NCT04969276

Title Page

Protocol Title:

A Phase II, open-label study to assess the safety and immunogenicity of Fluzone® High-Dose Quadrivalent (Influenza vaccine), 2021–2022 Formulation and a third dose of Moderna COVID-19 Vaccine (mRNA-1273 vaccine) administered either concomitantly or singly in adults 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 Vaccine

Study Code: QHD00028

Amendment Number: Amendment 2

Compounds: Fluzone® High-Dose Quadrivalent (Influenza inactivated vaccine) (2021–2022 Formulation)

Moderna COVID-19 Vaccine (mRNA-1273 vaccine)

Brief Title:

Study of a Quadrivalent High-Dose Influenza Vaccine and a Moderna COVID-19 Vaccine administered either concomitantly or singly in participants 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 Vaccine

Study Phase: II

Sponsor Name and Legal Registered Address:

Sanofi Pasteur
14 Espace Henry Vallée, 69007 Lyon, France

Manufacturers:

Fluzone High-Dose Quadrivalent (Influenza inactivated vaccine)

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

COVID-19 mRNA Vaccine

Moderna US, Inc.
200 Technology Sq, Cambridge, MA 02139

Regulatory Agency Identifier Number(s):

BB-IND: IND 017556

WHO UTN: U1111-1266-7472

Protocol Version Number: 4.0

Approval Date: 19 July 2021

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

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

Document History

Previous Version	Date	Comments
1.0	10 June 2021	Version not approved by the IEC/IRB
2.0	**22 June 2021**	**IEC/IRB-approved version not used in the study**
3.0	**01 July 2021**	**First version used in the study**

* Versions in bold font have been approved by the IEC(s) / IRB(s) and used in the study.

Overall Rationale for the Amendment:

The main reason for updating protocol version 3.0 (Amendment 1) to protocol version 4.0 (Amendment 2) was to add a 6-month safety follow-up phone call for all participants.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase II, open-label study to assess the safety and immunogenicity of Fluzone® High-Dose Quadrivalent (Influenza vaccine), 2021–2022 Formulation and a third dose of Moderna COVID-19 Vaccine (mRNA-1273 vaccine) administered either concomitantly or singly in adults 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 Vaccine

Brief Title:

Study of a Quadrivalent High-Dose Influenza Vaccine and a Moderna COVID-19 Vaccine administered either concomitantly or singly in participants 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 Vaccine

Rationale:

This study will evaluate the safety and immunogenicity of Fluzone High-Dose Quadrivalent vaccine and of a third or "booster" dose of Moderna COVID-19 Vaccine administered concomitantly or singly in different treatment groups. Participants in this study will be 65 years of age and older and will have received their second dose of the 2-dose schedule of Moderna COVID-19 Vaccine at least 5 months before enrollment in the study.

The concomitant administration of Fluzone High-Dose Quadrivalent vaccine with a booster dose of Moderna COVID-19 Vaccine has the potential to ease the implementation of national immunization programs both by shortening the overall period during which vaccination takes place and by reducing the number of visits to health care providers.

Objectives and Endpoints:

Objectives	Endpoints
Safety Objective	
• To describe the safety profile of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine administered concomitantly or singly, up to 21 days after injection in each study intervention group.	• Presence of immediate unsolicited systemic adverse events (AEs) reported in the 30 minutes after injection • Presence of solicited (pre-listed in the participant's diary card [DC] and CRF) injection site reactions and systemic reactions occurring up to 7 days after injection • Presence of unsolicited AEs reported up to 21 days after injection • Presence of serious adverse events (SAEs) reported up to 6 months after injection • Presence of adverse events of special interest (AESIs) reported up to 6 months after injection

Objectives	Endpoints
	• Presence of medically-attended AEs (MAAEs) reported up to 6 months after injection
Immunogenicity Objectives	
1) To describe the immune response elicited by Fluzone High-Dose Quadrivalent vaccine administered concomitantly or singly, in each study intervention group.	Endpoints for Immunogenicity Objective #1 • Hemagglutination inhibition (HAI) individual titer on Day (D) 01 and 21 days after injection of Fluzone High-Dose Quadrivalent vaccine (D22) • Individual HAI titers ratio D22/D01 • Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 21 days after injection of Fluzone High-Dose Quadrivalent (D22) • Seroconversion (titer < 10 [1/dil] at D01 and post-vaccination titer ≥ 40 [1/dil] at D22, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D22) • HAI titer ≥ 40 (1/dil) on D01 and 21 days after injection of Fluzone High-Dose Quadrivalent (D22)
2) To describe the immune response elicited by Moderna COVID-19 Vaccine administered concomitantly or singly, in each study intervention group.	Endpoints for Immunogenicity Objective #2 • Individual anti-S binding IgG concentration on D01 and 21 days after injection of Moderna COVID-19 Vaccine (D22) • Individual anti-S binding IgG concentration ratio D22/D01 • 2-fold-rise and 4-fold-rise in anti-S binding IgG concentration 21 days post-injection D01

Overall Design

Type of design	3-arm study with either concomitant or single administration of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine
Phase	II
Control method	Active-controlled (single administration versus coadministration)
Study population	Healthy adults 65 years of age and older
Countries	United States
Level and method of blinding	Open-label
Study intervention assignment method	Randomization

Brief Summary:

The main purpose of this Phase II study is to assess the safety and immunogenicity of a dose of Fluzone High-Dose Quadrivalent vaccine and a third dose or booster dose of Moderna COVID-19 Vaccine administered concomitantly or singly in adults 65 years of age and older having received their second dose of the 2-dose schedule of Moderna COVID-19 Vaccine at least 5 months before enrollment in the study.

Study Duration: 6 months (approximately 180 days)

Visit Frequency: 2 visits (ie, a visit on D01 and D22) and 2 telephone contacts (ie, on D08 and D181)

Condition/Diseases: influenza, COVID-19 disease

Study Hypothesis:

This will be a descriptive study. No hypothesis will be tested.

Health Measurement/Observation:

The study will assess whether the concomitant administrations of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine is safe, well tolerated, and immunogenic.

Number of Participants:

A total of 300 participants (approximately 100 participants in each arm) are planned to be enrolled.

Intervention Groups and Duration:

Eligible participants will be randomized in a 1:1:1 ratio corresponding to *i)* concomitant administration of Fluzone High-Dose Quadrivalent and COVID-19 mRNA Vaccine, *ii)* administration of Fluzone High-Dose Quadrivalent alone, and *iii)* administration of COVID-19 mRNA Vaccine alone.

Participants will be in the Active Phase from enrollment (Day 1 [D01]) until completion of Visit 2 (V02) and in the 6-Month Safety Follow-Up from completion of V02 until approximately 6 months after V01. Participants will thus be in the study for approximately 180 days.

Study intervention(s)

Investigational medicinal product 1: Fluzone High-Dose Quadrivalent vaccine (0.7 mL dose), 2021–2022 formulation for the Northern Hemisphere (NH) influenza season.

- Form: Sterile suspension for injection in a pre-filled syringe
- Composition: 60 mcg of HA of each of the following strains:
  - A/Victoria/2570/2019 IVR-215 (H1N1)
  - A/Tasmania/503/2020 IVR-221 (an A/Cambodia/e0826360/2020-like virus) (H3N2)
  - B/Phuket/3073/2013 (B Yamagata lineage)

- B/Washington/02/2019 (B Victoria lineage)

- Route of administration: intramuscular (IM)

Investigational medicinal product 2: Moderna COVID-19 Vaccine (mRNA-1273 vaccine)

- Form: Sterile suspension (white to off-white) in multidose vial
- Composition: 100 mcg of mRNA (formulated in SM-102 lipid nanoparticles)
- Route of administration: IM

Statistical Considerations:

Analyses of Study Objectives will be descriptive. Endpoints will be summarized and for the main parameters; 95% CIs for the point estimates will be calculated using the normal approximation after log transformation for quantitative data (eg. GMTs and GM of individual ratios) and exact binomial distribution (Clopper-Pearson method, quoted by Newcombe) for single proportions.

Safety Objective

For safety analyses the safety analysis set (SafAS) will be used. Results will be presented by actual study group and vaccine received.

Immunogenicity Objectives

For immunogenicity analyses the Immunogenicity analysis set (IAS) will be used. Results will be presented for each timepoint by actual study group and vaccine received.

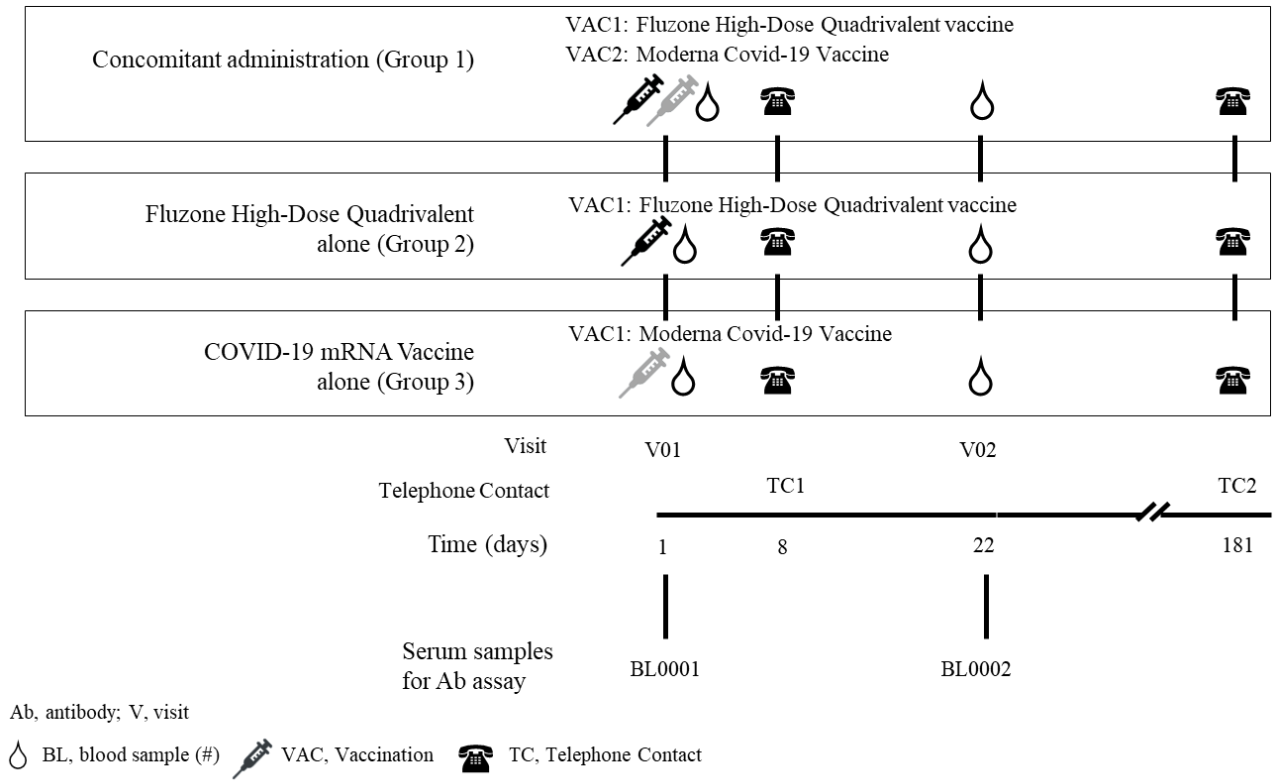
In addition, the ratios of post-vaccination GMTs between concomitant and single injections will be presented for the five antigens with 2-sided 95% CIs.

Data Monitoring/Other Committee: No

1.2 Schema

The graphical design of QHD00028 study is presented in Figure 1.1.

Figure 1.1 – Graphical study design



1.3 Schedule of Activities (SoA)

The study Schedule of Activities (SoA) for all 3 treatment groups is presented in Table 1.1.

Visit procedures are detailed in the Operating Guidelines.

Table 1.1: Schedule of activities

Phase II Study, 2 Visits, 2 Telephone Contacts, either 1 or 2 Vaccination, 2 Blood Samples, 180 Days' Duration Per Participant

Visit (V) / Telephone Contact (TC)	***Collection of information in the CRF***	**V01**	**TC1**	**V02**	**TC2 6-Month Safety Follow-up**
Study timelines (days [D])		D01	D08	D22	D181
Time interval (days)			V01 + 7 days	V01 + 21 days	V01 + 180 days
Time windows (days)			[+2 days]	[+3 days]	[+14 days]
Visit procedures:					
Informed consent	*X*	X			
Inclusion/exclusion criteria	*X*	X			
Collection of demographic data	*X*	X			
Collection of medical history *	*X* Significant Medical History	X			
History of seasonal influenza and COVID-19 vaccination	*X*	X			
Physical examination †		X			
Pre-vaccination temperature		X			
Randomization / Allocation of participant number	*X*	X			
Blood samples (BL) for Ab assays (20 mL) ‡	*X*	BL0001		BL0002	
Vaccination (VAC)	*X*	VAC1 (all groups) VAC2 (Group 1)			
Immediate surveillance (30 min)	*X*	X			
Diary card (DC) provided		DC1§			
DC reviewed			DC1**		
DC collected				DC1††	
Memory Aid (MA) provided				X	
MA reviewed					X
Collection of solicited injection site and systemic reactions	*X*	Up to 7 days after vaccination			
Collection of unsolicited AEs	*X*	Up to 21 days after vaccination			
Collection of concomitant medications	*X* Reportable concomitant medication	X		X	
Telephone contact			X		X‡‡
Collection of SAEs, AESIs, and MAAEs §§	*X*	To be reported at any time during the study			
End of Active Phase participation record ***	*X*			X	
End of 6-month safety follow-up ***					X

Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, case report form; D, Day; DC, diary card; SAE, serious adverse event; ; MAAE, medically-attended adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V, Visit; VAC, Vaccination; MA, Memory Aid.

* Including history of COVID-19 infection.

† Targeted physical examination will be performed at V01. If needed, targeted physical examination based on medical history and Investigator's discretion might be performed at the other vaccination visit(s).

‡ BL0001 must be collected before vaccine injection. Participants that consent to Future Research by ticking the corresponding box in the ICF will provide a 20 mL of blood instead of 10 mL for each BL0001 and BL0002.

§ Participants will use DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to D22.

** The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

†† The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC1 and will attempt to clarify anything that is incomplete or unclear.

‡‡ During this call the staff will review the MA with the subject and determine whether the subject experienced any SAE, AESI or MAAEs not yet reported.

§§ AESIs (serious and non-serious) will be collected throughout the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causal relationship. Full list of AESIs is available in Section 8.3.6.

*** Participants will be in the Active Phase from enrollment (D01) until completion of V02 and in the 6-Month Safety Follow-Up from completion of V02 until approximately 6 months after V01.

2 Introduction

Fluzone® High-Dose Quadrivalent *(Influenza Vaccine)*

Fluzone High-Dose Quadrivalent vaccine is an inactivated influenza vaccine containing 60 mcg of hemagglutinin (HA) of each of the A strains (A/H1N1 and A/H3N2) and of each of the B strains (from the Victoria lineage and from the Yamagata lineage), in compliance with the seasonal influenza World Health Organization (WHO). A recent systematic review and meta-analysis, including over 34 million participants and over 10 influenza seasons, showed that irrespective of circulating strain and antigenic match, the high-dose inactivated trivalent influenza vaccine is more effective than standard-dose vaccine in preventing both influenza-like illness and influenza-related hospitalizations in both controlled and real-world conditions (1). Fluzone High-Dose Quadrivalent vaccine is indicated for active immunization for the prevention of influenza in persons 65 years of age and older.

Moderna COVID-19 Vaccine (mRNA-1273 vaccine)

An outbreak of severe respiratory illnesses in Wuhan City, Hubei Province, China in December 2019 heralded the appearance of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in the human population. The rapid escalation of the outbreak led to a declaration by the WHO on 20 January 2020 of a Public Health Emergency of International Concern, followed by the declaration on 11 March 2020 of a pandemic (2). As of 21 June 2021, the virus has infected over 178 million individuals (3). A number of vaccine candidates are in clinical development including messenger RNA (mRNA) encoding the Spike (S) protein of SARS-CoV-2 that induce neutralizing antibodies.

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines may be given to people who cannot be administered live virus. At this stage of its characterization, there is a positive benefit/risk in administering the vaccine during pregnancy. RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Moderna COVID-19 Vaccine is a lipid-nanoparticle (LNP) –encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein, that was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), within the National Institutes of Health (NIH) (4). Emergency authorization or other forms of regulatory approval have been granted in multiple countries for this vaccine.

Under the current Emergency Use Authorization, Moderna COVID-19 Vaccine is currently used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The clinical efficacy of Moderna COVID–19 Vaccine is based on an ongoing Phase III randomized, placebo-controlled, observer-blind clinical trial conducted in adults aged 18 years and older. Vaccine efficacy of 94.1% (95% confidence interval of 89.3% to 96.8%) was

demonstrated with a median length of follow up for efficacy for participants in the study of 9 weeks post Dose 2 (5).

The safety Moderna COVID-19 Vaccine was evaluated in an ongoing Phase III involving 30 351 participants who received at least one dose of Moderna COVID-19 Vaccine or placebo. Overall, the vaccine was well tolerated. Moderate, transient reactogenicity after vaccination occurred more frequently in the Moderna COVID-19 Vaccine group. Serious adverse events were rare and incidence was similar in the two groups (5). Moderna COVID-19 Vaccine has been registered in multiple countries and has been administered to millions of vaccine recipients.

In May 2020, Moderna initiated a 3-part Phase IIa study in which 60 participants having previously received a 2-dose schedule of Moderna COVID-19 Vaccine (either 50 mcg or 100 mcg of mRNA-1273) received a 20 mcg of mRNA-1273.351 booster dose, a 50 mcg of mRNA-1273.351 booster dose, or a 50 mcg of mRNA-1273/mRNA-1273.351 mixture booster dose are evaluated (6). In May 2021, Moderna reported initial data demonstrating that a single booster dose of its COVID-19 vaccines, mRNA-1273 or mRNA-1273.351, enhanced neutralizing antibody (Ab) titer responses in previously vaccinated people (7).

2.1 Study Rationale

This study will evaluate the safety and immunogenicity of Fluzone High-Dose Quadrivalent vaccine and of a third or "booster" dose of Moderna COVID-19 Vaccine administered concomitantly or singly in different treatment groups. Participants in this study will be 65 years of age and older and will have received their second dose of the 2-dose schedule of Moderna COVID-19 Vaccine at least 5 months before enrollment in the study.

The concomitant administration of Fluzone High-Dose Quadrivalent vaccine with a dose of Moderna COVID-19 Vaccine has the potential to ease the implementation of national immunization programs both by shortening the overall period during which vaccination takes place and by reducing the number of visits to health care providers.

2.2 Background

Influenza disease

Influenza is a contagious, acute virus respiratory disease. It is typically characterized by the rapid onset of fever, myalgia, sore throat, and non-productive cough. Influenza can cause severe malaise, which lasts for several days. While influenza affects all age groups, the very young, older adults, and persons with underlying health problems are at increased risk for complications. Members of high-risk groups who become ill with influenza are more likely than the general population to require hospitalizations (8).

Influenza in humans can be caused by influenza type A and type B viruses belonging to the genus Orthomyxoviridae and characterized as enveloped, negative strand, segmented ribonucleic acid viruses. The virus envelope contains 2 virus-coded glycoprotein spikes, the HA and neuraminidase proteins, key antigens in the host response to influenza virus in both natural infection and vaccination.

Although influenza A accounts for the majority of circulating viruses in most countries and seasons, influenza B circulates every year, late in the season in comparison to influenza A viruses, and accounts for 20% of all influenza isolates worldwide since 2000 (9). In general, the burden of disease from influenza B is less than that from A/H3N2 but greater than A/H1N1 (10).

Vaccination with influenza vaccine is the primary method for preventing influenza and its severe complications. It has been shown to be effective in reducing influenza-associated morbidity and mortality in groups at increased risk for influenza-related complications such as infants and young children and persons 50 years of age and older. Of note, immune responses to the vaccine are lower in seniors than those in young healthy adults (11). Strategies to improve immune responses to the vaccine in the elderly population could provide substantial additional reductions in influenza-associated morbidity and mortality. One approach is to increase the dose of HA in inactivated vaccines. Previous studies evaluating the immune responses in terms of hemagglutination inhibition (HAI) antibodies with higher doses of HA per strain in different influenza vaccines support a dose-response effect (12).

Fluzone High-Dose Quadrivalent vaccine was developed for use in the elderly against influenza through the use of higher antigen content, with the goal of providing older adults with improved protection against the disease.

Fluzone High-Dose Quadrivalent vaccine belongs to the pharmacotherapeutic group of viral influenza vaccines. A detailed description of the chemistry, pharmacology, efficacy, and safety of Fluzone High-Dose Quadrivalent vaccine is provided in the prescribing information (13).

COVID-19 disease

SARS-CoV-2 is a novel coronavirus that emerged in the human population and has led to a pandemic of acute respiratory disease named COVID-19. The clinical profile of COVID-19, the illness caused by SARS-CoV-2, is variable (14). In the majority of cases, the manifestations are mild, or individuals may be asymptomatic (15). Among those with symptoms, typical presentations include fever, cough, and shortness of breath. More severe manifestations include acute hypoxemic respiratory failure requiring intubation and mechanical ventilation, in some cases resulting in death. While mostly self-limited, symptoms such as fatigue and dyspnea appear to persist for up to 2 months after illness onset despite viral clearance (16). Based on early data, adults over 50 years of age and individuals with chronic medical conditions are at a higher risk of severe outcomes and death (15) (17).

The burden of SARS-CoV-2 morbidity and mortality has been catastrophic with greater than 3.8 million deaths recorded since first emerging in December 2019 among over 178 million confirmed cases (as of 21 June 2021) (3). In many locations, the rapid emergence of COVID-19 has overwhelmed the capacity of health systems to provide care for COVID-19-affected patients, let alone unaffected patients. Interventions to reduce transmission through reduction of population contact (also called social distancing) has had profound economic consequences. Safe and effective vaccines with sufficient doses would be vital to address the significant medical and societal burden caused by the pandemic.

Moderna COVID-19 Vaccine belongs to the pharmacotherapeutic group of “other viral vaccines”.

The vaccine contains single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike protein of SARS-CoV-2.

A detailed description of the chemistry, pharmacology, efficacy, and safety of Moderna COVID-19 Vaccine is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events, the potential risks, and uncertainties of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine (in its 2-dose schedule) may be found in the US Prescribing Information and in the Investigator's Brochure, respectively.

2.3.1 Risks from Study Participation

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

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: Fluzone High-Dose Quadrivalent vaccine		
Refer to the package insert for more information regarding potential risks	Identified and potential risks observed in clinical trials and/or post-marketing surveillance.	Exclusion/inclusion criteria take into account contraindications, warnings and precautions as defined in product label.
Injection site reactions	Most common injection site reactions in adults ≥ 65 years of age: pain Injection site reactions are generally mild and usually resolve within 3 days. A Phase III study performed in persons ≥ 65 years of age demonstrated increased rates of solicited injection site reactions in participants receiving Fluzone High-Dose vaccine compared to persons receiving Fluzone vaccine but were typically mild and transient (18).	During the informed consent process, the participants enrolling in the study will be informed of these potential reactions, the need to attend the clinic if they are unwell, and the possibility to take analgesic / antipyretic drug
Systemic reactions	Most common solicited systemic reactions in adults ≥ 65 years of	During the informed consent process, the participants enrolling in the study will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	age: malaise, myalgia, and headache A Phase III study performed in persons ≥ 65 years of age demonstrated increased rates of solicited systemic reactions in participants receiving Fluzone High-Dose vaccine compared to persons receiving Fluzone vaccine but were typically mild and transient (18). Placebo-controlled trials suggest that in elderly persons and in healthy young adults, split-virus influenza vaccine is not associated with higher rates of systemic symptoms when compared with placebo injection (19). Safety monitoring of Fluzone High-Dose vaccine during the first year after licensure indicated a higher than expected number of gastrointestinal events compared with standard-dose vaccine, but otherwise no new safety concerns were identified (20).	informed of these potential reactions, the need to attend the clinic if they are unwell, and the possibility to take analgesic / antipyretic drug
Immediate allergic reactions	Immediate allergic reactions (eg, hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component (21) (22) (23). These types of reactions are exceedingly rare and would most likely occur in persons with a severe reaction to influenza vaccine in the past. Vaccine should not be administered to anyone who has had a severe allergic reaction to any component of the vaccine.	Exclusion criterion E02 for those at increased risk Observation period (30 min) after vaccination for early detection and treatment Addressed in IB (administration precautions, potential AEs)
Guillain-Barré syndrome	Among persons who received the swine influenza vaccine in	During the informed consent process, the participants

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	1976, the rate of GBS that exceeded the background rate was < 10 cases/1,000,000 persons vaccinated. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for such a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10–20 cases per 1,000,000 adults and stretches the limits of epidemiologic investigation (24). Investigations to date indicate that there is no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976) and that, if influenza vaccine does pose a risk, it is probably slightly more than 1 additional case per 1,000,000 persons vaccinated (25).	enrolling in the study will be informed of these potential risks and the need to attend the clinic if they are unwell. GBS is an AESI and will be collected until study end.
Investigated Vaccine: Moderna COVID-19 Vaccine		
Refer to the Investigator's Brochure for information regarding potential risks	Identified and potential risks observed in clinical trials and/or post-marketing surveillance.	Exclusion/inclusion criteria take into account contraindications, warnings and precautions as defined in product label.
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.	Observation period after vaccination for early detection and treatment.

2.3.2 Benefits from Study Participation

Participants vaccinated with the 2021–2022 NH formulation of Fluzone High-Dose Quadrivalent vaccine may be protected against those strains included in the vaccine and may be less likely to develop complications during the influenza season. However, in the context of this study, the influenza vaccine will be injected 4 to 6 months ahead of the NH influenza season which may lessen the influenza vaccine's potential protective effect during the influenza season.

Participants receiving Moderna COVID-19 Vaccine may be protected against SARS-CoV-2 infection and may be less likely to develop COVID-19 illness (26).

In addition, Fluzone High-Dose Quadrivalent vaccine will be offered to participants randomized to Group 3 at the conclusion of their participation to the Active Phase. Group 3 participants will be reminded that the Advisory Committee on Immunization Practices (ACIP) recommends yearly influenza vaccination, especially in high risk groups such as adults ≥ 50 years of age. This vaccination will be entirely voluntary, free of charge to participants, and will take place after all V02 study procedures have been completed. This vaccination will be offered as part of routine medical care and no additional data related to this vaccination will be collected. It is to be noted that vaccination with Fluzone High-Dose Quadrivalent vaccine offered to Group 3 participants at V02 will not be considered by the Sponsor as meeting exclusion criterion #14 (See Section 5.2).

2.3.3 Overall Benefit-Risk Conclusion

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

3 Objectives and Endpoints

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

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Safety Objective	
• To describe the safety profile of Fluzone High-Dose Quadrivalent vaccine and/or Moderna COVID-19 Vaccine administered concomitantly or singly, up to 21 days after injection in each study intervention group.	• Presence of immediate unsolicited systemic adverse events (AEs) reported in the 30 minutes after injection • Presence of solicited (pre-listed in the participant's diary card [DC] and CRF) injection site reactions and systemic reactions occurring up to 7 days after injection • Presence of unsolicited AEs reported up to 21 days after injection

Objectives	Endpoints
	• Presence of serious adverse events (SAEs) reported up to 6 months after injection • Presence of adverse events of special interest (AESIs) reported up to 6 months after injection • Presence of medically-attended AEs (MAAEs) reported up to 6 months after injection
Immunogenicity Objectives	
1) To describe the immune response elicited by Fluzone High-Dose Quadrivalent vaccine administered concomitantly or singly, in each study intervention group.	<u>Endpoints for Immunogenicity Objective #1</u> • Hemagglutination inhibition (HAI) individual titer on D01 and 21 days after injection of Fluzone High-Dose Quadrivalent vaccine (D22) • Individual HAI titers ratio D22/D01 • Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 21 days after injection of Fluzone High-Dose Quadrivalent (D22) • Seroconversion (titer < 10 [1/dil] at D01 and post-vaccination titer ≥ 40 [1/dil] at D22, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D22) • HAI titer ≥ 40 (1/dil) on D01 and 21 days after injection of Fluzone High-Dose Quadrivalent (D22)
2) To describe the immune response elicited by Moderna COVID-19 Vaccine administered concomitantly or singly, in each study intervention group.	<u>Endpoints for Immunogenicity Objective #2</u> • Individual anti-S binding IgG concentration on D01 and 21 days after injection of Moderna COVID-19 Vaccine (D22) • Individual anti-S binding IgG concentration ratio D22/D01 • 2-fold-rise and 4-fold-rise in anti-S binding IgG concentration 21 days post-injection D01

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	3-arm study with either concomitant or single administration of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine
Phase	II
Control method	Active-controlled (single administration versus coadministration)
Study population	Adults 65 years of age and older
Level and method of blinding	Open-label
Study intervention assignment method	Randomization
Number of participants	300 participants 65 years of age and older
Intervention groups	Participants will be randomly assigned to 1 of the 3 study groups in a 1:1:1 ratio, corresponding to *i)* concomitant administration of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine, *ii)* administration of Fluzone High-Dose Quadrivalent vaccine alone, and *iii)* administration of Moderna COVID-19 Vaccine alone
Total duration of study participation	Approximately 180 days (6 months after vaccination) for all participants.
Countries	United States
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

4.2 Scientific Rationale for Study Design

There is currently no data on the concomitant administration of high-dose quadrivalent influenza vaccine and mRNA based SARS-CoV-2 vaccines. Influenza vaccines, including Fluzone High-Dose Quadrivalent vaccine, are recommended in the national immunization program of several countries. Given the worldwide COVID-19 pandemic, many countries are currently implementing massive SARS-CoV-2 vaccination programs using one or more vaccines, including Moderna COVID-19 Vaccine. Therefore, the concomitant administration of both Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine is anticipated as immunization programs overlap.

Both vaccinations for the prevention of influenza and the prevention of COVID-19 disease are recommended in persons aged 65 years and older. While Fluzone High-Dose Quadrivalent vaccine is indicated for the prevention of influenza in population aged 65 years and older, Moderna COVID-19 Vaccine may be administered to adults aged 18 years and older.

The present study will investigate the safety and immunogenicity of Fluzone High-Dose Quadrivalent vaccine and a third/booster dose of Moderna COVID-19 Vaccine when administered concomitantly or singly in adults 65 years of age and older in the US.

4.3 Justification for Dose

A single dose of Fluzone High-Dose Quadrivalent vaccine is indicated for individuals 65 years of age and older to give protection against influenza.

So far, the safety and efficacy of Moderna COVID-19 Vaccine has been shown when the vaccine is administered as a course of 2 doses at least 28 days apart. However, repeated vaccination with a single dose of Moderna COVID-19 Vaccine (third or booster dose) is currently under evaluation in clinical studies and may be recommended. Although the Advisory Committee on Immunization Practices (ACIP) does not currently provide guidance for a booster (third) dose, adults 65 years of age and older are at the highest risk for COVID-19 and related complications and thus more likely to be prioritized in the event a third dose is recommended.

Therefore, participants in this study will be administered a dose of Fluzone High-Dose Quadrivalent vaccine and a dose of Moderna COVID-19 Vaccine either concomitantly or singly.

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 in the study.

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

5 Study Population

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

5.1 Inclusion Criteria

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

Age

I01: Aged ≥ 65 years of age on the day of inclusion[a].

Type of participant and disease characteristics

[a] "≥ 65 years" means from the day of the 65th birthday onwards.

I02: In good health or with underlying medical condition(s) that are judged to be stable by the Investigator. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.

I03: Participants who previously received 2 injections of Moderna COVID-19 Vaccine with the second dose received at least 5 months before V01[a].

Informed Consent

I04: Informed consent form has been signed and dated.

Other Inclusions

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:

Medical conditions

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

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

E03: Previous dermal filler injection (either lips or face fillers)

E04: Thrombocytopenia, contraindicating IM injection

E05: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination.

E06: Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion.[c]

E07: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of study intervention administration or febrile illness (temperature ≥ 100.4°F [38.0°C]). A

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[a] Confirmation of receipt of the 2-dose schedule of Moderna COVID-19 Vaccine will be documented by capturing the date and lot number of the second Moderna COVID-19 Vaccine injection in source document.

[b] The components of study interventions are listed in the Prescribing Information for the Fluzone High-Dose Quadrivalent vaccine and in the Investigator's Brochure for the Moderna COVID-19 Vaccine.

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

prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion

E09: History of serious adverse reaction to any influenza or COVID-19 vaccines

E10: Personal history of Guillain-Barré syndrome (GBS)

E11: Any condition that in the opinion of the Investigator would pose a health risk to the participant if enrolled or could interfere with the evaluation of the vaccine

E12: Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder

E13: Known seropositivity for human immunodeficiency virus, hepatitis B, or hepatitis C

Prior/concomitant therapy

E14: Receipt of **any vaccine in the 4 weeks preceding the study intervention(s) administration or planned receipt of any vaccine in the period between V01 and 4 weeks following the study intervention(s) administration**[a]

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

Prior/concurrent clinical study experience

E16: Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating vaccine, drug, medical device, or medical procedure

Other exclusions

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

E18: Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

5.3 Lifestyle Considerations

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

[a] It is to be noted that vaccination with Fluzone High-Dose Quadrivalent vaccine offered to Group 3 participants at the end of the Active Phase (V02) will not be considered by the Sponsor as meeting exclusion criterion #14.

5.4 Screen Failures

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

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

5.5 Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention, or Blood Draws

Not applicable.

6 Study Interventions and Concomitant Therapy

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

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.8). Study procedures (eg, blood sampling) are also 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	Fluzone High-Dose Quadrivalent vaccine, 2021-2022 formulation	Moderna COVID-19 Vaccine (mRNA-1273 vaccine)
Use	Experimental conditions or Other (as indicated in the prescribing material)	Experimental conditions or Other (as indicated in the prescribing material)
Type	Vaccine	Vaccine
IMP and NIMP	IMP	IMP
Dose Formulation	Sterile suspension for injection in a pre-filled syringe	Sterile suspension (white to off-white) in multidose vial
Unit Dose Strengths	60 mcg of HA of each of the following strains per dose: • A/Victoria/2570/2019 IVR-215 (H1N1)	Each dose will contain 100 mcg of mRNA (formulated in SM-102 lipid nanoparticles)

	• A/Tasmania/503/2020 IVR-221 (an A/Cambodia/e0826360/2020-like virus) (H3N2) • B/Phuket/3073/2013 (B Yamagata lineage) • B/Washington/02/2019 (B Victoria lineage)	
Excipients/Diluent	Octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution	Lipid SM-102 Cholesterol 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG) Tromethamol Tromethamol hydrochloride Acetic acid Sodium acetate trihydrate Sucrose Water for injections
Dosage Level	0.7 mL per dose	0.5 mL per dose
Number of Doses/Dosing Interval	One injection at V1 (D01) alone or co-administered with Moderna COVID-19 Vaccine	One injection at V1 (D01) alone or co-administered with Fluzone High-Dose Quadrivalent vaccine
Route of Administration	IM injection	IM injection
Site of Administration	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm
Injection Site Side for Concomitant Administration	Injection sites should be on opposite sides for participants enrolled in Group 1	
Sourcing	Provided by the Sponsor	Provided by the US Government
Packaging and Labeling	Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine will be supplied with their manufacturer's commercial labeling and packaging.	
Batch Number	TBD	TBD
Storage Conditions	2 to 8°C	2 to 8°C (up to 30 days) -25 to -15°C (long term)

Study arms and associated study intervention are summarized in Table 6.2.

Table 6.2: Arms and Associated Study Interventions

Arm name	Group 1	Group 2	Group 3
Associated study interventions	Concomitant administration of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine	Fluzone High-Dose Quadrivalent vaccine alone	Moderna COVID-19 Vaccine alone

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the Operating Guidelines.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

Participants will be randomized in a 1:1:1 ratio into Group 1, Group 2, and Group 3, using a permuted block method with stratification by site and by age group (< 75 years and ≥ 75 years).

The full detailed procedures for randomization are described in the Operating Guidelines.

Participant numbers will be 12 digits long, with a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier. The 5-digit participant identifier will correspond to the chronological order of enrollment in the center within each stratum. For example, Participant 8400001-00001 is the first participant enrolled in Center Number 1 (in the US) and Participant 8400002-00002 is the second participant enrolled in Center Number 2 (in the US), within the < 75 years stratum.

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

The Biostatistics platform of the Sponsor will provide randomization lists that will be printed as scratchable lists. These lists will mention the randomization order of the participant and the corresponding study group covered by a silver-colored patch. The Investigator will scratch off the list to know the study group. Once scratched, each randomization line will be dated and signed by the Investigator or the sub-investigator in charge of administering the study intervention(s).

Each participant will be vaccinated with the study intervention(s) corresponding to the group mentioned on the randomization list. If the dose initially taken for the vaccination is broken or cannot be used, the Investigator will take another dose of the same study intervention

6.3.2 Blinding and Code-breaking Procedures

Code-breaking procedures are not applicable for this open-label study. However, the laboratories conducting immunogenicity assays will be blinded to individual participant assignment or treatment.

6.4 Study Intervention Compliance

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

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

6.5 Dose Modification

Not applicable.

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

Not applicable.

6.7 Treatment of Overdose

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

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

1) Contact the RMO immediately.
2) Evaluate the participant to determine, in consultation with the RMO, whether study intervention should be interrupted

3) Closely monitor the participant for any AE/SAE.
4) Document the quantity of the excess of the overdose in the source documents.

6.8 Concomitant Therapy

Reportable medications include medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

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

The following reportable medications are defined:

- medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids)

  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.

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

Reportable medications will be collected in the CRF until the end of the solicited and unsolicited follow-up period.

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

Medications given in response to an AE will be captured in the “Action Taken” section of the AE CRF only. No details will be recorded in the concomitant medication Form of the CRF unless the medication(s) received belongs to one of the pre-listed categories. Medications will be coded.

6.8.1 Rescue Medicine

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

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable as there is only one vaccination visit.

7.2 Participant Discontinuation/Withdrawal from the Study

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

Follow-up of Discontinuations

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

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

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

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

8 Study Assessments and Procedures

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

Blood samples will be collected as described in the SoA table (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 40 mL, see Table 8.1. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 8.1: Blood sampling volume (mL) per visit

Visit Number (V) **Trial Timelines (Days)** **Time Windows (Days)**	**V01** **D01**	**V02** **D22** [+3 days]
	Vaccination	
Vaccination	X	
	Immunogenicity assessments related to Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine	

Serum antibodies (20 mL) • **HAI** • **Serum full-length S-binding IgG** • **Sample for Future Use**	X	X
TOTAL	20 mL	20 mL

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

8.1 Efficacy and Immunogenicity Assessments

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

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

The HAI assay will be performed by Global Clinical Immunology (GCI), Sanofi Pasteur laboratory (Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility. The SARS-CoV-2-Pre-Spike IgG ELISA will be performed by Nexelis (Laval, QC, Canada), a Contract Research Laboratory under the responsibility of GCI. The addresses are provided in the Operating Guidelines.

8.1.2.1 Immunogenicity Assessments Related to Fluzone High-Dose Quadrivalent Administration

Immunogenicity will be evaluated in all participants from the 3 study intervention groups using samples taken before vaccination and 21 days after Fluzone High-Dose Quadrivalent administration (21 [+3] days after V01) using the HAI test.

Test serum samples and quality control sera (sheep, ferret, and/or human sera) are incubated with Sigma Type III neuraminidase from Vibrio cholerae to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins is 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 two-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 an 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 is titrated in two independent assay runs, and the 2 values, which cannot differ by more than 1 two-fold dilution, are reported. The GMT between the 2 values is calculated at the time of statistical analysis. 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/dil). If the highest / last serum dilution used in the assay

exhibits complete inhibition of hemagglutination, the serum Ab titer will be reported as ≥ 10240 (1/dil).

8.1.2.2 Immunogenicity Assessments Related to Moderna COVID-19 Vaccine Administration

Human SARS-CoV-2 pre-Spike IgG ELISA

The human SARS-CoV-2 Pre-Spike IgG ELISA is an indirect ELISA which is based on the antibody/antigen interactions. This ELISA allows for the detection of SARS-CoV-2 Pre-Spike specific IgG antibodies in human serum samples and will be performed on all participants from the 3 study intervention groups.

Purified SARS-CoV-2 Pre-Spike Antigen is adsorbed to the wells of a microplate. Diluted serum samples (test samples, standard, and quality controls) are added in the wells. Anti-SARS-CoV-2 Pre-Spike antibodies, if present in the serum samples, bind to the immobilized SARS-CoV-2 Pre-Spike antigen. Unbound sample is then washed from the wells, and enzyme-conjugated anti-human IgG is added. The anti-human IgG enzyme conjugate binds to the antigen-antibody complex. Excess conjugate is washed away, and a specific colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction, which causes color development. After the established time period, the reaction is stopped. The intensity of the generated color is proportional to the amount of anti-SARS-CoV-2 Pre-Spike antibodies bound to the wells. The results are read on a spectrophotometer (ELISA plate reader). A reference standard on each tested plate is used to quantify antibodies against SARS-CoV-2 Pre-Spike in the sample according to the unit assigned by the standard (ELU/mL). At the time of the statistical analysis of the results, the following formula will be used for converting the concentration units from ELU/mL to BAU/mL:

Result (BAU/mL) = Result (ELU/mL)/7.9815

8.2 Safety Assessments

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRF.

Prior history of SARS-CoV-2 infection will be collected.

Collected information will not be coded.

8.2.2 Physical Examinations

At Visit 1, the Investigator or a designee will perform a targeted physical examination. Information will be recorded in the source document.

8.2.3 Vital Signs

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

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

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

AEs will be reported by the participants to the investigator, then by the investigator to the Sponsor.

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

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

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

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

Unsolicited Non-serious Adverse Events

Unsolicited non-serious adverse events will be collected from the day of vaccination (D01) until 21 days after vaccination (D22).

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

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected from D01 to D181.

Adverse Events of Special Interest (AESIs)

AESIs will be collected from D01 to D181.

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination (D01) until 6 months after vaccination (D181). However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the case report form (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 10.2. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.3.2 Method of Detecting AEs and SAEs

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These diary cards will include 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 a designee will interview the participants to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

The 6-month follow-up will be done by interviewing participants over the telephone to capture SAEs, AESIs, and MAAEs if applicable.

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

8.3.3 Follow-up of AEs and SAEs

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

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

8.3.4 Regulatory Reporting Requirements for SAEs

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

8.3.5 Pregnancy

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

8.3.6 Adverse Events of Special Interest

AESI will be captured as SAEs and will include:

Fluzone High-Dose Quadrivalent vaccine-related AESIs

- Guillain-Barré Syndrome
- Encephalitis/myelitis (including transverse myelitis)
- Neuritis (including Bell's palsy, optic neuritis, and brachial neuritis)

- Thrombocytopenia
- Vasculitis
- Convulsions
- Anaphylaxis or other hypersensitivity/allergic reactions

Moderna COVID-19 Vaccine-related AESIs

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure.
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, myopericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc) • Include all cases that meet the following criteria o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 μmol/l) within 48 hours; o OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days o OR Urine volume ≤0.5 ml/ kg/ hour for 6 hours

Medical Concept	Additional Notes
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc) • Include all cases that meet the following criteria o 3-fold elevation above the upper normal limit for ALT or AST o OR > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A)
Thrombocytopenia	• Platelet counts < 150 x10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: o Guillain-Barré Syndrome o Acute disseminated encephalomyelitis (ADEM) o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	
Other syndromes	• Fibromyalgia

Medical Concept	Additional Notes
	• Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes myalgic encephalomyelitis and Post Viral Fatigue syndrome) • Myasthenia gravis

8.3.7 Medically Attended Adverse Events

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

8.4 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study. However, other emerging biomarkers may be evaluated in this study which may be relevant for evaluating scientific aspects of COVID-19 illness, or SARS-CoV-2 infection, or for the evaluation of effect modification, correlates of risk/protection, or participants' baseline characteristics.

8.7 Immunogenicity Assessments

See Section 8.1.2.

8.8 Medical Resource Utilization and Health Economics

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

8.9 Leftover Biological Samples and Use of Data

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

In addition, participants will be asked to indicate in the ICF whether they will permit the future use by Sanofi Pasteur or one of its research partners, of any unused stored biological samples for other tests and the corresponding data, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of any unused biological samples will not be included in the site-specific ICF). If they refuse permission, the biological samples will not be used for any testing other than that directly related to this study. If they agree to this future use, they will not be paid for giving permission.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research). The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines and their mechanism of action, the knowledge of infectious diseases, or to improve existing tests or develop new tests to assess vaccines, or to help identify new vaccine targets or biomarkers that predict participant response to the vaccine. Such research may also include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, a specific individual consent will be obtained.

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

The biological samples will be securely stored at the Sanofi Pasteur laboratory (GCI) or Contract Research Laboratory up to 25 years after the end of the study. Unused samples may also be sent to another long-term repository at the NIH, BARDA, as well as other US Government-designated laboratories. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and sample related coded data will be anonymized unless otherwise required by applicable laws.

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

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

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

9 Statistical Considerations

9.1 Statistical Hypotheses

No hypothesis testing will be performed in this study.

9.2 Sample Size Determination

The study will enroll approximately 300 participants 65 years of age or older: approximately 100 participants will be concomitantly administered of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine (Group 1), approximately 100 participants will be administered Fluzone High-Dose Quadrivalent vaccine alone (Group 2), and approximately 100 participants will be administered Moderna COVID-19 Vaccine alone (Group 3).

No study power calculation was conducted for this study. Assuming a drop-out rate of 5%, a total of 95 evaluable subjects per study group is anticipated.

9.3 Analysis Sets

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

Participant Analysis Set	Description
Randomized	All participants that have a randomization number
Safety Analysis Set (SafAS)	Participants who have received the study vaccine(s). All participants will have their safety analyzed according to the vaccine they actually received and study intervention group. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Immunogenicity analysis set (IAS)	Subset of randomized participants who received at least 1 dose of study vaccine. Participants will be analyzed according to the vaccine they actually received and study intervention group.

9.4 Statistical Analyses

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

9.4.1 General Considerations

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above (SAS Institute, Cary, North Carolina, USA).

For the derivation of immunogenicity endpoints, all values strictly under the lower limit of quantification (LLOQ) will be treated as LLOQ/2, and all values above or equal to the upper limit of quantification (ULOQ) will be treated as ULOQ.

9.4.2 Study Endpoints

All analyses will be descriptive. No hypotheses are planned to be tested.

For the main parameters, 95% CIs for the point estimates will be calculated using the normal approximation after log transformation for quantitative data (GMCs and GM of individual ratios) and exact binomial distribution (Clopper-Pearson method, quoted by Newcombe) for single proportions.

For immunogenicity analyses the IAS will be used. Results will be presented by actual study group and vaccine received for each timepoint. For the analysis of SARS COV-2 immune response, the serological results will be received in ELU/mL but will be expressed in BAU/mL for the analysis. The following formula will be used for converting the concentration units from ELU/mL to BAU/mL:

$$\text{Result (BAU/mL)} = \text{Result (ELU/mL)}/7.9815$$

For safety analyses the SafAS will be used. Results will be presented by actual study group and vaccine received.

9.4.3 Other Analysis

The ratios of post-vaccination GMTs between concomitant and single injections will be presented for the five antigens with 2-sided 95% CIs.

Subgroup analyses will also be performed as complementary analyses; in particular, immunogenicity will be described according to serostatus at baseline, previous influenza vaccination, and age, as appropriate according to number of subjects in the respective subgroups.

Other analyses will be described in the SAP.

9.5 Interim Analyses

The statistical analysis will be performed in two or three steps, depending on the availability of immunogenicity data: the safety objectives up to D22 will be analyzed first and the immunogenicity objectives will be analyzed in a second step, after immunogenicity data have been released. No impact is expected on immunogenicity results as the conduct of immunogenicity assays will remain blinded. At last, the final analysis will be performed when safety data up to D181 is released.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

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

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, informed consent form (ICF), product-related information (ie, US PI for Fluzone High-Dose Quadrivalent vaccine and the Investigator's Brochure for Moderna COVID-19 Vaccine), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

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

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

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

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and 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 (HIPAA) 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 ICF.

- The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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

Recruitment Procedures

Before the start of the study, the Investigator or sub-investigator will contact an appropriate pool of potential participants and invite them to participate in the study. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur for review prior to submission to the IEC/IRB for approval.

10.1.4 Data Protection

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

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

Protection of participant data

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

- Participants race and ethnicity will be collected in this study because these data are required by the FDA (27).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

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

- Sanofi's Binding Corporate Rules for intra-group transfers.

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

10.1.5 Dissemination of Clinical Study Data

Study participants

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

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

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

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document

if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.6 Data Quality Assurance

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

10.1.7 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.8 Study and Site Start and Closure

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

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

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

For study termination:

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

For site termination:

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s)

used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

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

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

10.2.1 Definition of AE

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

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

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

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

Immediate Event/Reaction:

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

Reactogenicity / Solicited Reactions

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

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination and the next 7 days).

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

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

Injection / Administration Site Reactions:

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

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature

and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

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

Systemic AR:

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

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

Unsolicited AE/AR

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

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

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

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

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

Adverse Event of Special Interest (AESI):

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

Medically Attended AE (MAAE)

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

10.2.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is other medically important event

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

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

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

AE and SAE Recording

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

Assessment of Causal Relationship

By convention, all AEs reported at the injection site (either solicited or unsolicited) and all solicited systemic AEs are considered to be related to the IMP (see definition in Section 6) and

therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the Investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor (except for injection site reactions which will be related by default). Sponsor assessment is entered in the GPV database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:
  - Not related – The AE is clearly / most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)
  - Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.2.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

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

SAE Reporting to the Sponsor via Paper CRF

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

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

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

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

Safety Emergency Call

If, as per the Investigator's judgment, a participant experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.3.2.

10.2.5 Assessment of Intensity

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

10.2.5.1 Tables for Clinical Abnormalities

10.2.5.1.1 Solicited AR Intensity Grading Scale

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

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

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

MedDRA: Medical Dictionary for Regulatory Activities

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

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

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

	or ≥ 100.4°F to ≤ 101.1°F Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

MedDRA: Medical Dictionary for Regulatory Activities

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

Important notes for the accurate assessment of temperature:

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

10.2.5.1.2 Unsolicited AE Intensity Grading Scale

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

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

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

10.3 Appendix: Risk-based Approach

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

10.4 Appendix: Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
BL	blood sample
CRF	Case report form
DMC	Data Monitoring Committee
FAS	Full analysis set
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	geometric mean
GMT	geometric mean of titers
GPV	Global Pharmacovigilance
HA	Hemagglutinin
HAI	Hemagglutinin inhibition
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MA	memory aid
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMP	Non- Investigational Medicinal Product
PPAS	Per-protocol analysis set
PV	Pharmacovigilance
PT	Preferred Term
RMO	Responsible Medical Officer
SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TBD	to be determined
ULOQ	upper limit of quantification
WHO	World Health Organization
VAC	vaccination

10.5 Appendix: Protocol Amendment/Update History

The Protocol Amendment rationale for the current change in versions (from version 3.0 to version 4.0) is located directly before the Table of Contents.

Protocol version 2.0, dated 22 June 2021

Following the Institutional Review Board review, Protocol version 1.0 dated 10 June 2021 was updated to change the dosage of the Moderna COVID-19 Vaccine from 50 mcg to 100 mcg.

Protocol version 3.0 (Amendment 1), dated 01 July 2021

The main reason for updating protocol version 2.0 to protocol version 3.0 (Amendment 1) was to add the following items following the review of the Center for Biologics Evaluation and Research (United States Food and Drug Administration):

- Indicate the designated laboratory that will be performing the immunological assays.
- Offer participants enrolled in Group 3 (Moderna COVID-19 Vaccine alone) vaccination with Fluzone High-Dose Quadrivalent vaccine at the conclusion of their study participation (Visit 02) as part of routine medical care.

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12 Sponsor Signature Page

Signature Page for VV-CLIN-0614629 v4.0
FLZ-HD-HV-QIV-QHD00028-protocol

Approve & eSign	[redacted] Clinical [redacted]