NCT04024228

Immunogenicity and Safety of a High-Dose Quadrivalent Influenza Vaccine Administered by the Intramuscular Route in Subjects 60 Years of Age and Older

Phase III, randomized, modified double-blind, active-controlled, multi-center study evaluating the immunogenicity and safety of high-dose quadrivalent influenza vaccine (QIV-HD) in healthy subjects 60 years of age and older in Europe

Clinical Study Protocol

Health Authority File Number(s):	EudraCT #: 2019-000655-14
WHO Universal Trial Number (UTN):	U1111-1225-0952
Study Code:	QHD00011
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée, 69007 Lyon, France
Investigational Product:	High-Dose Influenza Vaccine (split virion, inactivated), Quadrivalent (QIV-HD)
Form / Route:	Liquid / Intramuscular
Indication For This Study:	Single dose for individuals 60 years of age and older
Manufacturer:	Same as Sponsor
Investigators:	This is a multi-center study with multiple investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Sponsor's Responsible Medical Officer:	[redacted]
Clinical Team Leader:	

Global Safety Officer: [redacted]

Regional Trial Manager:

Version and Date of the Protocol: Version 2.0 dated 23 August 2019

History of Protocol Versions

Version	Date	Comments
1.0	02 April 2019	IEC/IRB-approved version not used in the study

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	High-Dose Influenza Vaccine (split virion, inactivated), Quadrivalent (QIV-HD) 2019-2020 Northern Hemisphere formulation
Active Substances:	A/(H1N1)-like strain, A/(H3N2)-like strain, B (Victoria Lineage)-like strain, B (Yamagata Lineage)-like strain

Title of the Study:	Immunogenicity and Safety of a High-Dose Quadrivalent Influenza Vaccine Administered by the Intramuscular Route in Subjects 60 Years of Age and Older
Development Phase:	Phase III
Coordinating Investigator:	To be determined (TBD)
Study Sites:	This will be a multi-center study conducted at approximately 15 to 20 study sites in Europe. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Quarter (Q)3 2019 to Q2 2020
Study Design, Schedule of Study Procedures, and Methodology:	QHD00011 will be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in approximately 1540 healthy adults (770 adults 60 to 64 years of age and 770 adults 65 years of age and older) to evaluate the immunogenicity and safety of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) route in subjects in Europe. A standard-dose quadrivalent influenza vaccine (QIV-SD) will serve as a control arm. <u>Vaccination</u> In each age group, eligible subjects will be randomized in a 1:1 ratio to receive a single IM injection of either QIV-HD or QIV-SD at Day (D)0. Because the volumes for injection differ between the 2 vaccines (QIV-HD [0.7 milliliter (mL)] and QIV-SD [0.5 mL]), an unblinded administrator at each site will be in charge of administering the vaccines. This person will not be involved in any safety or immunogenicity assessments. Due to the different volumes for injection, the syringes will be masked to keep the blind of the subjects and other members of the clinical site. Additional details will be provided in the Operating Guidelines for the study. <u>Blood sampling</u> All subjects will provide a pre-vaccination (baseline) blood sample at Visit (V)01 (D0) and a post-vaccination blood sample at V02 (D28 [+7 days]) for immunogenicity assessment. If the D0 blood sample cannot be obtained, the subject should be given the opportunity to return to the study site for another attempt, as long as the study is still enrolling subjects and as long as the subject continues to remain eligible for the trial and that includes reviewing Inclusion/Exclusion criteria, medical history, and informed consent form (ICF) process. All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject should not be vaccinated and should be discontinued from the study.

Study Design, Schedule of Study Procedures, and Methodology: (continued)	Collection of safety data • All subjects will be observed for 30 minutes after vaccination. Any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited systemic AEs in the Case Report Book (CRB).
	• Solicited reactions will be collected up to 7 days after vaccination (D0 to D7), and unsolicited AEs will be collected up to 28 days after vaccination (D0 to D28 [V02]). Subjects will record this information in a diary card (DC). • Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected throughout the study (D0 through approximately D180 [6 month follow-up period]). Subjects will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study. • Staff will review the V01 (D0) to V02 (D28) safety data with subjects at V02. • Subjects will continue to collect information on SAEs and AESIs in a memory aid (D28 [V02]-D180). It is to be noted that AESIs will be captured as SAEs. These AESIs include new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis. • Staff will contact subjects by telephone at D180 post-vaccination to review the memory aid and to identify the occurrence of any SAEs and AESIs that had not yet been reported. • Interactive response technology (IRT) will be used to randomly assign subjects, in each age group, to one of the 2 vaccine groups and to assign subject numbers in each of the groups. • Electronic data capture will be used for the collection of data.
Interruption of the Study	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Independent Ethics Committees (IECs)/ Institutional Review Boards (IRBs), or the governing regulatory authorities in the countries where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	***Immunogenicity*** To demonstrate that QIV-HD induces an immune response that is superior to the responses induced by QIV-SD for all 4 virus strains 28 days post-vaccination in subjects 60 to 64 years of age and in subjects 65 years of age and older.

Primary Endpoints:	***Immunogenicity*** For subjects in each age group (60 to 64 years of age; 65 years of age and older) and for subjects in each vaccine group (QIV-HD; QIV-SD): • hemagglutination inhibition (HAI) antibody (Ab) titers obtained on D28
Secondary Objectives:	***Immunogenicity*** To further describe the immune response induced by QIV-HD and QIV-SD in all subjects by age group, in pooled age groups, and by vaccine group (QIV-HD; QIV-SD) ***Safety*** To describe the safety profile of all subjects by age group, in pooled age groups, and by vaccine group (QIV-HD; QIV-SD)
Secondary Endpoints:	***Immunogenicity*** For subjects in each age group (60 to 64 years of age; 65 years of age and older) and for subjects in each vaccine group (QIV-HD; QIV-SD): • HAI Ab titers obtained on D0 and D28 • Individual HAI titers ratio D28/D0 • Subjects with titers ≥ 40 [1/dilution (dil)] at D28 • Seroconversion (titer < 10 [1/dil] at D0 and post-vaccination titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28) ***Safety*** Safety will be described for all subjects: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, and action taken of solicited (prelisted in the subject's DC and CRB) injection site reactions and systemic reactions occurring up to 7 days after vaccination. • Occurrence, nature (MedDRA PT), time to onset, duration, intensity, and relationship to vaccination (for systemic AEs only) of unsolicited AEs up to 28 days after vaccination. • Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, and outcome of SAEs (including AESIs) throughout the study.
Observational Objectives:	1) To describe the immune response 28 days after vaccination by virus seroneutralization (SN) measurement method for at least 50% of subjects in each age group (60 to 64 years of age; 65 years of age and older), and in pooled age group by vaccine group (QIV-HD; QIV-SD) 2) To describe the anti-neuraminidase (NA) immune response in at least 50 subjects in each age group and in pooled age group by vaccine group (QIV-HD; QIV-SD)

<table>
<tr><td>Observational Endpoints:</td><td>
Immunogenicity Assessment by SN for subjects in each age group (60 to 64 years of age; 65 years of age and older) and for subjects in each vaccine group (QIV-HD; QIV-SD).
Neutralizing Ab titers will be measured for each influenza strain with the SN method. The analyses will be performed on blood samples obtained on D0 and D28.
• Individual neutralization test (NT) Ab titer on D0 and D28
• Individual NT Ab titer ratio (fold-rise in serum NT post-vaccination relative to D0) at D28
• Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28
• Fold-rise in NT Ab titer [post/pre] ≥ 2 and ≥ 4 at D28
• Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0 and D28

Immunogenicity Assessment by enzyme-linked lectin assay (ELLA) for subjects in each age group (60 to 64 years of age; 65 years of age and older) and for subjects in each vaccine group (QIV-HD; QIV-SD).
Anti-N1and -N2 titers will be measured for the 2 influenza A strains using ELLA. The analyses will be performed on blood samples obtained on D0 and D28.
• Individual ELLA Ab titer on D0 and D28
• Individual ELLA Ab titer ratio (fold-rise in serum ELLA post-vaccination relative to D0) at D28
• Subjects with ELLA Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28
• Fold-rise in ELLA Ab titer [post/pre] ≥ 2 and ≥ 4 at D28
• Detectable ELLA (ELLA Ab titer ≥ 10 [1/dil]) at D0 and D28
</td></tr>
<tr><td>Planned Sample Size:</td><td>
A total of 1540 subjects are planned to be enrolled as follows:
<table>
<tr><th>Vaccine</th><th>Number of subjects 60 to 64 years of age</th><th>Number of subjects 65 years of age and older</th><th>Total</th></tr>
<tr><td>QIV-HD Group</td><td>385</td><td>385</td><td>770</td></tr>
<tr><td>QIV-SD Group</td><td>385</td><td>385</td><td>770</td></tr>
<tr><td>Total</td><td>770</td><td>770</td><td>1540</td></tr>
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</td></tr>
</table>

Planned Sample Size: (continued)

For the assessment of the immune response by virus SN and ELLA methods, randomization to the observational subsets (Full Analysis Set-Seroneutralization [FAS-SN] subset and Full Analysis Set-Neuraminidase [FAS-NA] subset) will be performed with stratification on vaccine group, age groups (60 through 64 years of age or ≥65 years of age), and site. The FAS-NA subset is a subset of the FAS-SN subset.

A subset of the 1540 enrolled subjects will be randomly assigned to the observational subset to be assessed for neutralizing Ab titers (at least 50% of subjects in each age group and each vaccine group) and for Anti-N1and -N2 titers (at least 50 subjects in each age group and each vaccine group) at D0 and D28 as shown in the following table.

Vaccine/Assay	Number of subjects 60 to 64 years of age	Number of subjects 65 years of age and older	Total
QIV-HD Group/SN	≥193	≥193	≥386
QIV-SD Group/SN	≥193	≥193	≥386
QIV-HD Group/NA	≥50	≥50	≥100
QIV-SD Group/NA	≥50	≥50	≥100

Duration of Participation in the Study:

The duration of each subject's participation will be approximately 6 months including the safety follow-up (D0 through D180).

Investigational Product:

High-Dose Influenza Vaccine (split virion, inactivated), Quadrivalent (QIV-HD) 2019-2020 Northern Hemisphere formulation

Form:

Suspension for injection

Presentation:

Pre-filled syringe

Composition:

Each 0.7 mL dose of QIV-HD will contain:
Strains to be determined based on World Health Organization (WHO) recommendations for the 2019-2020 Northern Hemisphere (NH) influenza season, as determined by the WHO and European Union (EU) for the 2019/2020 season.

Composition: (continued)

Active Substances:

- A/(H1N1)-like strain — 60 microgram (µg) hemagglutinin (HA)
- A/(H3N2)-like strain — 60 µg HA
- B/(Victoria Lineage)-like strain — 60 µg HA
- B/(Yamagata Lineage)-like strain — 60 µg HA

Excipients:

- Octylphenol Ethoxylate (Octoxinol-9/Triton X-100®) — not more than 350 µg

Diluent:

- Buffered saline solution — quantity sufficient (qs) to appropriate volume

Route:

IM, injected into the upper arm (deltoid area)

Batch Number:	TBD
Control Product:	Standard-Dose influenza virus surface antigens (haemagglutinin and neuraminidase), Inactivated, Influenza Vaccine Quadrivalent, 2019-2020 Northern Hemisphere Strains (Influvac™ Tetra [QIV-SD])
Form:	Suspension for injection
Presentation:	Pre-filled syringe
Composition:	Each 0.5 mL dose of QIV-SD will contain: *Strains to be determined based on WHO recommendations for the 2019-2020 Northern Hemisphere (NH) influenza season, as determined by the WHO and EU for the 2019/2020 season.* **Active Substances:** • A/(H1N1)-like strain 15 µg HA • A/(H3N2)-like strain 15 µg HA • B/(Victoria Lineage)-like strain 15 µg HA • B/(Yamagata Lineage)-like strain 15 µg HA **Excipients:** Potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, sodium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, and water for injection.
Route:	IM, injected into the upper arm (deltoid area)
Batch Number:	TBD
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for trial enrollment: 1) Sixty years of age and older on the day of inclusion 2) Informed consent form has been signed and dated 3) Able to attend all scheduled visits and to comply with all trial procedures 4) Covered by health insurance if applicable in the country
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, or surgically sterile. 2) Participation at the time of trial enrollment (or in the 4 weeks [28 days] preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 3) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to V02 4) Previous vaccination against influenza (in the previous 6 months) with either the trial vaccine or another vaccine

Exclusion Criteria: (continued)	5) Receipt of immune globulins, blood or blood-derived products in the past 3 months 6) 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 past 3 months) 7) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances. 8) Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on Investigator's judgment 9) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 10) Alcohol or substance abuse that, in the opinion of the Investigator might interfere with the trial conduct or completion 11) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion. It is to be noted that chronic illness may include, but is not limited to, cardiac disorders, renal disorders, autoimmune disorders, diabetes, psychiatric disorders, or chronic infection. 12) Moderate or severe acute illness/infection (according to Investigator judgment) or febrile illness (temperature ≥ 38.0°C) on the day of vaccination. A prospective subject should not be included in the trial until the condition has resolved or the febrile event has subsided. 13) Identified as an Investigator or employee of the Investigator or trial center with direct involvement in the proposed trial, 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 trial. 14) Personal or family history of Guillain-Barré syndrome (GBS). 15) Neoplastic disease or any hematologic malignancy (except localized skin or prostate cancer that is stable at the time of vaccination in the absence of therapy and subjects who have a history of neoplastic disease and have been disease-free for ≥ 5 years).
Statistical Methods:	The per-protocol analysis set (PPAS) and full analysis set (FAS) will be used for the main immunogenicity analyses. Conclusions will be made based on the FAS results. The safety analysis set (SafAS) will be used for all safety analyses. The statistical analysis will be performed in at least 2 steps: • First analysis on immunogenicity and safety results obtained on data collected within the 28 days following the vaccination (from D0 to D28). The study blind will be broken at that time. • Second analysis after the 6-month data have been collected. ***Primary Objective*** A superiority approach will be used to compare post-vaccination geometric mean titers (GMTs) between QIV-HD and QIV-SD groups for each strain and in each age group using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses:

Statistical Methods: (continued)	$$H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{QIV-SD}} \leq 1 \Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{QIV-SD}) \leq 0$$ $$H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{QIV-SD}} > 1 \Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{QIV-SD}) > 0$$ where s: strain If superiority is demonstrated for post-vaccination GMTs for the 4 strains within a same age group, then the immunogenicity of QIV-HD will be considered as superior to QIV-SD in the corresponding age group. The statistical methodology will be based on the use of the lower bound of the 2 sided 95% confidence intervals (CIs) of the ratio of post-vaccination GMTs between the QIV-HD and QIV-SD groups. The CIs will be calculated by normal approximation of log-transformed titers for GMTs. ***Secondary Objective -*** Immunogenicity Immunogenicity endpoints will be summarized per vaccine group (by age group and in pooled age groups) with 95% CIs. CIs of geometric mean (GM) of titers and individual titer ratios will be calculated assuming normal approximation of log-transformed values. CIs of proportions will be calculated using Clopper-Pearson method. Reverse cumulative distribution curves against each strain will be performed for each time point additional parameters may be displayed as appropriate. ***Secondary Objective -*** Safety Safety endpoints will be summarized per vaccine group (by age group and in pooled age groups), with 95% CI for the main endpoints. CIs will be calculated using Clopper-Pearson method. **Calculation of Sample Size:** A total of approximately 1540 adults 60 years of age and older (770 adults 60 to 64 years of age and 770 adults 65 years of age and older) will be enrolled. This sample size is determined per simulations based on an overall power of 90% for demonstrating the primary objective. The thresholds for superiority are defined as 1 for GMTs. No alpha adjustment is needed. Other assumptions are listed as follows: • Allocation ratio: 1:1 (QIV-HD versus QIV-SD) • GMT ratio: 1.5 for all strains • Standard deviations of log10-transformed titers in QIV-SD group of 0.6 for 2 strains and 0.5 for the other 2 strains • Attrition rate: 5% in FAS It should be noted that the power per strain is 97.7% when the standard deviation is 0.6 and 99.7% when the standard deviation is 0.5.

Table of Study Procedures

Phase III Study, 2 Visits, 1 Telephone Call, 1 Vaccination, 2 Blood Samples, Approximately 180 Days Duration Per Subject

Visit (V)/Contact	**V01**	**V02**	**D180 Safety Follow-up Call**
Study timelines (day [D])	D0	D28	D180
Time windows (days)	Not applicable	[+7 days]	[+14 days]
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data*	X		
Urine pregnancy test (if applicable)	X		
Medical history	X		
History of seasonal influenza vaccination/influenza infection (diagnosis laboratory confirmed) in the previous 3 years	X		
Collection of reportable concomitant medications	X	X	
Physical examination†	X	X	
Contacting interactive response technology (IRT)	X		
Randomization/allocation of subject number and unique treatment number using IRT	X		
Blood sampling (BL), 10 mL‡	BL0001§	BL0002	
Vaccination	X		
Immediate surveillance (30 minutes)	X		
Diary card (DC) provided**	X		
Collection of solicited injection site and systemic reactions	D0-D7		
Collection of unsolicited adverse events (AEs)	D0-V02		
DC reviewed and collected		X††	
Memory aid provided‡‡		X	
Study termination record for the active phase of the trial		X	
Follow-up telephone call			X§§
Memory aid reviewed			X
Study termination for the 6-month safety follow-up			X
Collection of serious adverse events (SAEs) and adverse events of special interest (AESIs)***	To be reported at any time during the study		

* To comply with US FDA expectations, Sponsors are to enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race, and ethnicity as described in https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf. Please note that ethnicity will not be collected during this study.

† Targeted physical examination based on medical history will be performed at V01. Targeted physical examination may also be performed at V02, as necessary.

‡ If the D0 blood sample cannot be obtained, the subject should be given the opportunity to return to the study site for another attempt, as long as the study is still enrolling subjects and as long as the subject continues to remain eligible for the trial and that includes reviewing Inclusion/Exclusion criteria, medical history, and ICF process. All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject should not be vaccinated and should be discontinued from the study.

§ Collection of the first blood sample (BL0001) is to occur before vaccination.

** Subjects will use this diary card to record information about solicited reactions from D0 to D7, as well as unsolicited AEs, SAEs, and AESIs from D0 to V02 after vaccination.

†† Staff will collect the diary card at V02, and review any solicited reactions ongoing at V02, unsolicited AEs, concomitant medications, SAEs, and AESIs.

‡‡ Subjects will use this memory aid to collect information on SAEs and AESIs from V02 to the D180 Safety Follow-up Call.

§§ During the D180 telephone call, staff will review the memory aid to identify the occurrence of any SAEs and AESIs that had not yet been reported.

*** AESIs will have the same detailed information collected as SAEs. These include new onset of Guillain-Barré Syndrome (GBS), encephalitis/myelitis (including transverse myelitis), Bell's Palsy, optic neuritis, and brachial neuritis.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BL, blood sampling; D, day; DC, diary card; FDA, Food and Drug Administration; GBS, Guillain-Barré Syndrome; ICF, informed consent form; SAE, serious adverse event; US, United States; V, visit.

List of Abbreviations

µg	microgram(s)
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling
CI	confidence interval
CDM	Clinical Data Management
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CRO	contract research organization
CTL	Clinical Team Leader
D	day
DC	diary card
dil	dilution
DO	Doctor of Osteopathic Medicine
DP	drug product
DS	drug substance
ELISA	enzyme-linked immunosorbent assay
ELLA	enzyme-linked lectin assay
EDC	electronic data capture
EU	European Union
FAS	full analysis set
FAS-NA	full analysis set-neuraminidase subset
FAS-SN	full analysis set-seroneutralization subset
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	Global Data Protection Regulation
GM	geometric mean

GMT	geometric mean titer
GPV	Global Pharmacovigilance
HA	hemagglutinin
HAI	hemagglutination inhibition
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IME	important medical event
IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
MD	Doctor of Medicine
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NA	neuraminidase
NH	Northern Hemisphere
NSAID	non-steroidal anti-inflammatory drug
NT	neutralization test
OD	optical density
OPD	o-Phenylenediamine dihydrochloride
PMDA	Pharmaceuticals and Medical Devices Agency
PNA	peanut-agglutinin
PPAS	per-protocol analysis set
PT	preferred term
Q	quarter
QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
qs	quantity sufficient
RBC	red blood cell
RMO	Responsible Medical Officer
RNA	ribonucleic acid
RWE	real world evidence

SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SAS	Statistical Analysis System
SC	subcutaneous(ly)
SD	standard dose
SMT	Safety Management Team
SN	seroneutralization
TBD	to be determined
TIV	trivalent influenza vaccine
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
TMF	trial master file
UN	United Nations
US	United States
ULOQ	upper limit of quantification
V	visit
WHO	World Health Organization

1 Introduction

1.1 Background

Influenza is a highly contagious, acute viral respiratory disease caused by influenza A subtype and type B viruses and is typically characterized by the rapid onset of fever, myalgia, sore throat, and nonproductive cough. Influenza can also cause severe malaise lasting for several days. Influenza virus types A and B belong to the genus Orthomyxoviridae and are characterized as enveloped, negative strand, segmented ribonucleic acid (RNA) viruses. The viral envelope contains 2 virus coded glycoproteins, hemagglutinin (HA) and neuraminidase (NA), which form spikes on the viral surface and are key antigens in the host response in both natural infection and vaccination (1) (2).

Genetic and antigenic variations are an important feature of the influenza virus. The viral HA and NA antigens are subject to continuous, sequential evolution within immune or partially immune populations. Genetic and antigenic drift results from single or multiple mutations affecting the RNA segment coding for either NA or, more commonly, HA proteins. As a result, there is alteration in the receptor binding domain of HA involving one or more amino acids resulting in minor changes in antigenicity. Antigenic variants within the A subtype (eg, H1 or H3) that emerge through natural selection gradually become the predominant circulating virus strain, while the preceding antigenic variant is suppressed by a specific immunity in the population. In contrast to antigenic drift, antigenic shift occurs when completely new viral subtypes emerge typically through gene reassortment with other circulating strains and acquisition of antigenically different gene sequences. Occurring at irregular intervals, antigenic shift may lead to pandemics (3).

Influenza A viruses (of subtypes H1N1 and H3N2) account for the majority of circulating influenza viruses in most countries and seasons, although influenza B is common in all regions of the world with approximately 20% of the reported influenza cases (4). Influenza B often co-circulates with influenza A, although it is rarely dominant, and usually circulates later in the season than influenza A viruses. According to data from the European Influenza Network, from 2001–2002 through 2010–2011 (excluding the 2009–2010 pandemic), on average 23% (range: 1%–60%) of influenza samples annually were identified as influenza B (5). For several decades, 2 distinct lineages of influenza B (the Victoria and Yamagata lineages) have circulated worldwide with varying intensity. Different B lineages have predominated or co-circulated in different regions, making the prediction of the circulating B lineage challenging (5) (6) (7).

The burden of influenza morbidity and mortality is high with a greater number of infections attributable to influenza A than influenza B. In Europe, nearly 40 000 people die prematurely each year due to influenza (8). In the United States (US), the burden of influenza in all ages is currently estimated to be 25 to 50 million cases per year, leading to 150 000 hospitalizations and 30 000 to 40 000 deaths. If these figures were extrapolated to the rest of the world, the average global burden of seasonal influenza would be in the order of 600 million cases, 3 million cases of severe illness and 290 000 to 650 000 deaths per year (9).

Influenza B outbreaks have been described among older adults, and have led to excess mortality in some annual epidemics (10) (11). Among the elderly, influenza B is associated with excess pneumonia and influenza hospitalizations, and while excess population-based hospitalization rates

associated with influenza B are lower than those associated with A/H3N2, they are twice as high as those associated with A/H1N1 (12). During the 2017-2018 season, the dominant circulating influenza B virus (B/Yamagata) was of high (11) severity, causing long duration of peak influenza activity and all-cause excess mortality in the European Union (EU) (11). Overall, influenza B is a significant cause of employee absenteeism, clinic visits, hospitalizations and deaths (13) (14) (15).

1.2 Background of the Investigational Product

The World Health Organization (WHO) recommends annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (9).

Traditional trivalent and quadrivalent inactivated influenza vaccines (TIV and QIV) administered by the intramuscular (IM) route contain a standard dose (SD) of 15 µg HA of each of the virus strains (one A/H1N1 strain, one A/H3N2 strain and one B strain for TIV and 2 B strains [B Yamagata lineage and B Victoria lineage for QIV]) with a total of 45 µg and 60 µg of HA antigen per dose, respectively.

However, the effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age, underlying conditions, and immune competence of the vaccine recipient and on the similarity between the virus strains present in the vaccine and the strains circulating in the community.

The immune response to SD influenza vaccines (15 µg HA per strain) is sub-optimal in adults 65 years of age and older compared to healthy young adults (16). A strategy to improve protection against influenza in adults 65 years of age and older is to increase the antigen dose. Therefore, Sanofi Pasteur has developed a high-dose quadrivalent influenza vaccine (QIV-HD) containing 60 µg of HA of each of 4 virus strains (A/H1N1, A/H3N2, and 1 B strain from each of the Victoria and the Yamagata lineages).

The QIV-HD has been developed based on the experience gained with Sanofi Pasteur's high-dose trivalent influenza vaccine (TIV-HD) which contains 60 µg HA of each of 3 virus strains and is manufactured in the US. TIV-HD was licensed by Sanofi Pasteur under the name of Fluzone® High-Dose for use in adults 65 years of age and older in the US since 2009, Canada since 2015, Australia since 2017, Brazil since 2018, and the United Kingdom since 2019. The production of QIV-HD uses the same drug substance (DS) and drug product (DP) manufacturing processes except for the DP formulation step, which includes the addition of a 2nd influenza B strain at the same HA content as the other 3 strains (60 micrograms [µg] HA/strain/dose). This results in a slightly higher fill volume of 0.7 mL.

Results of clinical studies conducted in adults 65 years of age and older have shown that TIV-HD resulted in superior immune responses (17) and improved vaccine efficacy (18) compared to a standard-dose trivalent influenza vaccine (TIV-SD). The benefit of TIV-HD was further confirmed by post-licensure real world evidence (RWE) studies conducted in more than 6 million people (19) (20) (21) (22). Approximately 26 546 subjects have been exposed to TIV-HD through its clinical development program and after post-marketing surveillance up to 30 September 2018 (ie, more than 109 million doses distributed), and the safety profile of TIV-HD in humans has been shown to be well tolerated with no safety concerns.

A Phase III clinical study (QHD00013) was conducted in adults 65 years of age and older in the US during the 2017-2018 Northern Hemisphere influenza season. QHD00013 demonstrated the non-inferior immunogenicity of QIV-HD compared to the TIV-HD controls for all strains. QIV-HD was also found to be safe and well tolerated and showed comparable reactogenicity (solicited injection site reactions and solicited systemic reactions) to TIV-HD. These results support the objective of the clinical development of QIV-HD by demonstrating that QIV-HD is able to induce robust immune responses to the 4 influenza strains contained in the vaccine while offering the possibility of increased protection by containing both B lineages, without compromising vaccine safety.

In addition, a Phase II descriptive safety and immunogenicity study (QHD00008) has also been conducted in adults 65 years of age and older in Japan to describe the safety and immunogenicity of QIV-HD in the Japanese population and support further clinical development in Japan.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects participating in Study QHD00011 will receive influenza vaccination with either the investigational QIV-HD or the control, standard-dose quadrivalent influenza vaccine (QIV-SD). All subjects will therefore be vaccinated against the influenza viruses recommended by the WHO for the 2019-2020 Northern Hemisphere (NH) influenza season. Thus, these older adults may be protected against those strains and be less likely to catch influenza or develop complications from an influenza infection during the respective influenza season.

Regarding immunogenicity, QIV-HD has been shown to induce an effective immune response against the 4 influenza strains included in the vaccine in adults 65 years of age and older. In adults 60 to 64 years of age, the immune response of TIV-HD is expected to be similar to the response induced in adults 65 years of age and older. The QIV-HD is also expected to induce an effective immune response against 4 influenza strains and higher geometric mean titers (GMTs) and seroconversion rates than the control QIV-SD. Therefore, the investigational QIV-HD is likely to bring an increased benefit versus QIV-SD in terms of immunogenicity against influenza virus strains.

1.3.2 Potential Risks to Subjects

1.3.2.1 Potential Risks and Possible Side Effects of QIV-HD Vaccination

The QIV-HD is safe and well tolerated in this population. Safety data of QIV-HD observed in adults 65 years of age and older can be anticipated to be at least similar in adults 60 to 64 years of age. However, as with any vaccine, the QIV-HD vaccine may cause side effects in certain people.

Expected Adverse Events

The safety of QIV-HD is based on adverse reactions (ARs) that were recorded following vaccination with QIV-HD during study QHD00013 (1,777 adults 65 years of age and older) and ARs reported during clinical development and post-marketing experience with TIV-HD.

The very common reactions (may affect more than 1 in 10 people) occurring after QIV-HD administration were injection site pain, myalgia, headache and malaise.

The following reactions have been also observed:

- Reactions at the injection site such as erythema, swelling, bruising, and induration. Their frequencies have been estimated as common (may affect up to 1 in 10 people)
- Systemic reactions such as pruritus, fever, nausea, diarrhea, cough, and vertigo. Their frequencies have been estimated as uncommon (may affect up to 1 in 100 people)
- Fatigue, flushing, arthralgia, dizziness, vomiting pruritus, urticaria and pain in extremities. Their frequencies have been estimated as rare (may affect up to 1 in 1000 people)
- Muscle weakness, dyspepsia, night sweats, lethargy and rash. Their frequencies cannot be estimated from available data

Most of these reactions usually occurred within the 3 days following vaccination, and resolved within 3 days of vaccination. The intensity of these reactions was mostly Grade 1 (mild) to Grade 2 (moderate).

Other Potential Adverse Events

In addition to the expected adverse events (AEs), the following additional AEs have been spontaneously reported during the post-marketing use of TIV-HD (23) or during clinical trials conducted on TIV-HD, and may occur in people receiving QIV-HD:

These events are reported voluntarily from a population of uncertain size, consequently it is not always possible to reliably estimate the frequency of the events or establish a causal relationship to vaccine exposure. The AEs were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to TIV-SD:

- *Blood and Lymphatic System Disorders*: thrombocytopenia, lymphadenopathy
- *Immune System Disorders*: anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- *Eye Disorders*: ocular hyperemia
- *Nervous System Disorders*: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), paresthesia
- *Vascular Disorders*: vasculitis, vasodilatation
- *Respiratory, Thoracic and Mediastinal Disorder*s: dyspnea, wheezing, throat tightness, oropharyngeal pain, rhinorrhea
- *General Disorders and Administration Site Conditions*: chest pain

1.3.2.2 Potential Risks and Possible Side Effects of QIV-SD Vaccination

Refer to the package inserts of the marketed QIV-SD vaccine (Influvac™ Tetra) for information regarding potential risks.

1.3.2.3 Possible Reactions to Blood Draw

Venipuncture causes transient discomfort and may cause temporary hypotension from a vasovagal response (eg, fainting). If pressure is not applied long enough to the venipuncture site, bruising due to bleeding beneath the skin may occur. Infection at the site of needle insertion could theoretically occur but is exceedingly rare when the standard sterile technique is utilized.

1.4 Rationale for the Study

While federal health agencies in European countries recommend that elderly persons receive influenza vaccination, the results of a European seasonal influenza vaccination survey, reported by the European Centre for Disease Prevention and Control, reveal that the recommended ages for influenza vaccination of the elderly vary from country to country (24). During the 2014-2015 influenza season, all 30 participating countries recommended seasonal influenza vaccination for people in the "older" age groups, but the actual age specified as "older" differed between countries. The recommended age of "older" adults who should be vaccinated against influenza was ≥ 65 years of age in 18 countries. A cut-off of ≥ 60 years was reported by 6 countries (Germany, Greece, Hungary, Iceland, the Netherlands, and Portugal). Slovakia recommended vaccination of persons 59 years of age and older. Malta and Poland recommended vaccination of persons 55 years of age and older. Three countries (Austria, Belgium, and Ireland) recommended vaccination of those who are 50 years of age and older.

Clinical data generated with TIV-HD or QIV-HD support an indication in persons starting at 65 years of age and older. To extend the age indication downwards to 60 to 64 years of age in Europe, the QHD00011 study is being proposed to collect and analyse immunogenicity and safety data in the 60 to 64 years of age population. In addition, as no data comparing the QIV-HD to the QIV-SD standard of care licensed in Europe have been generated to date, a group of subjects 65 years of age and older is also proposed to be evaluated in QHD00011.

QHD00011 will be a Phase III, randomized, modified double-blind , active-controlled, multi-center trial to assess the immunogenicity and safety of the QIV-HD in approximately 1540 healthy subjects 60 years of age and older in Europe. The goal of this study is to show that vaccination with QIV-HD induces an immune response (as assessed by hemagglutination inhibition [HAI] GMTs) that is superior to responses induced by the QIV-SD for the 4 virus strains at 28 days post-vaccination in subjects 60 to 64 years of age and in subjects 65 years of age and older.

2 Study Objectives

2.1 Primary Objective

Immunogenicity

To demonstrate that QIV-HD induces an immune response that is superior to the responses induced by QIV-SD for all 4 virus strains 28 days post-vaccination in subjects 60 to 64 years of age and in subjects 65 years of age and older.

The endpoints for the primary objective are presented in Section 9.1.2.

2.2 Secondary Objectives

Immunogenicity

To further describe the immune response induced by QIV-HD and QIV-SD in all subjects by age group, in pooled age groups, and by vaccine group (QIV-HD; QIV-SD).

Safety

To describe the safety profile of all subjects by age group, in pooled age groups, and by vaccine group (QIV-HD; QIV-SD).

The endpoints for the secondary objectives are presented in Section 9.2.1 and Section 9.2.2 for safety and immunogenicity, respectively.

2.3 Observational Objectives

Immunogenicity

- To describe the immune response 28 days after vaccination by virus seroneutralization (SN) measurement method for at least 50% of subjects in each age group (60 to 64 years of age; 65 years of age and older) and in pooled age group by vaccine group (QIV-HD; QIV-SD).
- To describe the anti-NA immune response in at least 50 subjects in each age group and in pooled age group by vaccine group (QIV-HD; QIV-SD).

Blood samples from at least 50% of subjects in each age group and each vaccine group will be analyzed for SN. And among these subjects, blood samples from at least 50 subjects in each age group and each vaccine group will be analyzed for NA.

The endpoint(s) for the observational objective(s) are presented in Section 9.3.2.

3 Investigators and Study Organization

This study will be conducted in approximately 15 to 20 centers in the EU including Belgium, France, and Germany. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator in each country or each region. Details of the study centers, the Investigators at each center, and the Coordinating Investigator(s) are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal safety management team (SMT) will perform an analysis of safety data during the conduct of the study.

Monitoring activities on site, development activities for data management, and conduct of the data management activities will be conducted by a contract research organization (CRO) under the responsibility of Sanofi Pasteur SA.

No Independent Data Monitoring Committee (IDMC) is planned for this trial as no safety concerns emerged during the previous clinical trials conducted with the QIV-HD, and the fact that the safety profile of TIV-HD in humans has been shown to be well tolerated with no safety concerns, in 25,564 subjects who received at least one dose of TIV-HD in the clinical development studies and observational studies as well as after 8 years of post-marketing surveillance with more than 90 million doses distributed (see Section 5.1.2).

The Sponsor's Responsible Medical Officer (the RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is Sanjay Gurunathan, MD, Associate Vice President and Head, Global Clinical Development Centers of Excellence (Europe/North America).

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent forms (ICFs), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).
In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator (if the Investigator is responsible for the submission of the dossier to the IEC / IRB) to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

The Investigator or Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the study will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy, and according to local regulations.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

QHD00011 will be a Phase III, randomized, modified double-blind , active-controlled, multi-center study to assess the immunogenicity and safety of the QIV-HD in approximately 1540 healthy subjects 60 years of age and older in Europe. The goal of this study is to show that vaccination with one dose of QIV-HD induces an immune response (as assessed by HAI GMTs) that is superior to responses induced by one dose of QIV-SD for the 4 virus strains at 28 days post-vaccination in subjects 60 to 64 years of age and in subjects 65 years of age and older.

In each age group, eligible subjects will be randomized in a 1:1 ratio to receive a single IM injection of either QIV-HD or QIV-SD at Day (D)0 as follows:

1. QIV-HD; stratified by age (60 to 64 years of age; 65 years of age and older)
2. QIV-SD; stratified by age (60 to 64 years of age; 65 years of age and older)

For further details concerning the number of subjects allocated to each study group, see Table 6.1.

All subjects will provide a pre-vaccination (baseline) blood sample at D 0 and a post-vaccination blood sample at Visit (V) 02 (D28 [+7 days]) for HAI testing. A randomized subset of these subjects (observational subset) will be used for SN and NA testing.

Solicited injection site and systemic reactions will be collected up to 7 days after vaccination, and unsolicited AEs will be collected up to V02, which is the active phase of the trial (V01 to V02 [D0-D28]). SAEs and adverse events of special interest (AESIs[a]) will be collected throughout the trial (D0 through approximately D180 [6-month follow-up period]).

Interactive response technology (IRT) will be used to randomly assign subjects to one of the 2 study groups and to assign subject numbers in each of the groups. In addition, IRT will be used to randomly assign subjects to the observational subsets. Electronic data capture (EDC) will be used for the collection of data.

5.1.2 Justification of the Study Design

Clinical data generated in studies of TIV-HD or QIV-HD support an indication in persons from 65 years of age and older. To extend the age indication downwards to 60 to 64 years of age in Europe, the QHD00011 study is being proposed to collect and analyze immunogenicity and safety data in the 60 to 64 years of age population. In addition, as no data comparing the QIV-HD to the QIV-SD standard of care licensed in Europe have been generated to date, a group of subjects 65 years of age and older is also proposed to be evaluated in QHD00011.

[a] **Note:** AESIs will be captured as SAEs. These include new onset of GBS, encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.

The primary objective of QHD00011 is to demonstrate that QIV-HD induces an immune response (as assessed by HAI antibody [Ab] titers of all 4 virus strains on D 28) that is superior to the responses induced by QIV-SD in subjects 60 to 64 years of age and in subjects 65 years of age and older.

Given the acceptable safety data generated from over 1800 subjects vaccinated with the QIV-HD in the US (Phase III QHD00013 study) and Japan (Phase I/II QHD00008 study), and the fact that the safety profile of TIV-HD in humans has been shown to be well tolerated with no safety concerns, in 25,564 subjects who received at least one dose of TIV-HD in the clinical development studies and observational studies as well as after 8 years of post-marketing surveillance with more than 90 million doses distributed, neither an early safety data review nor IDMC is planned for this trial.

The QHD00011 study will be a modified double-blind study with unblinded designated vaccine preparer(s)/administrator(s) used at each study site. The designated vaccine prepare(s)/administrator(s) will be unblinded given the different volumes in the QIV-HD and QIV-SD vaccines (0.7 milliliter [mL] for QIV-HD and 0.5 mL for QIV-SD), but neither the subject nor the investigator nor the study staff in charge of vaccination will know which vaccine will be administered (the syringes will be masked to maintain the blind of the subjects and other members of the clinical site). The unblinded designated vaccine preparer(s)/administrator(s) will not be involved in any of the blinded study assessments (eg, immunogenicity, safety). The Investigators (or delegates) in charge of safety assessment, the trial staff who collect the safety data, and the laboratory personnel who analyze the blood samples will not know which product was administered.

Additional details will be provided in the Operating Guidelines for the study.

5.1.3 Study Plan

The study plan is summarized in the Table of Study Procedures.

Vaccination

All eligible subjects will be randomized to receive a single injection of either the QIV-HD vaccine or QIV-SD at V01 (D0).

Blood Sampling

All subjects will provide a pre-vaccination blood sample at V01 (D0) and a post-vaccination blood sample at V02 (D28 [+ 7 days]).

Collection of Safety Data

Subjects will be asked to notify the site immediately about any potential SAEs at any time during the study.

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

Subjects will record information about solicited reactions (D0-D7), unsolicited AEs (D0-V02), SAEs (D0-V02), and AESIs (D0-V02) in a diary card (DC).

Staff will review the D0 to V02 safety data with subjects at V02.

Subjects will continue to collect information on SAEs and AESIs in a memory aid (from V02-D180). Staff will contact subjects by telephone at D180 (+14 days) post-vaccination to review the memory aid and to identify the occurrence of any SAEs and AESIs that had not yet been reported.

5.1.4 Visit Procedures

Visit 1 (D0): Inclusion, Randomization, Blood Sample, and Vaccination

1) Explain the trial to the subject, answer any of his / her questions and ensure that he / she has been informed of all aspects of the trial that are relevant to his / her decision and obtain a written informed consent signed by the subject.

   The Investigator / delegate will also sign and date the ICF. The Investigator / delegate will then retain one original and give the copy to the subject.

2) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through physical examination and medical interview for eligibility.

3) Collect relevant demographic information (eg, age, year of birth, gender, and race).

4) Collect significant medical history and record any planned hospitalization during the trial in the CRB and other source documents.

5) Obtain information about history of influenza vaccination / influenza infection (diagnosis laboratory confirmed) in the previous 3 years.

6) Perform a urine pregnancy test (women of childbearing potential only).

7) Collect reportable concomitant medications (see Section 6.7).

8) Perform and document a targeted physical examination per standard site-specific immunization practices and record oral temperature[a] in the medical chart.

9) If the subject satisfies all eligibility criteria, contact the IRT to assign to the subject a 12-digit subject number and allocate a treatment number (see Section 6.5). At this time, some subjects will be assigned to the observational subsets (ie, Full Analysis Set-Seroneutralization [FAS-SN] Subset and FAS-NA Subset).

10) Draw an approximately 10 mL blood sample (This blood sample should be drawn before vaccination). Process the blood sample as specified in the "Management of Samples" section (see Section 7).
    Note: If the subject withdraws consent before blood sampling (before any invasive procedure has been performed), do not vaccinate the subject. The subject should be terminated from the study.
    Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), then the subject is still to be included in the study and vaccinated.
    Note: If the blood sample cannot be obtained, the subject should be given the opportunity to

[a] Tympanic and temporal artery thermometer should not be used.

return to the study site for another attempt, as long as the study is still enrolling subjects and as long as the subject continues to remain eligible for the trial and that includes reviewing Inclusion/Exclusion criteria, medical history, and ICF process. All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject should not be vaccinated and should be discontinued from the study.

11) Unblinded designated vaccine administrator administers the appropriate study vaccine by IM injection into the region of the deltoid muscle, although it may also be given subcutaneously (SC). The vaccine must be administered on the side opposite to that of blood sampling.

12) Record the injection site / side / route / treatment number in the CRB and affix the detachable corresponding label in the source document and vaccination card if any.

13) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any AE in the CRB.

14) Give the subject the DC to record any injection site reactions and systemic AEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs.

15) Give the subject a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement, and instructions on how to use them.

16) Instruct on the need to promptly report any SAE that may occur at any time during the trial.

17) Complete the relevant case report forms (CRFs) for this visit and schedule an appointment for Visit 2.

Visit 2 (D28 [+7] days after Visit 1): Collection of Safety Information and Blood Sample

1) Collect and review the DC since Visit 1, including any AEs, medications, or therapy that occurred since vaccination. The occurrence of any injection site reaction, systemic event/reaction, and/or any SAE (including AESI) should have been reported in the DC.

2) Perform a targeted physical examination, as necessary, based on medical history.

3) Draw an approximately 10 mL blood sample for the titration of Abs.
Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), the subject should be given the opportunity to return to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRB. The subject will continue to be followed-up for safety purposes.

4) Provide the subject with a memory aid and review the directions for its use.

5) Remind the subject to expect a safety follow-up telephone call 180 days after Visit 1.

6) Remind the subject to report any SAE (including AESI) that may occur between Visit 2 and the 6-month follow-up call.

7) Complete the V02 termination record of the CRF for all subjects.

D180 Safety Follow-up Telephone Call (180 days [+14 days], approximately 6 months after vaccination): Collection of SAEs

1) This telephone call must be made by a qualified person, such as a physician or a qualified study nurse.
2) Inquire whether the subject has received any vaccinations since the last contact (to be taken into account for the collection of information in the "Concomitant Vaccination" section) (see Section 6.7).
3) Review the memory aid to identify any SAEs and AESIs that occurred since Visit 2 that had not yet been reported. Perform follow-up on any SAEs and AESIs.
4) Explain that this will be the last contact with the site for this trial (except for subjects with SAEs (including AESI) that need further follow-up, as stated below).
5) A follow-up visit can be arranged depending on the information recorded during the phone call.
6) Complete the relevant CRFs for this telephone call.

If the first contact attempt to complete the last telephone call is unsuccessful, at least 2 separate additional attempts, conducted on different days, should be made to contact these subjects. All attempts must be documented in the subject's source notes. If, after at least 3 documented attempts, contact cannot be established, the subject should be classified as lost to follow-up (see Section 5.2.9 for further details).

The exceptions for the final phone calls are as follows:

- Subjects who voluntarily withdrew
- Subjects who have been previously classified as lost to follow-up

Follow-up of Subjects With Related AEs or With AEs That Led to Study/Vaccination Discontinuation:

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

- The AE is considered by the Investigator to be related to the product administered.
- The AE caused the discontinuation of the subject from the study or from vaccination.

5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained.

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject): October 2019 to May 2020

Planned inclusion period - FVFS to FVLS (first visit, last subject): October 2019 to November 2019

Planned primary vaccination period: October 2019 to November 2019

Planned end of study: May 2020

Planned date of final clinical study report: November 2020

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

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

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject voluntarily confirms his or her willingness to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

In accordance with GCP, prior to signing and dating the consent form, the subject must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

The 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 subject'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.

Informed consent forms will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject.

Documentation of the consent process should be recorded in the source documents.

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment:

1) Sixty years of age and older on the day of inclusion
2) Informed consent form has been signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures
4) Covered by health insurance if applicable in the country

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from study enrollment:

1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, or surgically sterile.
2) Participation at the time of study enrollment (or in the 4 weeks [28 days] preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
3) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to V02
4) Previous vaccination against influenza (in the previous 6 months) with either the trial vaccine or another vaccine
5) Receipt of immune globulins, blood or blood-derived products in the past 3 months
6) 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 past 3 months)
7) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[a]
8) Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on Investigator's judgment
9) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

[a] The components of QIV-HD are listed in Section 6.1 and in the Investigator's Brochure. The components of QIV-SD are listed in Section 6.2 and in the QIV-SD prescribing information.

10) Alcohol or substance abuse that, in the opinion of the Investigator might interfere with the trial conduct or completion

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

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

13) 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

14) Personal or family history of Guillain-Barré syndrome (GBS)

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

Depending on local or country regulations, if the subject has a primary physician who is not the Investigator, the site should contact this physician with the subject's consent to inform him / her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject 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 CRB. The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not

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

be coded. Its purpose is to assist in the later interpretation of safety data collected during the study.

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable since only one dose of vaccine will be administered in this trial.

5.2.8 Conditions for Withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time.

A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns or significant noncompliance with the protocol (based on the Investigator's judgment), without the subject's permission (withdrawal)
- At the request of the subject (dropout)

The reason for a withdrawal or dropout should be clearly documented in the source documents and in the CRB.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "Adverse Event") or for another reason.

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.2.1.1
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the investigator and returned unsigned, and the subject or parent/guardian did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • The subject or the parent/guardian signed the certified letter sent by the investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative	To be used: • When the subject or parent/guardian indicated unwillingness to continue in the study • When the subject or parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the study because of an AE or a protocol deviation.

For subjects where the reason for early termination was lost to follow-up or if the subject withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the subject's status at the end of the study is "Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative", the site will attempt to contact them for the D180 (6-month) follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.2.12 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy and if at least 1 dose of the study vaccine(s) has been administered, the subject will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the subject will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

All pregnancy cases should be reported if they occurred during the study and during the 6 month follow-up period. To report the pregnancy case, the Investigator must fill out Pregnancy Reporting forms in the EDC system and inform the Sponsor within 1 month of identifying a pregnancy case.

If the EDC system is not available, the investigator must fill out a paper Pregnancy Reporting Form (provided by the Sponsor at the start of the study) and inform the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome (ie, details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery.

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

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's 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 (please refer to Section 10).

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.4.

5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (eg, those that affect the conduct of the study or the safety of subjects) require IEC / IRB approval, and must also be forwarded to regulatory authorities.

An administrative / nonsubstantial amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. Administrative / nonsubstantial changes do not require IEC / IRB approval; however, the IEC / IRB must be notified whenever one is made.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IEC / IRB approval has already been given, are not initiated without IEC / IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.5 Interruption of the Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the countries where the study is taking place.

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

6 Products Administered

Given that different vaccines will be administered to subjects in each group, an unblinded administrator will be used at each study site to administer the vaccines. The administrator will not be involved in any of the blinded study assessments (eg, safety and immunogenicity). Taking into account the fact that the volumes to be injected will be different (0.7 mL for QIV-HD and 0.5 mL for QIV-SD), the syringes will be masked to keep the blind of the subjects and other members of the clinical site. Additional details will be provided in the Operating Guidelines for the study.

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product (QIV-HD)

The investigational QIV-HD is a split virion quadrivalent influenza vaccine (60 µg HA/strain) containing virus strains chosen by the WHO / EU for the NH 2019-2020 influenza season. The vaccine contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages). Each pre-filled syringe contains a total of 240 µg HA antigen per 0.7 mL dose provided in sterile suspension for IM injection into the upper arm (deltoid area). The QIV-HD vaccine is thimerosal-free and prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.1.1 Composition

Each 0.7 mL dose of QIV-HD vaccine contains the following components:

(Strains are based on WHO / EU recommendations for the 2019-2020 NH influenza season.)

Active Substances:

- A/(H1N1)-like strain 60 µg HA
- A/(H3N2)-like strain 60 µg HA
- B/(Victoria Lineage)-like strain 60 µg HA
- B/(Yamagata Lineage)-like strain 60 µg HA

Excipients:

- Octylphenol Ethoxylate (Triton X-100®) not more than (NMT) 350 µg

Diluent:

- Buffered saline solution quantity sufficient (qs) to appropriate volume

Preservative is not used in the manufacture of QIV-HD.

Batch number: to be determined (TBD)

6.1.1.2 Preparation and Administration

Vaccination is not to be performed in subjects allergic to one of the constituents of the vaccine.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

The vaccination schedule of a single dose for the influenza season is per standard practice for receipt of annual influenza vaccination.

6.1.2 Identity of Control Product (Licensed QIV-SD)

A QIV-SD vaccine licensed in Europe will be the control vaccine. Influvac Tetra is an influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated QIV-SD influenza vaccine. (https://www.medicines.org.uk/emc/product/9381/smpc). The licensed QIV-SD is a subunit quadrivalent influenza vaccine (15 µg HA/strain) containing virus strains chosen by the WHO / EU for the NH 2019-2020 influenza season. The vaccine contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages). Each pre-filled syringe contains a total of 60 µg HA antigen per 0.5 mL dose provided in sterile suspension for IM injection into the upper arm (deltoid area). QIV-SD vaccine is thimerosal-free and prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.2.1 Composition

Each 0.5 mL dose of licensed QIV-SD vaccine contains the following components:

(Strains are based on WHO / EU recommendations for the 2019-2020 NH influenza season.)

Active Substances:

- A/(H1N1)-like strain 15 µg HA
- A/(H3N2)-like strain 15 µg HA
- B/(Victoria Lineage)-like strain 15 µg HA
- B/(Yamagata Lineage)-like strain 15 µg HA

Excipients:

- Potassium chloride
- Potassium dihydrogen phosphate
- Disodium phosphate dehydrate
- Sodium chloride
- Calcium chloride dehydrate
- Magnesium chloride hexahydrate
- Water for injection

Batch number: TBD

6.1.2.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

The vaccination schedule of a single dose for the influenza season is per standard practice for receipt of annual influenza vaccination.

6.2 Identity of Other Product

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

All products for this modified double-blind trial will be administered by IM injection.

All study vaccines will be supplied with investigational labeling and packaging. Each single dose of investigational product will be identified by a unique treatment number on the label and on the carton. The control product will not have a unique identifier on the syringe label. The control product will only have a unique identifier on the carton label. The carton label will also have a detachable label for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator or designee will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (ie, verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

The Investigator will designate an unblinded staff member to assume the product management responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the study site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.3.2.3 Product Accountability

The unblinded person in charge of product management at the site will maintain records of product delivery to the study site, product inventory at the site, the dose(s) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRB. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the study site's product accountability records against the record of administered doses in the CRBs and the communication from the IRT (if applicable).

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.3.3 Replacement Doses

If a replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

Unused or wasted products will be either disposed of or returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the study period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

To ensure that objective data are obtained, the trial is designed as a modified double-blind study as follows:

- The unblinded qualified trial staff member, independent of the immunogenicity and safety evaluations and other trial evaluations will administer the vaccine
- The Investigators (or delegates) in charge of safety assessment, the trial staff who collect the safety data, and the laboratory personnel who analyze the blood samples will not know which product was administered
- The subject will not know which product was administered

The Investigator responsible for safety assessment will not attend the vaccination session but will be available in case of emergency (eg, anaphylactic shock).

Treatment numbers will be used to identify each vaccine syringe for the purpose of randomization, vaccination and the recording of vaccine administered. Treatment numbers will be randomly assigned to QIV-HD and QIV-SD syringes. The IRT vendor will be responsible for assigning the treatment group identification and treatment number to be received by the enrolled subject. The subject, the Investigator, and study staff members who collect the safety data and laboratory personnel who analyze the blood samples will all be blinded to the group assignment. The individual responsible for preparing / administering vaccine will not be authorized to collect any safety / serology data.

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

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

A request for the code to be broken may also be made:

- by the GPV Department through an internal system for reporting to health authorities in the case of an SAE as described in International Council for Harmonisation (ICH) E2A.[a] In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (ie, the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

The IEC / IRB must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site's study records and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

In any case, the code will be broken after the first database lock, for the primary statistical analysis planned to analyze the data collected within the 28 days following the vaccination, but the randomization list will not be provided to Investigators and will be kept internally until the final database lock.

6.5 Randomization and Allocation Procedures

The study will be a randomized, modified double-blind study for 2 vaccine groups. Table 6.1 shows the allocation of subjects to each vaccine group.

Table 6.1: Randomization of subjects by vaccine group (QIV-HD; QIV-SD)

	QIV-HD		QIV-SD	
	60 to 64 years of age	**≥65 years of age**	**60 to 64 years of age**	**≥65 years of age**
Subjects to be Randomized per Age Group	385	385	385	385
Subjects to be Randomized per Vaccine Group	770		770	

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

Randomization of subjects will be performed with the permuted block method with stratification by site and age group. Each subject who meets the inclusion/exclusion criteria and signs the ICF will be randomly assigned according to his/her age group, to one of the 2 vaccine groups (either the QIV-HD group or the QIV-SD group) via an IRT, according to a 1:1 ratio.

For the assessment of the immune response by virus SN and enzyme-linked lectin assay (ELLA) methods, randomization to the observational subsets (FAS-SN subset and FAS-NA subset) will be performed with stratification on vaccine group, age groups (60 through 64 years of age or ≥65 years of age), and site. The FAS-NA subset is a subset of the FAS-SN subset.

Table 6.2: Randomization to the Observational Subsets

	QIV-HD		QIV-SD		Total
	60 to 64 years of age	≥65 years of age	60 to 64 years of age	≥65 years of age	
Subjects to be randomized to FAS-SN subset	≥193	≥193	≥193	≥193	≥386
Subjects to be randomized to FAS-NA subset	≥50	≥50	≥50	≥50	≥100

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 250000100005 is the fifth subject enrolled in Center Number 1 in France (250 being the country code for France). The 5-digit subject identifier is detailed in the Operating Guidelines.

The IRT will also indicate inclusion into the observational subsets (FAS-SN and FAS-NA). As previously noted, the FAS-NA observational subset is a subset of the FAS-SN observational subset.

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

6.6 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified study personnel

- The person in charge of product management at the site will maintain accountability records of product delivery to the study site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

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

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of vaccination (D0) to the end of the solicited and unsolicited follow-up period (D28 +7days).

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Four categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], steroids/corticosteroids)
- Category 2: medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Global Clinical Immunology [GCI] department, steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, steroids/corticosteroids)
- Category 4: the statin family of anti-hyperlipidemia medications (eg, atorvastatin, rosuvastatin, simvastatin, pravastatin, and fluvastatin)

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

- Trade name
- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables
- Medication category (1, 2, 3, or 4)
- Start and stop dates

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

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 CRF unless the medication(s) received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visit 1 (D0, pre-vaccination) and at Visit 2 (D28). See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At Visits 1 and 2, 10 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label, and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of one hour and a maximum of 24 hours in order to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

After centrifugation, the serum is transferred to the appropriate number of aliquoting tubes. These tubes are pre-labeled with adhesive labels that identify the trial code, the subject's number, and the sampling stage or visit number.

The subject's number, the date of sampling, the number of aliquots obtained, the date and time of preparation, and the subject's consent for future use of his / her samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

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

Assays will be performed by the Sponsor's laboratory (GCI, Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility.

7.4 Future Use of Stored Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for up to 25 years after the end of the study. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and to revalidate the results of the study.

Subjects will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, DCs, memory aids, and other study documents, as well as with the following study materials: all study vaccines, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

The means for performing EDC will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and / or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Safety

There are no primary objectives for safety.

9.1.2 Immunogenicity

9.1.2.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity for subjects in each age group (60 to 64 years of age; 65 years of age and older) and for subjects in each vaccine group (QIV-HD; QIV-SD) are the following:

- HAI Ab titers obtained on D28

9.1.2.2 Immunogenicity Assessment Methods

9.1.2.2.1 Hemagglutination Inhibition

To support the primary and secondary objectives of this study, HAI Ab titers will be determined on all blood samples obtained at D0 and D28.

Anti-Influenza Virus Ab Titration by Inhibition of Hemagglutination

Assays will be performed by the Sponsor's laboratory (GCI, Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility. The address is provided in the Operating Guidelines.

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 unit (HAU)/25 µL. Influenza antigen is not added to the serum control wells containing only serum and RBCs. The mixture is then incubated and a RBC suspension is added. Following incubation, the results are read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample is titrated in 2 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/dilution [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).

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Safety

9.2.1.1 Safety Definitions

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

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

Therefore an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event (IME)

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or autoimmune disease.

Adverse Reaction:

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

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

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

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[a] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

Solicited Reaction:

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (eg, fever, headache, malaise, myalgia, shivering, or injection site pain, erythema, swelling, induration, or bruising).

By definition, solicited reactions are to be considered as being related to the product administered.

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

The assessment of these reactions by the investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D7 is a solicited reaction (ie, prelisted in the protocol and CRB), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

An AESI is one of scientific and medical concern specific to the Sponsor's product 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.

9.2.1.2 Safety Endpoints

The secondary endpoints for the evaluation of safety are the description of the following in all subjects:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's DC and CRB) injection site reactions and systemic reactions occurring up to 7 days after vaccination.

- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to 28 days after vaccination.
- Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the study.

9.2.1.3 Safety Assessment Methods

At each visit, the Investigator or a delegate will perform a medically-driven physical examination and will ask the subject about any solicited reactions and unsolicited AEs recorded in the DC, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.2.1.3.1 Immediate Post-vaccination Observation Period

Subjects 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. Any AE that occurs during this period will be noted on the source document and recorded in the CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected).
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination.
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

9.2.1.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After Vaccination)

After vaccination, subjects will be provided with a DC, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the DC on the day of vaccination and for the next 7 days (ie, D 0 through D 7) until resolution:

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

  The action(s) taken by the subject to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

Subjects will be contacted by telephone 180 days after vaccination to capture follow-up safety data.

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

Table 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the DCs and CRB, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales

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

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Intensity scale*	Grade 1: A type of adverse event (AE) that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

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

Table 9.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Shivering**
MedDRA preferred term [PT]	Pyrexia	Headache	Malaise	Myalgia	Chills
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Shivering
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event (AE) that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

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

Important Notes for the Accurate Assessment of Temperature:

Subjects are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC / memory aid, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is oral. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

9.2.1.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects will be instructed to record any other medical events that may occur during the 28-day period after vaccination. Space will be provided in the DC for this purpose.

Information on SAEs will be collected and assessed throughout the study, from inclusion until 6 months after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). See Section 10 for further details on SAE reporting.

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

- Start and stop dates[a]
- Intensity of the event:

  For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1 and Table 9.2).

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

  - Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

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

  - Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.2.1.3.6.

- Action taken for each AE (eg, medication)

  The action(s) taken by the subject to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

  For each SAE, the investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)

- Whether the AE caused study discontinuation

9.2.1.3.4 Medically-Attended Adverse Events

Medically-attended adverse events will not be captured during this study.

9.2.1.3.5 Adverse Events of Special Interest

An AESI is defined as event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. AESIs will be captured as SAEs (ie, collected throughout the trial). AESIs include the following:

- new onset of GBS
- encephalitis / myelitis (including transverse myelitis)
- Bell's palsy
- optic neuritis
- brachial neuritis

9.2.1.3.6 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the product 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 an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)

Related – There is a "reasonable possibility" that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all AEs reported at the injection site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

Adverse events likely to be related to the product, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

9.2.2 Immunogenicity

9.2.2.1 Immunogenicity Endpoints

For subjects in each age group (60 to 64 years of age; 65 years of age and older) and for subjects in each vaccine group (QIV-HD; QIV-SD):

- HAI Ab titers obtained on D0 and D28
- Individual HAI titers ratio D28/D0
- Subjects with titers ≥ 40 [1/dil] at D28
- Seroconversion (titer < 10 [1/dil] at D0 and post-vaccination titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28)

9.2.2.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 9.1.2.2.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Safety

There are no observational objectives for safety.

9.3.2 Immunogenicity

9.3.2.1 Immunogenicity Endpoints

9.3.2.1.1 Immunogenicity Assessment by Seroneutralization

Neutralizing Ab titers for subjects in the observational subset will be measured for each influenza strain with the SN method.

For each vaccine strain, the secondary immunogenicity endpoints are as follows:

- Individual neutralization test (NT) Ab titer on D0 and D28
- Individual NT Ab titer ratio (fold-rise in serum NT post-vaccination relative to D0) at D28
- Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28
- Fold-rise in NT Ab titer [post/pre] ≥ 2 and ≥ 4 at D28
- Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0 and D28

9.3.2.1.2 Immunogenicity Assessment by ELLA

Anti-N1and -N2 titers for subjects in the observational subset will be measured for the 2 influenza A strains using ELLA.

For each A strain, the secondary immunogenicity endpoints are as follows:

- Individual ELLA Ab titer on D0 and D28
- Individual ELLA Ab titer ratio (fold-rise in serum ELLA post-vaccination relative to D0) at D28
- Subjects with ELLA Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28
- Fold-rise in ELLA Ab titer [post/pre] ≥ 2 and ≥ 4 at D28
- Detectable ELLA (ELLA Ab titer ≥ 10 [1/dil]) at D0 and D28

9.3.2.2 Immunogenicity Assessment Methods

9.3.2.2.1 Seroneutralization

To support the observational objectives of this study, the virus SN method will be used to describe the immune response 28 days after vaccination in an observational subset.

Influenza Virus Neutralization Test

Assays will be performed by the Sponsor's laboratory (GCI, Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility.

This NT measures Abs directed against the viral neutralization epitopes of the influenza virus, which may be different from the hemagglutination epitopes, therefore, the NT titers may be different from the HAI titers.

To measure NT, serially diluted, heat-inactivated human serum samples will be pre-incubated with a fixed amount of challenge virus prior to the addition of Madin-Darby canine kidney (MDCK) cells. After overnight incubation, the viral nucleoprotein production in infected MDCK cells is measured by enzyme-linked immunosorbent assay (ELISA), using monoclonal Ab specific to either influenza A nucleoprotein or influenza B nucleoprotein. Since serum neutralizing Abs to the influenza virus inhibits the viral infection of MDCK cells, the ELISA optical density results are inversely proportional to the titers of neutralizing Ab present in the serum. The LLOQ is set at the reciprocal of the lowest dilution used in the assay, ie, 10 (1/dil). Titers below this level are reported as < 10 (1/dil). Titers > 10240 (1/dil) are pre-diluted, retested, and the end titer is reported.

9.3.2.2.2 Enzyme-Linked Lectin Assay for the Measurement of Anti-Neuraminidase

To also support the observational objectives of this study, the ELLA for the measurement of anti-neuraminidase immune response in subjects in an observational subset.

Enzyme-Linked Lectin Assay

Assays will be performed by the Sponsor's laboratory (GCI, Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility.

The ELLA measures neuraminidase inhibiting Ab by quantifying enzymatic activity using peanut-agglutinin (PNA) to bind to terminal galactose moieties that are exposed after enzymatic cleavage.

Serum samples, quality control sera, and a determined amount of virus will be added into duplicate wells of a fetuin-coated 96-well plate and incubated overnight. The following day, peroxidase-conjugated PNA will be added to the washed plate and incubated, followed by washing and color development with o-Phenylenediamine dihydrochloride (OPD) substrate. The absence of color indicates inhibition of NA activity due to the presence of NA-specific inhibiting Abs. The titer of each determination will be the reciprocal of the last dilution with an optical density (OD) equal to or less than the midpoint between the mean OD of the virus only control wells and the mean OD of the background wells on each plate. The LLOQ is set at the reciprocal of the lowest dilution used in the assay, ie, 10 (1/dil). Titers below this level will be reported as < 10 (1/dil). There is no defined upper limit of quantification (ULOQ) for the NA1 and NA2 ELLAs. There are assay ranges which have upper bounds that are established during method qualification. Samples which result in titers greater than these upper bounds would be retested using an additional 1:8 pre-dilution to bring the titer into the assay range and then back calculated to account for the pre-dilution factor of 1:8.

9.3.3 Efficacy

No clinical efficacy data will be obtained in the study.

10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product(s). It is the responsibility of the Investigator to request all necessary documentation (eg, medical records, discharge summary, physical autopsy report if performed) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

Serious adverse events occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The investigator (licensed physician [Doctor of Medicine (MD) or Doctor of Osteopathic Medicine (DO)]) must validate the information entered on the AE CRF by completing the investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the Clinical Team Leader (CTL) with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the Operating Guidelines.

The Investigator must complete the paper copies of the AE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by one of the following means:

- By fax, to the following number: +33 4 37 37 71 32
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address
  Global PharmacoVigilance, Sanofi Pasteur SA
  14, Espace Henry Vallée
  69007 LYON, France

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

If there is need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (eg, outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and to the CRA. Copies of documents (eg, medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), other products (eg, a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.2.1.3.6.

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

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor's RMO will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the study protocol.

All unexpected and related SAEs submitted to competent authorities will be unblinded by the GPV Department through an internal system for reporting to health authorities as described in ICH E2A. In this case, the information resulting from code-breaking (ie, the subject's vaccine or group assignment) will be communicated to health authorities. To maintain the blind, this information will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual DCs, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.2.1.3. These DCs will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Subjects will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A memory aid may be provided to the subjects at the preceding study visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the AE CRF. Any SAEs captured during this 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

At specified intervals, the Investigator or an authorized designee will interview the subjects to collect the information recorded in the DC, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the DC will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

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

11.2 Data Management

Management of SAE and Pregnancy Data

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) and pregnancy data (reported by the Investigator on ePregnancy Forms) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information from the GPV database cases will be reconciled with that in the clinical database.

Management of Clinical and Laboratory Data

Clinical data, defined as all data reported in the CRB, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and / or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency before integration into the clinical Datawarehouse.

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

11.3 Data Review

A blind review of the data is anticipated through the data review process led by Data Management before database lock.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical database data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor, US, with the Statistical Analysis System (SAS) software, at least version 9.4 (SAS Institute, Cary, North Carolina, USA).

A statistical analysis plan (SAP) will be written and peer reviewed before any analyses are performed. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

For the purposes of the statistical methods section, the 4 virus strains in the QIV-HD trial groups and the QIV-SD trial groups will be labeled as follows:

- A/(H1N1)-like strain A1
- A/(H3N2)-like strain A2
- B/(Victoria Lineage)-like strain B1
- B/(Yamagata Lineage)-like strain B2

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Immunogenicity

12.1.1.1.1 Hypotheses

A superiority approach will be used to compare post-vaccination GMTs between QIV-HD and QIV-SD groups for each strain and in each age group using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses:

$$H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{QIV-SD}} \leq 1 \Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{QIV-SD}) \leq 0$$

$$H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{QIV-SD}} > 1 \Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{QIV-SD}) > 0$$

where

s: strain

If superiority is demonstrated for post-vaccination GMTs for the 4 strains within a same age group, then the immunogenicity of QIV-HD will be considered as superior to QIV-SD in the corresponding age group.

12.1.1.1.2 Statistical Methods

The statistical methodology will be based on the use of the lower bound of the 2 sided 95% confidence intervals (CIs) of the ratio of post-vaccination GMTs between the QIV-HD and QIV-SD groups. The CIs will be calculated by normal approximation of log-transformed titers for GMTs.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Immunogenicity

12.1.2.1.1 Hypotheses

No hypotheses will be tested.

12.1.2.1.2 Statistical Methods

Immunogenicity endpoints will be summarized by age group, in pooled age groups, and by vaccine group with 95% CIs. The CIs of geometric mean (GM) of titers and individual titer ratios will be calculated assuming normal approximation of log-transformed values. CIs of proportions will be calculated using the Clopper-Pearson method. Reverse cumulative distribution curves against each strain will be performed for each time point. Additional parameters may be displayed as appropriate.

12.1.2.2 Safety

12.1.2.2.1 Hypotheses

No hypotheses will be tested.

12.1.2.2.2 Statistical Methods

Safety endpoints will be summarized by age group, in pooled age groups, and by vaccine group, with 95% CI for the main endpoints. The CIs will be calculated using the Clopper-Pearson method.

12.1.3 Statistical Methods for Observational Objectives

The analyses will be descriptive. The main parameters will be described by age group, in pooled age groups, and by vaccine group with 95% CI.

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

The FAS is defined as the subset of randomized subjects who received one dose of the study vaccine and had a post-vaccination blood sample.

For the assessment of the immune response by virus SN and ELLA method, the analysis will be performed on the subjects from the FAS randomized into the respective observational subsets (FAS-SN subset and FAS-NA subset). The FAS-NA subset is a subset of the FAS-SN subset.

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received one dose of the study vaccine and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

12.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window (ie, 28 to 35 days after vaccination) or a post-dose serology sample was not drawn at Visit 2
- Subject received medications impacting or that may have an impact on the immune response (Category 2 or 3)

The above protocol deviations leading to exclusion from the PPAS may be detailed and completed if necessary in the SAP, following the review of protocol deviations during the study conduct. In any case, the PPAS definition will be finalized before the first database lock.

12.2.4 Populations Used in Analyses

All subjects with data in the CRB will be taken into account in the description of the population (eg, the disposition, the demographic or baseline characteristics).

All immunogenicity analyses from HAI method for primary and secondary objectives will be performed on both FAS and PPAS.

The safety analyses will be performed on the SafAS.

The observational objective analyses will be performed on subsets of the FAS (FAS-SN and FAS-NA subsets).

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done. Nevertheless, a missing relationship will be considered as related at the time of statistical analysis. Details will be described in the SAP.

12.3.2 Immunogenicity

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

12.3.3 Efficacy

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

12.4 Interim / Preliminary Analysis

No formal interim analyses are planned.

The statistical analysis will be performed in at least 2 steps:

- First analysis on immunogenicity and safety results obtained on data collected within the 28 days following the vaccination (from D0 to D28). The study blind will be broken at that time.
- Second analysis after the 6-month data have been collected.

A limited statistical analysis of the safety and immunogenicity data obtained up to D 28 will be conducted once data are available and an interim database lock has been conducted. A final analysis will be conducted once the 6-month safety data have been collected and the final database lock has occurred. No statistical adjustment is necessary because there are no repeat analyses of the same parameter.

12.5 Determination of Sample Size and Power Calculation

A total of approximately 1540 adults 60 years of age and older (770 adults 60 to 64 years of age and 770 adults 65 years of age and older) will be enrolled. This sample size is determined per simulations based on an overall power of 90% for demonstrating the primary objective. The thresholds for superiority are defined as 1 for GMTs. No alpha adjustment is needed. Other assumptions are listed as follows:

- Allocation ratio: 1:1 (QIV-HD versus QIV-SD)
- GMT ratio: 1.5 for all strains
- Standard deviations of log10-transformed titers in QIV-SD group of 0.6 for 2 strains and 0.5 for the other 2 strains
- Attrition rate: 5% in FAS

It should be noted that the power per strain is 97.7% when the standard deviation is 0.6 and 99.7% when the standard deviation is 0.5.

An arbitrary number of subjects, ie, at least 50% of subjects in each age group and each vaccine group will be randomly assigned to the observational subset of subjects for SN testing and at least 50 subjects in each age group and each vaccine group for NA testing as shown in Table 12.1.

Table 12.1: Random assignment of subjects to observational subsets

Vaccine/Assay	Number of subjects 60 to 64 years of age	Number of subjects 65 years of age and older	Total
QIV-HD Group/SN	≥193	≥193	≥386
QIV-SD Group/SN	≥193	≥193	≥386
QIV-HD Group/NA	≥50	≥50	≥100
QIV-SD Group/NA	≥50	≥50	≥100

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

13.2 Source Data and Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, DCs, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a DC, the study coordinator will obtain verbal clarification from the subject, enter the response into the "investigator's comment" page of the DC, and transfer the information to the CRB.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the study, regardless of the outcome.

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

13.3 Confidentiality of Data, Data Protection, and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur.

In the event a subject's medical records are not at the investigational site, it is the responsibility of the investigator to obtain those records if needed.

All personal data collected related to subjects, investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation). 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.

The race of the subjects will be collected in this study because these data are required by regulatory agencies (eg, on the African American population for the Food and Drug Administration [FDA] in the US or on the Japanese population for the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan).

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical record may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (ie, before the inclusion of the first subject in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB (available online in the EDC system), and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

After the start of the study, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject medical files and CRBs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.

- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department (CQA) or by independent auditors to verify that the study has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to study documents during these inspections and audits.

13.4.3 Archiving

The Investigator and the study site shall retain and preserve 1 copy of the Study File containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- such longer period as required by applicable regulatory requirements

If during the Retention Period, the study site is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the study site shall contact the Sponsor to organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, the Investigator and/or the study site are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the study will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement will be signed by all the parties involved in the study's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and / or the study protocol.

13.6 Stipends for Participation

Subjects may be provided with a stipend according to local practice to compensate for the time and travel required for trial visits and procedures.

13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study at least 90 days prior to submission for publication / presentation. Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this study are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

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15 Signature Page

Sponsor Signature

I confirm that this protocol (version 2.0 dated 23 August 2019) is in accordance with applicable regulations and Good Clinical Practice.

Function	Name	Date	Signature
Sponsor's Responsible Medical Officer	[redacted]		
Clinical Department Sanofi Pasteur, Inc.	Global Clinical Sciences, Sanofi Pasteur, Inc.		