, WHO convenes technical consultations in February and September to recommend viruses for inclusion in influenza vaccines for the NH and the Southern Hemisphere (SH) influenza seasons, respectively. Generally, countries in East Asia experienced increased influenza activity from December 2019, with influenza A(H3N2) predominant in China and Mongolia and A(H1N1)pdm09 viruses predominant in Japan and South Korea (8).

Influenza comprises not only a burden on the medical system but also has a huge socioeconomic burden in Korea. The national influenza surveillance system has played an important role in identifying influenza epidemic patterns and virus characteristics in Korea (9).

The current surveillance system operated by the Korea Centers for Disease Control & Prevention (KCDC) provides an understanding of the characteristics of serious influenza and its disease burden. The hospitalization and mortality surveillance system are being operated, but the data collected are limited and cannot be used to fully understand the clinical course (9).

Nevertheless, it's known that in South Korea, approximately 7 000 patients are hospitalized and 400 000 are treated as outpatients annually for seasonal influenza (10).

According to data from 2003 through 2013 (10-year period), the overall all-cause excess annual mortality rate per 100 000 people was 5.97, whereas it was 46.98 for adults ≥ 65 years of age. In this same period, a total of 2 570 939 deaths were reported with an average crude mortality rate of around 10 deaths per 100 000 people each week, and a slightly higher mortality rate during the winter. During this period, South Korea experienced 2 influenza epidemics in most years, with the first peak in the early winter (December through January) followed by a smaller peak in the late spring (April through May) (11).

To reduce the disease burden of influenza, the South Korean government has recommended influenza vaccination for the target groups, including children under 18, people 50 years of age and above, pregnant women, and those with chronic diseases (12).

Since 2005, free trivalent influenza vaccine (TIV) has been provided in South Korea for the elderly above 65 years of age by the National Immunization Program (NIP). Despite the successful implementation of the influenza NIP, more than 2 900 deaths occur annually due to influenza, most of them in the elderly (11).

Since 2000, 2 strains of influenza B have circulated concurrently. There are 2 lineages of the influenza B virus, namely, Victoria, and Yamagata. However, only 1 lineage is included in the TIV as recommended by the WHO. As both lineages circulate simultaneously, vaccine mismatch is the foremost problem. In South Korea, the degree of influenza B mismatch was estimated to be 41.7% based on analysis during 4 influenza seasons (2007-2008, 2009-2010, 2011-2012, and 2013-2014). To overcome this problem, a quadrivalent influenza vaccine (QIV) was developed, and since 2014, people can receive either TIV or QIV (12).

KCDC recommends annual vaccinations for those at high risk. As part of the NIP, seasonal influenza vaccines are reimbursed each year during the flu season for adults ≥ 65 years of age, and more recently (for the 2017-2018 flu season) for children between 6 and 59 months of age (13).

The estimated all-cause mortality rate associated with any influenza virus infection was highest in the elderly (≥ 65 years of age) and middle-aged adults 45-64 years of age, with an average of 46.98 and 2.73 excess deaths per 100 000 people, respectively (11).

Deaths caused by 7 major causes, including respiratory, cardiovascular, cancer, diabetes mellitus, renal, chronic liver, and degenerative nervous system diseases, accounted for almost 70% of the all-cause excess mortality attributable to influenza (11).

Background of the Study Intervention

RIV4 is a recombinant hemagglutinin (rHA) influenza vaccine indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses consisting of 4 full-length rHA derived from the 4 influenza strains (2 A subtypes and 2 B lineages) selected by the WHO. These proteins are produced in a continuous insect cell line *expres*SF+®, derived from Sf9 cells of the fall armyworm *Spodoptera frugiperda*, and grown in a serum-free medium composed of chemically defined lipids, vitamins, amino acids, and mineral salts. Each of the 4 hemagglutinins (HAs) is expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus [AcNPV]) (14).

The HA genes are cloned independently into a baculovirus expression vector plasmid. After confirmation of the correct sequence, the deoxyribonucleic acid (DNA) sequences are inserted into AcNPV by homologous recombination. Recombinant viruses containing the respective HA genes are then used to express the HAs in the high-yielding insect *expres*SF+ cell line under serum-free conditions. Use of recombinant DNA techniques to produce vaccine antigen expressed in cell culture is a method that avoids growing the influenza viruses in embryonated hen's eggs or any cell line, thus avoiding genetic mutations that may reduce the efficacy of the vaccine. The recombinant proteins are highly purified, and the vaccine contains no egg protein, preservatives or antibiotics, any of which may produce hypersensitivity reactions in some individuals (14).

RIV4 is a sterile liquid preparation for IM injection in a single-dose pre-filled syringe. RIV4 contains 45 µg of rHA antigen per virus strain per 0.5 mL dose (total recombinant HA of 180 µg). The high purity of a recombinant antigen enables the administration of a higher concentration of rHA antigen without an increase in adverse reactions (ARs) (14).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected AEs, the potential risks, and uncertainties of RIV4 may be found in the current Investigator's Brochure (IB), US Package Insert, patient information leaflet or Summary of Product Characteristics.

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: RIV4		
Anaphylaxis	Anaphylaxis is an identified risk for RIV4 (see IB (15) for more information regarding the data from previous experience with RIV4). No case of anaphylaxis was reported as related to RIV3 or RIV4 during the clinical development. Cumulatively two case of anaphylaxis of the level 1 definition of Brighton Case Collaboration (Definite Certainty of Diagnosis) were reported for RIV3. With a cumulative distribution of 10 273 172 doses, the effective Reporting Rate for Anaphylaxis is approximately 0.02 per 100 000 doses for RIV3/RIV4 combined. Post-marketing observational study of safety comparing RIV3 with licensed IIV in adults using adjusted logistic regression 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 (16). 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 (17).	Exclusion criterion E06 for those at increased risk. Addressed in IB (15) (administration precautions, potential adverse events), defined AESI in the trial. Each site must have measures to treat Anaphylaxis available at the time vaccination
Guillain-Barré Syndrome	No cases of Guillain-Barré syndrome (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. The incidence rate (IR) in the USA has been observed to range from 1.24 to 2.4 per	Exclusion criterion E12 for those at increased risk. Addressed in IB (15) (administration precautions, potential adverse events), defined AESI in the trial)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	100 000 Person Year (PY) in various studies (18-20); a wider range than this was observed in a meta-analysis of rates in the USA, Canada, Italy, Spain and Sweden: IR ranging from 0.62 to 2.66 per 100 000 PY (21).	
Comparator: IIV4		
Anaphylaxis	All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine.	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label.
GBS	Guillain-Barré Syndrome is considered a potential risk for influenza vaccines since the 1976 mass vaccination campaign against H1N1 influenza strain in the USA was suspended due to an excess of GBS cases in the vaccinated population.	Exclusion criterion E12 for those at increased risk. Observation period after vaccination for early detection and treatment.
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 either the investigational RIV4 or the control vaccine IIV4 (Fluarix® quadrivalent). These participants will benefit from coverage against influenza and may be less likely to catch influenza or develop complications during the 2021-2022 NH influenza season.

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

The recombinant influenza HA antigens are produced using a scalable, reproducible, and sterile cell culture process, resulting in a consistent protein-based vaccine with low endotoxin content and absolute fidelity to the HA of interest. Using this production technology, the rHA in RIV4 has exact fidelity to the active HA receptor site of the virus strains selected for seasonal vaccines without the mutations that may occur when the virus is adapted to growth in a culture matrix that is foreign to the wild-type strain, such as eggs or mammalian cells, assuring that the vaccine will provide an appropriate antigen to induce the desired immune reaction that provides protective efficacy against WHO-recommended strains (22, 23). Given the acceptable safety data generated from 5 326 participants vaccinated with RIV4 in the United States (US) (Phase III PSC12 and PSC16 studies) and the fact that no changes will be made to the drug substance manufacturing process of RIV4 and no safety signal has been detected from over 21 000 000 doses of licensed RIV4 sold to date of this protocol, Sanofi Pasteur considers the risk/benefit ratio appropriate for conducting a Phase III clinical study without an early safety data review.

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

Primary* Objectives	Primary Endpoints
Immunogenicity	
• To describe the immune response induced by RIV4 and IIV4 in 18-49 and ≥ 50 years of age participants by HAI measurement method	• HAI antibody (Ab) titers obtained on Day (D) 01 and D29 • Individual HAI titers ratio D29/D01 • Seroconversion: titer < 10 (1/dilution [1/dil]) at D01 and post-injection titer ≥ 40 (1/dil) at D29, or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold increase in titer (1/dil) at D29 • Titer ≥ 40 (1/dil) at D01 and D29 • Detectable titer ≥ 10 (1/dil) on D01 and D29
Safety †	
• To describe the safety profile of all participants in RIV4 and IIV4 groups	• Presence of any unsolicited systemic AE reported in the 30 minutes after vaccination • Presence of solicited injection site, and systemic reactions occurring up to 7 days after vaccination, (ie, pre-listed in the participant's diary and CRF) • Presence of unsolicited (spontaneously reported) AEs up to 28 days after vaccination • Presence of SAEs, including AESIs, throughout the trial period Other endpoints recorded or derived as described in the SAP. Depending on the item, these could include: nature (MedDRA PT), time of onset, duration, number of days of occurrence, grade of severity, relationship to the vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

*This study has no secondary or exploratory objectives

† Details on safety endpoints (terminology, definitions, and intensity scales) are presented in Table 10.1 and Table 10.2.

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Parallel, multi-center
Phase	III
Control method	Active-controlled (control=IIV4)
Study population	Participants 18 years of age and older (2 age groups: participants 18-49 years of age and participants ≥ 50 years of age)
Level and method of blinding	Modified double-blind (Participant, Investigator and staff in charge of the sampling, safety assessment and immunogenicity assays are blinded. Designated administrator at each study site is unblinded)
Study intervention assignment method	Randomization
Number of participants	300 participants
Intervention groups	In each age group (18-49 years of age and ≥ 50 years of age), randomization in a 1:1 ratio to receive a single IM injection of either RIV4 or IIV4 at D01
Total duration of study participation	Approximately 6 months
Country	South Korea
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

Disclosure Statement:

This is a parallel-group prevention study with 2 arms that is participant and Investigator blinded.

A designated unblinded administrator at each study site knows which vaccine has been administered. The Investigator/sub-investigator/staff involved in the sampling and safety assessment are blinded. The staff in charge of the immunogenicity assays are blinded.

Number of Participants:

A total of 300 participants are planned to be randomized.

Intervention Groups and Duration:

In each age group (18-49 years of age and ≥ 50 years of age) eligible participants will be randomized in a 1:1 ratio to receive a single IM injection of either RIV4 or IIV4 at D01.

The duration of each participant's participation will be approximately 6 months.

Data Monitoring Committee: No

Collection of safety data:

Participants will be asked to notify the site immediately about any potential serious adverse events (SAEs) at any time during the study.

All participants will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the Case Report Form (CRF).

Participants will use a diary card to record information about solicited reactions (D01-D08), unsolicited AEs (D01-D29), and SAEs and AESIs* (D01-D29). At D08, a telephone call will be made to check participant's status, and to remind them to capture solicited reactions or any AEs in the diary card and of the planned next visit (V02). The diary card will be reviewed by study staff at V02. The 6-month follow-up will be done by interviewing participants over the telephone to capture SAEs and AESIs. A memory aid will be provided to the participants at V02 to help them record information on events occurring between this visit and the 6-month safety follow-up phone call.

*Note: New onset of anaphylaxis, GBS, convulsion, encephalitis / myelitis (including transverse myelitis), neuritis (including Bell's palsy, optic neuritis, and brachial neuritis), thrombocytopenia, and vasculitis will be considered as AESIs and collected as SAEs. Reporting of SAEs as well as all AESI will be conducted on an expedited basis by the clinical site staff and Investigators (within 24 hours of receipt).

Study Interruption: The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Independent Ethics Committees / Institutional Review Boards (IECs/IRBs), or the governing regulatory authorities in the country where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the 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 study participants and should assure appropriate therapy and/or follow-up.

For further details regarding the safety data collection, see Section 8 (Study Assessments and Procedures) and Section 10 (Supporting Documentation and Operational Considerations).

4.2 Scientific Rationale for Study Design

The choice of IIV4 (Fluarix® quadrivalent) as the comparator vaccine was based on the fact that it is a licensed product in South Korea which was also used in the RIV4's previous clinical studies PSC12 and PSC16 assessing its immunogenicity, protective efficacy, and safety.

The study design is similar to previous clinical studies PSC12 and PSC16 in order to ease bridging with foreign clinical study data.

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 Active Phase if he/she completed V02. Likewise, a participant is considered to have completed the 6-month safety follow-up if he/she completed the 6-month telephone contact planned in the SoA.

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

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:

I01: Aged ≥ 18 years on the day of inclusion.

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

I03: Participants aged 18 years: Assent Form has been signed and dated by the participant or by an independent witness, and Informed Consent Form (ICF) has been signed and dated by at least one parent or another legally acceptable representative or by an independent witness.
Participants aged 19 and older: ICF has been signed and dated.

I04: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies[a]:
Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal 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 study intervention administration until at least 4 weeks after study intervention administration.
A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine) before the first dose of study intervention

I05: Able to attend all scheduled visits and to comply with all study procedures.

5.2 Exclusion Criteria

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

E01: Participation at the time of study enrollment, or in the 6 months preceding the study vaccination, or planned participation during the present study period in another clinical study investigating involving an IMP (vaccine, drug), medical device, or medical procedure or in any other type of medical research.

E02: Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine prior to Visit 2.

E03: Previous vaccination against influenza (in the preceding 6 months) with either the study vaccine or another vaccine.

[a] Refer to Appendix 10.4

E04: Receipt of immune globulins, blood, or blood-derived products in the past 3 months or planned treatment during the present study period.

E05: Known or suspected abnormal immune function: immunosuppression, suspected congenital or acquired immunodeficiency based on medical history and physical examination, or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy, or radiation therapy, within the preceding 6 months or planned treatment during the present study period; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months) or planned treatment during the present study period.

E06: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances.

E07: Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on the Investigator's judgment.

E08: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

E09: Current alcohol abuse or drug addiction that in the opinion of the Investigator might interfere with the study conduct or completion.

E10: Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[a].

E11: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided.

E12: Personal or family history of Guillain-Barré syndrome (GBS).

E13: Neoplastic disease or any hematologic malignancy (except localized skin or prostate cancer that is stable at the time of vaccination in the absence of therapy and participants who have a history of neoplastic disease and have been disease-free for ≥ 5 years).

E14: 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) 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 participant's consent to inform him/her of the participant's participation in the

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

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.

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.

6 Study Intervention

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: routine vaccines administered outside of study protocol are not considered as study interventions.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study interventions

Intervention Name	RIV4	IIV4
Use	Experimental	Active comparator
IMP and NIMP	IMP	IMP
Type	Vaccine	Vaccine
Dose Formulation	Solution for injection	Suspension for injection
Unit Dose Strengths	45 µg of HA of each of the following strains* per dose: • A/Wisconsin/588/2019 (H1N1) • A/Tasmania/503/2020 (an A/Cambodia/e0826360/2020-like virus) (H3N2) • B/Washington/02/2019 • B/Phuket/3073/2013	Inactivated viral preparations containing 15 µg of HA of each of the following strains* per dose: • A/Victoria/2570/2019 (H1N1) IVR-215 • A/Tasmania/503/2020 (H3N2) IVR-221 [an A/Cambodia/e0826360/2020 (H3N2)-like virus]) • B/Washington/02/2019 • B/Phuket/3073/2013
Excipients/Diluent	Each 0.5 mL dose of RIV4 will contain: Sodium chloride 4.4 mg Monobasic sodium phosphate 0.195 mg Dibasic sodium phosphate 1.3 mg Polysorbate 20 (Tween® 20) 27.5 µg Octylphenol ethoxylate (Triton X-100®) ≤ 100 µg	Each 0.5 mL dose of IIV4 will contain: Octylphenol-10 (Triton X-100) ≤ 0.115 mg α-Tocopheryl hydrogen succinate ≤ 0.135 mg Polysorbate 80 (Tween 80) ≤ 0.550 mg

	Preservative is not used in the manufacture or formulation of RIV4	Preservative is not used in the manufacture or formulation of IIV4
Dosage Level	0.5 mL per dose	0.5 mL per dose
Number of Doses/ Dosing Interval	1 dose per participant	1 dose per participant
Route of Administration	IM injection	IM injection
Site of Administration	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each study intervention will be provided in an individual box. Each study intervention (pre-filled syringe) will bear 1 fixed label and each box will bear detachable labels and 1 fixed label containing the dose number. All will be labeled as required per country requirement.	
Current/Former Name(s) or Alias(es)	NA	NA
Batch Number	TBD	TBD
Storage Conditions	2-8°C	2-8°C

Abbreviations: IMP, Investigational Medicinal Product; NIMP, Non-Investigational Medicinal Product; TBD, to be determined; NA, not applicable; HA, hemagglutinin; IM, intramuscular
* Strains based on WHO recommendations for the 2021-2022 NH influenza season

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

In each age group (18-49 years of age and ≥ 50 years of age), eligible participants will be randomized in a 1:1 ratio through the Interactive Response Technology (IRT) to receive a single IM injection of either RIV4 or IIV4 at D01.

Site staff will connect to the IRT, enter the identification, security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the dose number assignment and the site staff confirm it. The full detailed procedures for dose number allocation are described in the Operating Guidelines. 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 consisting of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier).

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT system.

6.3.2 Blinding and Code-breaking Procedures

The study will be performed in a modified double-blind fashion:

- Participant, Investigators/sub-investigator/staff involved in the sampling, the immunogenicity assays and safety assessment will not know which vaccine is administered.
- Only the study site staff who prepare and administer the vaccine and are not involved with the safety evaluation will know which vaccine is administered

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the participant. Code-breaking should be limited to the participant(s) experiencing the AE.

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur Responsible Medical Officer if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking CRF is to be completed.

The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

A request for the code to be broken may also be made by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related, as described in International Council for

Harmonization (ICH) E2A[a]. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

The code-breaking procedures are described in the Operating Guidelines.

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

6.5 Concomitant Therapy

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

All medications will be reportable and will be collected in the CRF until last contact date of the participant.

Dosage, administration route and indication will be collected in the e-CRF.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF. Medications will not be coded.

6.5.1 Rescue Medicine

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

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Not applicable.

[a] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

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, compliance, or administrative reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: AE, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant.
- 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 samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn participants may 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 the 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), or at least to determine his/her health status while fully respecting his/her rights. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of the 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), 10 mL of blood 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.

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

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).

All methods will be performed at a Sanofi Pasteur laboratory or at a qualified contract laboratory under Sanofi Pasteur's responsibility, as described below. Test serum samples and quality control sera (sheep, ferret, and / or human sera) are incubated with Sigma Type III neuraminidase (NA) from *Vibrio cholerae* to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins are then performed by incubating the test serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures are centrifuged and the supernatants containing the treated sera are collected for testing. Ten 2-fold dilutions (starting at 1:10) of the treated test serum samples and quality control sera are incubated with a previously titrated influenza antigen at a concentration of 4 hemagglutination units (HAU) / 25 µL. Influenza antigen is not added to the serum control wells containing only serum and RBCs. The mixture is then incubated and a RBC suspension is added. Following incubation, the results are read. The

endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample can either be tested in singleton (ie, one assay run) or in 2 independent assay runs (duplicate) which will include 2 independent samplings of the original serum and 2 independent preparations of influenza virus antigen. The lower limit of quantitation (LLOQ) is set at the lowest dilution used in the assay, 1:10. Titers below this level are reported as < 10 (1/dilution [dil]). If the highest / last serum dilution used in the assay exhibited complete inhibition of hemagglutination, the serum Ab titer is reported as ≥ 10 240 (1/dil).

8.2 Safety Assessments

This section presents safety assessments other than AEs which are presented in Section 8.2.5.

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. The history of seasonal influenza vaccination will be collected in the CRF.

8.2.2 Physical Examinations

Targeted physical examination based on medical history will be performed at Visit 1. Targeted physical examination may also be performed at Visit 2, as necessary. Information will be recorded in the source document.

8.2.3 Vital Signs

Pre-vaccination temperature (axillary) will be systematically collected by the Investigator on the source document. Tympanic, skin and temporal artery thermometers must not be used.

8.2.4 Clinical Safety Laboratory Assessments

Not applicable.

8.2.5 Viremia/Vaccinemia

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants 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).

8.3.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events 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 D01 to D08 after vaccination.

Solicited systemic reactions will be collected from D01 to D08 after vaccination.

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards (DCs) and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious AEs will be collected from D01 to D29 after vaccination.

The intensity grading scale for unsolicited non-serious AEs is presented in Appendix 10.3.5.1.2.

Adverse Events of Special Interest

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.

Serious Adverse Events

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be recorded on the AE section of the CRF.

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 10.3. 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 AE or SAE 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 Adverse Events and Serious Adverse Events

Individual DCs, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These DCs 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 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 on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. Any information that was not documented in the DC will first be captured in the source document and then reported electronically.

The 6-month follow-up will be done by interviewing participants over the telephone. During this call the staff will review the MA with the participant and determine whether the participant experienced any SAE or AESI not yet reported.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

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 Adverse Events and Serious Adverse Events

Unless a participant refuses further contact, each participant who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the participant's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the study intervention administered
- The AE caused the discontinuation of the participant from the study or from vaccination

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- 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, IRB/IEC, and Investigators.

- For all studies except those investigating medical devices, Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an 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.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery by the Investigator and recorded in the Pregnancy CRF. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 1 month of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

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

8.4 Treatment of Overdose

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

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

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for any AE/SAE.
3) Document the quantity of the excess of the overdose in the source documents.

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study.

8.9 Immunogenicity Assessments

See Section 8.1.2.

8.10 Medical Resource Utilization and Health Economics

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

9 Statistical Considerations

9.1 Statistical Hypotheses

No hypotheses will be tested. The analyses will be descriptive.

9.2 Sample Size Determination

A total of approximately 300 participants will be enrolled as follows:

- 75 participants from 18 to 49 years of age in RIV4 group
- 75 participants ≥ 50 years of age in RIV4 group
- 75 participants 18 to 49 years of age in IIV4 group
- 75 participants ≥ 50 years of age in IIV4 group

Assuming a drop-out rate of 5%, a total of 71 evaluable participants per group of age and vaccine is anticipated.
No formal power calculation has been performed but based on the planned sample size the estimation precision is provided as follows. For proportions, the expected precision of estimation (using PASS14) is: 71 participants per treatment group provide a maximum width of 95% confidence interval (CI) of 24.2% for single proportions and a maximum width of 95% CI of 32.0% for differences between proportions (when the group proportions are 50%). For quantitative data, the distance from the mean to the limits of 95% CI is equal to 0.154 for single mean and 0.216 for difference in means (when the estimated standard deviation is 0.65).

In case of any unexpected situations where this planned number is not reached (due to an unexpected high number of withdrawals or unevaluable data) then additional participants might be recruited before database lock to achieve that planned sample size. Such assessment and decision will be performed in a blind manner during the course of the trial before database lock or any statistical analysis.

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Safety Analysis Set (SafAS)	Participants who have received a 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 randomized participants who received a dose of the study vaccine and had a post-vaccination blood sample. Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following conditions 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 • Participant received a vaccine other than the one that he/she was randomized to receive • Preparation and/or administration of vaccine was not done as per-protocol • Participant did not receive vaccine in the proper time window • Participant did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn • Participant received a protocol-prohibited therapy/medication/vaccine

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.

The endpoints for immunogenicity and safety are shown in Table 3.1.

9.4.1 General Considerations

All analyses will be descriptive and be provided by age groups and overall. No replacement will be done for safety and immunogenicity missing data and outliers. Analysis will be done using the collected values. Nevertheless, for unsolicited systemic AEs, missing relationship will be

considered as related to study vaccine(s) at the time of analysis. Details will be provided in the SAP.

9.4.2 Immunogenicity

Descriptive analyses on HAI Ab response measured at D01 and D29 will be performed in each age, intervention group and pooled age group, including but will not be limited to:

- Geometric mean of HAI Ab titer (GMT) and 95% CI at D01 and D29
- Geometric mean fold-rise (GMFR) of HAI Ab titer and 95%CI. Fold-rise is computed as individual titer ratio of post-vaccination value divided by baseline value.
- Number and percentage of participants with seroconversion (seroconversion rate): titer < 10 (1/dilution [1/dil]) at D01 and post-injection titer ≥ 40 (1/dil) at D29, or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold increase in titer (1/dil) at D29
- Number and percentage of participants with titer ≥ 40 (1/dil) at D01 and D29
- Number and percentage of participants with detectable titer ≥ 10 (1/dil) at D01 and D29

The 95% CIs for the GMTs and GMT ratios (GMTRs) will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of GMTs (RIV4/IIV4) in each age group will be obtained between groups with the 95% CIs calculated using a normal approximation of log-transformed titers. The differences in the seroconversion rates between groups in each age group will be computed along with the 2-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

In addition, as a complementary analysis to support bridging discussion, Bayesian method will be used to evaluate the probability of non-inferiority in GMTs. The posterior probability of the true ratio of GMTs (RIV4/IIV4) to be higher than the commonly accepted non-inferiority margin (0.667) will be calculated using the Bayesian approach to support bridging with previous non-inferiority trials. Further details about the statistical methodology will be provided in the SAP.

Reverse cumulative distribution curves in each age group against each strain will be performed for baseline (D01) and post-vaccination immunogenicity (D29).

The Full Analysis Set (FAS) and Per-Protocol Analysis Set (PPAS) will be used for the main immunogenicity analyses. Details of both analyses' sets are described in Section 9.3.

9.4.3 Safety

Safety endpoints will be analyzed descriptively for participants in the safety analysis set (SafAS). The following safety parameters will be described by the 95% CI based on the Clopper-Pearson method in each age, intervention group and pooled age group. Additional parameters may be displayed as appropriate. The current MedDRA version will be used for the coding of all AEs/reactions.

Solicited Reactions

Number and percentage of participants with:

- Presence of solicited injection site reactions and systemic reactions occurring up to 7 days after injection
- Each solicited reaction according to time of onset, maximum intensity, and number of days of occurrence and action taken

Unsolicited Events and Reactions

Number and percentage of participants with:

- Any unsolicited immediate systemic event in the 30 minutes after injection according to System Organ Classes (SOC) and Preferred Terms (PT)
- Any unsolicited event and reaction 28 days after injection according to SOC and PT
- Any unsolicited event/reaction according to time of onset, maximum intensity, and duration

SAEs

Number and percentage of participants with:

- Any SAE within 28 days after injection and throughout the entire study according to SOC and PT, seriousness and outcome

AESIs

- Number and percentage of participants with:
- Any AESI within 28 days after injection and throughout the entire study according to SOC and PT, seriousness and outcome

9.5 Interim Analyses

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

9.6 Data Monitoring Committee

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 requirements.

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 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, protocol amendments, Assent Form, 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.
- 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), and all other applicable local regulations.

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants 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 requirements, where applicable, and the IRB/IEC or study center.
- 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 Assent Form and/or ICF.
- The actual Assent Form and ICF used at each center may differ, depending on local regulations and IRB/IEC requirements. However, all versions must contain the standard information found in the sample Assent Form and ICF provided by the Sponsor. Any change to the content of the Assent Form and/or ICF must be approved by the Sponsor and the IRB/IEC prior to the form being used.
- If new information becomes available that may be relevant to the participant's 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 Assent Form and/or ICF or an addendum to the original Assent Form and ICF.
- Participants must be re-consented to the most current version of the Assent Form(s) and/or ICF(s) during their participation in the study.
- A copy of the Assent Form(s) and/or ICF(s) must be provided to the participant or the participant's legally authorized representative.

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.

10.1.4 Data Protection and Future Use of Stored Samples

- All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR. 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 will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; 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 local 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.
- 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.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.
- Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) up to 25 years after the end of the study. These 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.
  The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they 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.
  In addition, participants will be asked to indicate in the Assent Form and/or ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent

10.1.5 Committees Structure

There will be no Data Monitoring Committee.

10.1.6 Dissemination of Clinical Study Data

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.

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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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 non-compliance 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 [CROs]).
- 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.

- Records and documents, including signed Assent Forms and 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, Assent Forms, ICFs, 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.

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 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 Site Close Out Form submitted to the IRB, as required.

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:

- 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 recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(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: Clinical Laboratory Tests

Not applicable.

10.3 Appendix: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient or 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 Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, 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 drug-drug 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 Adverse Event 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:

All noxious and unintended responses to a study intervention related to any dose should be considered ARs.

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

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the study intervention administered) that occur within the first 30 minutes after vaccination.

Injection Site Reaction/Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site. Injection/administration site reactions are commonly inflammatory reactions. They are considered to be related to the study intervention administered.

Systemic Adverse Event/Adverse Reaction:

Systemic AEs are all AEs 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 vaccination or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Systemic AEs assessed as related to study intervention are referred as systemic ARs.

Adverse Event of Special Interest:

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

Reactogenicity/Solicited Reactions:

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

By definition, solicited reactions are considered as being related to the study intervention administered.

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

Unsolicited Adverse Event/Adverse Reaction:

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/or onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (headache starting on D10 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 study intervention. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

10.3.2 Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event is defined as any untoward medical occurrence 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 detained (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 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. Other important medical event • Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the 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 are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, new onset diabetes or autoimmune disease

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.

10.3.3 Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event 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 in the CRF
- 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 (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the study intervention (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. 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[a] 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 an 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 is evidence or arguments to suggest a causal relationship
- The Investigator will use clinical judgment to determine the relationship

[a] Study intervention administered can correspond to either the investigational product or other products when no investigational product is administered at the visit

- 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 make 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 Adverse Events and Serious Adverse Events

- 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 completed CRF
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information
- AEs likely to be related to the study intervention, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment

10.3.4 Reporting of Serious Adverse Events

Serious Adverse Event 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) in order 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

Serious Adverse Event Reporting to the Sponsor via Paper Case Report Form

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

10.3.5 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".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited Adverse Reaction Intensity Grading Scale

Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising	Injection site tenderness
MedDRA preferred	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising	Tenderness
Diary card term	Pain	Redness	Swelling	Hardening/Firmness	Bruising	Tenderness
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.	Discomfort elicited through touch or pressure

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising	Injection site tenderness
Intensity scale*	Grade 1: A type of adverse event (AE) 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 AE 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 AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	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: ≥ 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: A type of AE 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 AE 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 AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Table 10.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Shivering**	**Fatigue**	**Nausea**	**Arthralgia**
MedDRA preferred term [PT]	Pyrexia	Headache	Malaise	Myalgia	Chills	Fatigue	Nausea	Arthralgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills	Fatigue	Nausea	Joint Pain
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 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	Overall tiredness and lack of energy	Upper abdominal discomfort associated with an urge to vomit	Pain in a joint or joints

CRB term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Shivering**	**Fatigue**	**Nausea**	**Arthralgia**
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event (AE) 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 1: A type of AE 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 1: A type of AE 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 1: A type of AE 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 1: A type of AE 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 1: A type of AE 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 1: A type of AE 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.

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Shivering	Fatigue	Nausea	Arthralgia
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of AE 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 AE 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 AE 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 AE 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 AE 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 AE 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 AE 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.

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Shivering	Fatigue	Nausea	Arthralgia
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

* For all reactions but fever, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important Notes for the Accurate Assessment of Temperature:

Participants 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, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is axillary.

10.3.5.1.2 Unsolicited Adverse Event 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 10.3.5.1.1).

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

- Grade 1
  - CRF: A type of AE 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 usual activities
- Grade 2
  - CRF: A type of AE 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 usual activities
- Grade 3
  - CRF: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention
  - DC: Significant; prevents usual activities

10.4 Appendix: Collection of Pregnancy Information

DEFINITIONS:

Women of Childbearing Potential
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 Women of Childbearing Potential

1) Premenarchal
2) Premenopausal female with one 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 1 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.

COLLECTION OF PREGNANCY INFORMATION

Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information together with the contraceptive method if any will be recorded on the appropriate form and submitted to the Sponsor within 1 month of learning of a participant's pregnancy. If the Electronic DC (EDC) system is not available, the Investigator must fill out a paper Pregnancy Reporting Form (provided by the Sponsor at the start of the study) and inform the Sponsor within 1 month of identifying a pregnancy case.
- The participant will be followed to determine the outcome of the pregnancy. Study staff must maintain contact with the participant to obtain information about the outcome (ie, details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery by Investigator.
- For live births, an additional follow-up will be conducted 6 months after the delivery date to determine if any congenital anomalies in the infant not detected at birth have been diagnosed. An Infant Data Collection Form will be used for this purpose. Up to 3 follow-up attempts will be conducted with the child's physician or hospital (in cases of adverse outcome involving hospitalization). Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- 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.

- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- 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.

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 (IUD)
• Intrauterine hormone-releasing system (IUS) [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)[c]

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 (LAM) are not acceptable methods of contraception.

e) Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 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

1/dil	1/dilution
Ab	Antibody
AcNPV	*Autographa californica* nuclear polyhedrosis virus
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
BL	Blood sampling
CI	Confidence interval
CRF	Case report form
CRO	Contract Research Organization
D	Day
DC	Diary card
DNA	Deoxyribonucleic acid
FAS	Full analysis set
FSH	Follicle stimulating hormone
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	Geometric mean titer
GMTR	Geometric mean titer ratio
GPV	Global Pharmacovigilance
HA	Hemagglutinin
HAI	Hemagglutination inhibition
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IIV4	Quadrivalent-inactivated influenza vaccine
IM	Intramuscular
IMP	Investigational Medicinal Product

IRB	Institutional Review Board
IRT	Interactive response technology
KCDC	Korea Centers for Disease Control & Prevention
LLT	Lowest level term
MA	Memory aid
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NH	Northern Hemisphere
NIMP	Non- Investigational Medicinal Product
NIP	National Immunization Program
PC	Phone call
PPAS	Per-protocol analysis set
PT	Preferred term
PY	Person Year
QIV	Quadrivalent influenza vaccine
rHA	Recombinant hemagglutinin
RIV4	Recombinant Influenza Vaccine, Quadrivalent
SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SH	Southern Hemisphere
SoA	Schedule of Activities
SOC	System Organ Classes
TBD	To be determined
TIV	Trivalent influenza vaccine
US	United States
USPI	US Prescribing Information
V	Visit
WHO	World Health Organization

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