NCT03233217

CLINICAL STUDY PROTOCOL

Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine (SP0178) Administered by Intramuscular or Subcutaneous Route in Subjects Aged 65 Years and Older in Japan

Phase I/II, randomized, modified double-blind, multi-center study evaluating the safety and immunogenicity of QIV-HD administered intramuscularly or subcutaneously in healthy subjects aged 65 years and older in Japan

Study Number:	QHD00008-DFI15130
Development Phase:	Phase I/II
Sponsor:	Sanofi K.K. 3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1488, Japan
Investigational Product(s):	High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017–2018 Strains (QIV-HD)
Form / Route:	Suspension / Intramuscular or Subcutaneous injection
Indication For This Study:	Single dose for individuals aged 65 years and older
Manufacturer:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA

Version number:	1.0	EudraCT and/or IND number(s): WHO universal trial number:	Not applicable U1111-1183-5525
Date:	12-May-2017	Total number of pages:	79

NAMES AND ADDRESSES OF

INVESTIGATORS	Name: Address: Tel: Fax: E-mail:	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 study.
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	[redacted]
SPONSOR'S RESPONSIBLE MEDICAL OFFICER	Name: Address: Tel: Fax: E-mail:	[redacted]
OTHER EMERGENCY TELEPHONE NUMBERS	Name: Address: Tel:	[redacted]

TABLE OF CONTENTS

LIST OF TABLES

SYNOPSIS

Company:	Sanofi K.K.
Investigational Product:	High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017–2018 Strains (QIV-HD)
Active Substance(s):	A/Michigan/45/2015 (H1N1) strain, A/Hong Kong/4801/2014 (H3N2) strain, B/Brisbane/60/2008 strain, B/Phuket/3073/2013 strain

Title of the Study:	Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine (SP0178) Administered by Intramuscular or Subcutaneous Route in Subjects Aged 65 Years and Older in Japan
Development Phase:	Phase I/II
Coordinating Investigator	Not applicable
Study Centers:	This will be a multi-center study conducted at approximately 2 sites in Japan. Investigators and sites are listed in the list of investigators, study centers, and sponsor's personnel involved in the study.
Planned Study Period:	First visit, first subject: 15 September 2017 Last visit, last subject: 30 November 2017
Study Design and Methodology:	QHD00008-DFI15130 will be a Phase I/II, randomized, modified double-blind, multi-center study to be conducted in 175 healthy adults aged 65 years and older to assessing the safety and immunogenicity of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) method and QIV-HD administered by subcutaneous (SC) method. A local standard-dose quadrivalent influenza vaccine (QIV-SD) administered by SC method will serve as a control arm. In order to assess the safety and tolerability of QIV-HD in Japanese adults aged 65 years and older in an initial smaller cohort, the first 10 subjects enrolled will be randomized 1:1 to receive either QIV-HD by IM route or QIV-HD by SC route (Cohort 1). After review of the local and systemic adverse events occurring for 7 days post-vaccination (Day [D] 0 to D7) in Cohort 1, enrollment of the remaining 165 subjects randomized 1:1:1 to receive QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route (Cohort 2) will occur. The subjects in Cohort 1 will follow the same study schedules and procedures as the subjects in Cohort 2. All subjects will provide a pre-vaccination (baseline) blood sample at D0 and a post-vaccination blood sample at Visit (V) 3 (D28 [+ 7 days]) for hemagglutination inhibition (HAI) testing. Solicited reactions will be collected up to 7 days after vaccination and unsolicited adverse events (AEs) will be collected up to V3. Serious adverse events (SAEs) and adverse events of special interest (AESI)* will be collected throughout the study (D0 through

	V3). *Note: AESIs will have the same detailed information collected as SAEs. These include new onset of Guillain-Barré syndrome, encephalitis/myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis. For Cohort 1, interactive response technology (IRT) will be used to assign subjects to one of 2 study groups (QIV-HD by IM route or QIV-HD by SC route) and to assign subject numbers in each of the groups. However, the randomization will be performed without stratification. For Cohort 2, IRT will also be used to assign subjects to one of 3 study groups (QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route) and to assign subject numbers in each of the groups. The randomization will be stratified by value of age (<75, ≥75), sex (Male, Female), and sites. Electronic data capture (EDC) will be used for the collection of data.
Early Safety Data Review:	The safety of the investigational product will be continuously monitored by the Sponsor. Early safety data review (ESDR) will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration. An initial safety review for this study is planned when the first 10 subjects (Cohort 1, 5 subjects for QIV-HD by IM route and 5 subjects for QIV-HD by SC route) have been vaccinated and have provided safety data for D0-D7 post-vaccination, using the data collection methods described in the clinical study protocol. During this review, enrollment of subjects in Japan will be paused. Following a satisfactory safety review, enrollment of subjects will resume. The safety data collected will be entered into the case report book (CRB), and will be summarized and reviewed by the Sponsor. The site will remain blinded except for the site's designated unblinded administrator. The review of Cohort 1's safety data for D0-D7 post-vaccination will occur in an unblinded manner by the Sponsor at a planned Safety Management Team (SMT) meeting. It is understood that this review is based on preliminary data that have not been subject to validation and database lock. (The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined ESDR will continue unchanged.) The following safety parameters will be assessed as part of the ESDR review in an unblinded manner by the SMT. They will be collected during a period of 7 days after the vaccination: • Immediate reactions • Solicited injection site and systemic reactions • Unsolicited AEs • SAEs • AESIs The detection/fulfillment of any of the following safety signals may put the study on a temporary hold: • One SAE (including serious AESIs) considered as related

	to the vaccination by the Investigator and Sponsor • One death considered as related to vaccination by the Investigator and Sponsor • At least 40% of subjects of a study group experiencing a Grade 3 solicited injection site reaction(s) within 7 days after vaccination and persisting at least 48 hours (reactions not explained by any other possible etiology) • At least 40% of subjects of a study group experiencing a Grade 3 solicited systemic reaction(s) within 7 days after vaccination and persisting at least 48 hours (reactions not explained by any other possible etiology) • At least 20% of total subjects of Cohort 1 experiencing a Grade 3 unsolicited, non-serious reaction (s) within 7 days after vaccination and persisting at least 48 hours and reported as related by the investigator (reactions not explained by any other possible etiology) If any of the above criteria are met, a decision will be made by the SMT as to whether enrollment in the study will be allowed to resume. Apart from the ESDR review, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees/Institutional Review Boards (IECs/IRBs), or the governing regulatory authorities in the country where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects and should assure appropriate therapy and follow-up. Throughout the course of the study, additional internal SMT meetings may be convened to conduct blinded analyses of safety data.
Objective(s):	**Safety** To describe the safety profile of subjects in each group. **Immunogenicity** To describe the immune responses induced by each group (as assessed by HAI geometric mean titers [GMTs] and seroconversion rates) for the 4 common virus strains at 28 days post-vaccination.
Endpoint(s)	**Safety** Safety will be described for all subjects. • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, maximum 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, maximum intensity, action taken, and whether the reaction

	led to early termination from the study, of solicited (prelisted in the subject's diary card 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 SAE led to early termination from the study, of SAEs throughout the study (D0 through V3) • Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the study (D0 through V3) **Immunogenicity** • HAI antibody titers obtained on D0 and D28 • Individual titer ratios of HAI at D28/D0 • Seroconversion (titer <10 [1/dil] at D0 and post-injection titer ≥40 [1/dil] at D28, or titer ≥10 [1/dil] at D0 and a ≥4-fold increase in titer [1/dil] at D28) • Seroprotection (titer ≥40 [1/dil]) at D0 and D28
Planned Sample Size:	A total of 175 subjects are planned to be enrolled in the study. A total of 10 subjects are planned to be enrolled and randomized into 2 groups in Cohort 1, as shown below: • QIV-HD by IM route: n = 5 • QIV-HD by SC route: n = 5 A total of 165 subjects are planned to be enrolled and randomized into 3 groups in Cohort 2, as shown below: • Group 1 (QIV-HD by IM route): n = 55 • Group 2 (QIV-HD by SC route): n = 55 • Group 3 (QIV-SD by SC route): n = 55
Schedule of Study Procedures:	**Vaccination** All eligible subjects in Cohort 1 will be randomized to receive a single injection of either QIV-HD by IM route or QIV-HD by SC route at V1 (D0). All eligible subjects in Cohort 2 will be randomized to receive a single injection of either QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route at V1 (D0). **Blood sampling** All subjects will provide a pre-vaccination blood sample at V1 (D0) and a post-vaccination blood sample at V3 (D28 [+ 7 days]). **Collection of safety data** Subjects will be asked to notify the site immediately about any potential SAEs and AESIs 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 CRB. Subjects will record information about solicited reactions (D0 to D7), unsolicited AEs (D0 to V3), SAEs (D0 to V3), and AESIs (D0 to V3) in a diary card. Subjects will return to the site at V2 (D8 [+ 2 days]). Staff will review the recorded solicited reactions and unsolicited AEs, and determine whether the subject experienced any SAEs and AESIs not yet reported. Staff will review the safety data (V2 to V3) with subjects at V3 (D28 [+ 7 days]).
Duration of Participation in the Study:	The duration of each subject's participation in the study will be approximately 28 days.
Investigational Product:	High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017–2018 Strains (QIV-HD), provided in a pre-filled single-dose syringe.
Form:	Suspension
Composition:	Each 0.7 mL dose of QIV-HD will contain: Strains to be determined based on World Health Organization (WHO) / Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2017–2018 NH influenza season. **Active substances:** • A/Michigan/45/2015 (H1N1) strain 60 µg HA • A/Hong Kong/4801/2014 (H3N2) strain 60 µg HA • B/Brisbane/60/2008 strain 60 µg HA • B/Phuket/3073/2013 strain 60 µg HA **Excipients:** • Buffered saline solution quantity sufficient to appropriate volume • Octylphenol Ethoxylate (Triton X-100®) not more than 350 µg Preservative is not used in the manufacture of QIV-HD.
Route:	IM or SC, injected into the upper arm (IM injected into the deltoid area or SC injected into the posterior region)
Batch Number:	To be determined
Control Product:	[redacted] (Influenza HA Vaccine, [redacted]): Local Standard-Dose Inactivated Influenza Vaccine Quadrivalent, 2017–2018 Strains (QIV-SD), provided in a pre-filled single-dose syringe.
Form:	Suspension

Composition:	Each 0.5 mL dose of QIV-SD will contain: Strains determined based on NIID (Japan National Institute of Infectious Diseases) recommendations for the 2017–2018 NH influenza season. • A/(H1N1)-like strain 15 µg HA • A/(H3N2)-like strain 15 µg HA • B/(B from primary lineage)-like strain 15 µg HA • B/(B from alternate lineage)-like strain 15 µg HA • Buffered saline solution quantity sufficient to appropriate volume
Route:	SC, injected into the upper arm (posterior region)
Batch Number	To be determined
Inclusion Criteria:	An individual must fulfill all of the following criteria in order to be eligible for study enrollment: I 01. Aged ≥65 years on the day of inclusion I 02. Informed consent form has been signed and dated I 03. Able to attend all scheduled visits and to comply with all study procedures
Exclusion Criteria:	An individual fulfilling any of the following criteria is to be excluded from study enrollment: E 01. Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure E 02. Receipt of any vaccination with live vaccines within the past 27 days preceding the study vaccination or any vaccination with inactivated vaccines within the past 6 days preceding the study vaccination, or planned receipt of any vaccine prior to V3 E 03. Previous vaccination against influenza (in the preceding 6 months) with either the study vaccine or another vaccine E 04. Receipt of immune globulins, blood or blood-derived products in the past 3 months E 05. 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) E 06. Known systemic hypersensitivity to eggs, chicken proteins, or any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the study or to a vaccine containing any of the same substances E 07. Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on Investigator's judgment

	E 08. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily E 09. Alcohol or substance abuse that, in the opinion of the Investigator might interfere with the study conduct or completion. E 10. Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion E 11. 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 (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study E 12. Personal or family history of Guillain-Barré syndrome E 13. 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) E 14. Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥37.5°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided E 15. History of convulsions
Statistical Methods:	No hypotheses for safety and immunogenicity are planned. All analyses are descriptive. **Safety** Describe the safety results in subjects who received QIV-HD (either IM or SC) or the QIV-SD. The main parameters will be described by the 95% confidence interval (CI) based on the Clopper-Pearson method. The safety analysis set will be used for the safety analyses. **Immunogenicity** Immunogenicity in terms of GMTs, seroconversion, and seroprotection rates will be summarized for each strain. The 95% CIs for the GMTs will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The GMT ratios will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the 2-sided 95% CIs by the Newcombe-Wilson method without continuity correction. Additional parameters may be displayed as appropriate. Details of the above analyses will be described in a Statistical Analysis Plan (SAP). The per-protocol analysis set (PPAS) and full analysis set (FAS) will be applied for the immunogenicity analyses. The main immunogenicity analyses will be conducted on Cohort 2 for the PPAS. Immunogenicity analyses will also be conducted on Cohort 2 for the FAS and on all 175 subjects.

	Calculation of Sample Size There is no statistical powered hypothesis test for sample size calculation.

TABLE OF STUDY PROCEDURES

Phase I/II Study, 3 Visits, 1 Vaccination, 2 Blood Samples, 28 Days Duration per Subject

Visit/Contact	**Visit 1 (V1)**	**Visit 2 (V2)**	**Visit 3 (V3)**
Study timelines (days)	Day 0 (D0)	Day 8 (D8)	Day 28 (D28)
Time windows (days)	NA	[+ 2 days]	[+ 7 days]
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
History of seasonal influenza vaccination	X		
Reportable concomitant medications	X	X	X
Physical examination	X		
Height	X		
Body weight	X		
Contacting interactive response technology[a]	X		X
Randomization/allocation of subject number	X		
Blood sampling (BL), 10 mL	BL1[b]		BL2
Vaccination	X		
Immediate surveillance (30 min)	X		
Diary card provided	X[c]	X[d]	
Recording of solicited injection site & systemic reactions	D0-D7		
Collection of unsolicited adverse events	D0-V3		
Diary card collected and reviewed		X[e]	X[f]
Study termination record			X
Collection of SAEs and AESIs[g]	To be reported at any time during the study		

AE = adverse event, AESI = adverse event of special interest, SAE = serious adverse event

a Targeted physical examination based on medical history will be performed at V1. Targeted physical examination may also be performed at V2 and V3, as necessary.

b Collection of the first blood sample (BL1) to occur before vaccination.

c Subjects will use this diary card to record information about solicited reactions from D0 to D7, unsolicited AEs, SAEs, and AESIs from D0 to V2 after vaccination.

d Subjects will use this diary card to record information about unsolicited AEs, SAEs, and AESIs from V2 to V3.

e Staff will collect the diary card at V2, and review the solicited reactions, unsolicited AEs, concomitant medications, SAEs, and AESIs.

f Staff will collect the diary card at V3, and review any solicited reactions ongoing after V2, unsolicited AEs, concomitant medications, SAEs, and AESIs.

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

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
CDM	Clinical Data Management
CI	confidence interval
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
EDC	electronic data capture
ESDR	early safety data review
FAS	full analysis set
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPE	Global Pharmacovigilance & Epidemiology
GMT	geometric mean titer
GMTR	geometric mean titer ratio
HA	hemagglutinin
HAI	hemagglutination inhibition
HAU	hemagglutination unit
HIV	human immunodeficiency virus
IATA	International Air Transport Association
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
LLT	lowest level term
LLOQ	lower limit of quantification

LVLS	last visit, last subject
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
NH	northern hemisphere
NIID	Japan National Institute of Infectious Diseases
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
PT	preferred term
QIV	quadrivalent influenza vaccine
QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
RBC	red blood cell
RMO	Responsible Medical Officer
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SMT	Safety Management Team
SOC	system organ class
TIV	trivalent influenza vaccine
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
UAR	unexpected adverse reaction
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 INTRODUCTION

1.1 BACKGROUND

This study will evaluate the safety and immunogenicity of high-dose quadrivalent influenza vaccine (hereafter referred to as QIV-HD) administered by intramuscular (IM) route and subcutaneous (SC) route in subjects aged 65 years and older.

Influenza is a highly contagious, acute viral respiratory disease caused by influenza type A and type B viruses. Typically characterized by the rapid onset of fever, myalgia, sore throat, and nonproductive cough, influenza can also cause severe malaise lasting for several days.

Individuals in high-risk groups (e.g., adults aged 65 years and older and persons with underlying medical conditions) are at an increased risk of influenza and its complications including primary viral pneumonia, secondary bacterial pneumonia, and/or exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and congestive heart failure (1) (2).

Vaccination currently represents the most effective medical intervention against influenza and its severe complications. The World Health Organization (WHO) (the Advisory Committee on Immunization Practices [ACIP] in the United States [US]) recommends annual vaccination for all persons aged 65 years or older against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (1) (3). The routine vaccination to influenza has begun for adults aged 65 years and older and adults aged 60 to 64 years with respiratory, cardiac, renal disease, or human immunodeficiency virus (HIV) by the Preventative Vaccination Law in Japan since 2015. The effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age and immune competence of the vaccine recipient.

Standard-dose trivalent influenza vaccines (TIVs) (hereafter referred to as standard-dose TIV [TIV-SD]) administered by the IM route contain 15 µg hemagglutinin (HA) of each of the 3 virus strains recommended for use in the Northern or Southern hemisphere's upcoming influenza season, for a total of 45 µg of HA antigen per dose. Despite high vaccination rates, adults aged 65 years and older remain at increased risk for influenza because their immune response to a TIV-SD (15 µg/strain/dose) is lower than the immune response generated in younger healthy adults (4). Thus, Fluzone® High-Dose vaccine (hereafter referred to as TIV-HD), containing 60 µg HA of each of the 3 virus strains (4-times more antigen than the TIV-SD, for a total of 180 µg of HA antigen per dose), was developed and subsequently licensed by Sanofi Pasteur in the US and Canada to improve immune responses to influenza vaccine and vaccine efficacy in adults aged 65 years and older (5).

In parallel, to reduce the risk of B-lineage mismatch and offer broader protection against seasonal influenza virus strains, Sanofi Pasteur has been transitioning the influenza vaccines portfolio from trivalent to quadrivalent formulations with the launch of Fluzone® Quadrivalent (a quadrivalent standard-dose influenza vaccine administered via IM route [hereafter referred to as QIV-SD] for persons aged 6 months and older, licensed in the US in 2013). In contrast to TIVs, which contain

only one B-strain, the quadrivalent influenza vaccines (QIVs) contain two B strains, one from each of the Victoria and Yamagata lineages, which have been co-circulating globally since the early 2000s. Thus, QIVs offer protection against both lineages simultaneously and reduce the risk of lack of protection against the alternate B lineage.

Thus, the goal of the QIV-HD project is to license a seasonal quadrivalent influenza high-dose vaccine for adults aged 65 years and older for IM administration.

1.2 BACKGROUND OF THE INVESTIGATIONAL MEDICINAL PRODUCT

Sanofi Pasteur's TIV-HD, contains 60 µg HA of each of 3 virus strains (4-times more antigen than the standard-dose influenza vaccine), for a total of 180 µg of HA antigen per dose. This vaccine was developed by Sanofi Pasteur to improve the effectiveness of the influenza vaccine in adults aged 65 years and older (5). TIV-HD is currently licensed in the US and Canada.

The improvement in efficacy of TIV-HD when compared with TIV-SD was demonstrated in a large scale, multi-center trial (FIM12), which enrolled 31,989 adults aged 65 years and older from 126 research centers during the 2011-2012 and 2012-2013 influenza seasons in the Northern Hemisphere (NH). In FIM12, the TIV-HD was found to be 24.2% (95% confidence interval [CI], 9.7 to 36.5) more effective in preventing laboratory-confirmed influenza relative to the TIV-SD, indicating that about 1 in 4 breakthrough cases of influenza could be prevented in this population if the TIV-HD was used instead of TIV-SD. Additionally, relative efficacy was 35.4% (95% CI, 12.5 to 52.5) in an analysis restricted to influenza cases caused by vaccine-similar strains (6). This efficacy study concluded that the high-dose vaccine is safe, induces significantly higher antibody responses, and provides superior protection against laboratory-confirmed influenza illness compared to TIV-SD among adults aged 65 years and older.

Until recently, the influenza vaccines contained a single B strain. However, the B strain included in seasonal influenza vaccines was not the dominant circulating B lineage (mismatched strains) in approximately 25% of the seasons between 2000 and 2013 (7). To overcome the difficulty of B-strain selection and improve protection of the population against seasonal influenza virus strains, Sanofi Pasteur has been transitioning the Fluzone influenza vaccine portfolio from trivalent to quadrivalent formulations which contain one B strain each from the Victoria and Yamagata lineages. Thus, the issue of having to choose a strain from only one B lineage for the seasonal influenza vaccine and the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage is eliminated (8).

As part of this transition, Fluzone QIV-HD is being developed for initial licensure in adults aged 65 years and older. QIV-HD contains 60 µg HA of each of 4 virus strains for a total of 240 µg of HA antigen per dose. The QIV-HD drug substance will be manufactured according to the same process used for the TIV-HD licensed in the US and Canada. The addition of the second B strain will increase the per dose volume from 0.5 mL to 0.7 mL.

Japan has one of the largest aging populations in the world. In 2014, 26% of Japan's population (approximately 33 million people) was estimated to be aged 65 years or older (9). During the 2014-2015 influenza season, adults aged 60 years and older represented more than 60% of

influenza-related hospitalizations and adults aged 65 years and older accounted for more than 80% of influenza-related deaths (10). The influenza vaccine has been introduced into the routine vaccination schedule for adults aged 65 years and older and adults aged 60 to 64 years with respiratory, cardiac, renal disease, or HIV since 2015. With a growing population of adults aged 65 years and older, an influenza vaccine which can offer improved immunogenicity and thus better prevention of influenza infection would have a significant public health impact in this vulnerable population.

1.3 POTENTIAL BENEFITS AND RISKS

1.3.1 Potential Benefits to Subjects

All subjects participating in Study QHD00008-DFI15130 will receive a quadrivalent influenza vaccination. These subjects should benefit from coverage against influenza and may be less likely to catch influenza or develop complications during the 2017–2018 influenza season.

Subjects who will receive QIV-HD will be vaccinated against the influenza A/H1N1, A/H3N2 and the B strains from both the Victoria and Yamagata lineages chosen and recommended by WHO / Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the composition of QIVs for the 2017–2018 NH season.

Subjects who will receive QIV-SD will be vaccinated against influenza A/H1N1, A/H3N2 and the B strains from both the Victoria and Yamagata lineages chosen and recommended by the Japan National Institute of Infectious Diseases (NIID) for the composition of QIVs for the 2017–2018 influenza season in Japan.

Regarding immunogenicity, the investigational QIV-HD is expected to induce a higher immune response against the 4 influenza strains compared to QIV-SD. Therefore, the investigational QIV-HD is likely to bring an increased benefit versus QIV-SD in terms of immunogenicity against the 4 influenza strains with a risk-benefit profile that is expected to be favorable.

1.3.2 Potential Risks to Subjects

As with any vaccine, it is important to note that vaccination with QIV-HD may not protect all recipients against the disease it is designed to prevent (i.e., influenza). See below for other potential risks.

Possible Reactions to Blood Draw

Venipuncture causes transient discomfort and may cause temporary hypotension from a vasovagal response (e.g., 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.

Possible Reactions to Vaccination

Vaccine injection into the deltoid muscle causes transient discomfort. Immediate and potentially life-threatening allergic reactions to the vaccine could be manifested by adverse events (AEs) such as laryngeal edema, asthma, or hypotension. These types of reactions are exceedingly rare and would most likely occur in persons with a severe reaction to influenza vaccine in the past.

The rate of injection site reactions is expected to be higher with the SC route compared to the IM route due to the fact that the inflammatory reactions induced by the vaccines are closer to the surface of the skin and therefore more visible to direct examination.

Post-marketing Experience with QIV-SD (Fluzone Quadrivalent), TIV-HD (Fluzone High-Dose) and TIV-SD (Fluzone)

There is no post-marketing experience for QIV-HD as it has not been licensed yet.

Post-marketing experience with QIV-SD and TIV-HD has not identified any events other than those described below, which were spontaneously reported during the post-approval use of TIV-SD, for addition to the QIV-SD package insert (11).

The following events have been spontaneously reported during the post-approval use of TIV-SD and TIV-HD (12). 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. 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)

  Note: This type of reaction is rare and would most likely occur in persons with a severe reaction to influenza vaccine in the past.
- *Eye Disorders:* ocular hyperemia
- *Nervous System Disorders:* Guillain-Barré syndrome, convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- *Vascular Disorders:* vasculitis, vasodilation/flushing
- *Respiratory, Thoracic and Mediastinal Disorders:* dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* pruritus, asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders:* vomiting

Other events reported during post-approval use of the TIV-HD vaccine include the following:

- *Gastrointestinal Disorders:* nausea, diarrhea
- *General Disorder and Administration Site Conditions:* chills

1.4 RATIONALE

The Phase I/II study QHD00008-DFI15130 will be conducted in 175 adults, aged 65 years and older, in Japan to generate safety and immunogenicity data.

QHD00008-DFI15130 will be a randomized, modified double-blind, multi-center study of the safety and immunogenicity of QIV-HD administered SC, QIV-HD administered IM and a local QIV-SD administered SC. The objectives of QHD00008-DFI15130 will be to assess the safety and immunogenicity (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion rates at 28 days post-vaccination) of QIV-HD when administered SC and IM compared with the local QIV-SD. Of note, in Japan, the recommended route of administration for seasonal influenza vaccines is by the SC route.

Given the acceptable safety data generated from the millions of doses of licensed TIV-HD administered in the US and Canada and the fact that no changes will be made to the drug substance manufacturing process of QIV-HD compared to the currently licensed TIV-HD process, it is considered that the risk/benefit ratio is appropriate for the conduct of a Phase I/II clinical study with QIV-HD with a small group included for an early safety data review.

2 STUDY OBJECTIVES

Safety

To describe the safety profile of subjects in each group.

Immunogenicity

To describe the immune responses induced by each group (as assessed by HAI GMTs and seroconversion rates) for the 4 common virus strains at 28 days post-vaccination.

3 INVESTIGATORS AND STUDY ORGANIZATION

This study will be conducted in approximately 2 centers in Japan. Details of the study centers and the Principal Investigators at each center are provided in the list of investigators and centers involved in the study.

Sponsor's Responsible Medical Officer (RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted], [redacted], Sanofi.

4 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

As required by local regulation, the Investigator or the Sponsor must submit this clinical study protocol to the health authorities (competent regulatory authority) and the appropriate Independent Ethics Committees/Institutional Review Boards (IECs/IRBs), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IECs/IRBs composition.

The clinical study (study number, clinical study protocol title and version number), the documents reviewed (clinical study protocol, informed consent form [ICF], Investigator's Brochure [IB] with any addenda, Investigator's curriculum vitae, etc.) and the date of the review should be clearly stated on the written IECs/IRBs approval/favorable opinion.

The investigational product (IP) will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical study, any amendment or modification to the clinical study protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IECs/IRBs before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the health authorities (competent regulatory authority) and the IECs/IRBs should be informed as soon as possible. It should also be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study, in particular any change in safety. All updates to the IB will be sent to the IECs/IRBs and to health authorities (competent regulatory authority), as required by local regulation.

A summary of the clinical study's outcome is sent to the IECs/IRBs at the end of the clinical study.

5 INVESTIGATIONAL PLAN

5.1 DESCRIPTION OF THE OVERALL STUDY DESIGN AND PLAN

5.1.1 Study Design

QHD00008-DFI15130 will be a Phase I/II, randomized, modified double-blind, multi-center study to be conducted in 175 healthy adults aged 65 years and older to assess the safety and immunogenicity of the QIV-HD administered by IM method and QIV-HD administered by SC method. A local QIV-SD administered by SC method will serve as a control arm.

A total of 10 subjects will be randomized into 2 groups in Cohort 1, as shown below:

- QIV-HD by IM route: n = 5
- QIV-HD by SC route: n = 5

A total of 165 subjects will be randomized into 3 groups in Cohort 2, as shown below:

- Group 1 (QIV-HD by IM route): n = 55
- Group 2 (QIV-HD by SC route): n = 55
- Group 3 (QIV-SD by SC route): n = 55

In order to assess the safety and tolerability of QIV-HD in Japanese adults aged 65 years and older in an initial smaller cohort, the first 10 subjects enrolled will be randomized 1:1 to receive either QIV-HD by IM route or QIV-HD by SC route (Cohort 1). After review of the local and systemic adverse events occurring for 7 days post-vaccination (Day [D] 0 to D7) in Cohort 1, enrollment of the remaining 165 subjects randomized 1:1:1 to receive QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route (Cohort 2) will occur (see Section 5.1.6).

The subjects in Cohort 1 will follow the same study schedules and procedures as the subjects in Cohort 2.

All subjects will provide a pre-vaccination (baseline) blood sample at Visit (V) 1 (D0) and a post-vaccination blood sample at V3 (D28 [+ 7 days]) for HAI testing.

Solicited reactions will be collected up to 7 days after vaccination and unsolicited AEs will be collected up to V3. Serious adverse events (SAEs) and adverse events of special interest (AESI) will be collected throughout the study (D0 through V3).

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

For Cohort 1, interactive response technology (IRT) will be used to assign subjects to one of 2 study groups (QIV-HD by IM route or QIV-HD by SC route) and to assign subject numbers in each of the groups. However, the randomization will be performed without stratification.

For Cohort 2, IRT will also be used to assign subjects to one of 3 study groups (QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route) and to assign subject numbers in each of the groups. The randomization will be stratified by value of age (<75, ≥75), sex (Male, Female), and sites.

Electronic data capture (EDC) will be used for the collection of data.

5.1.2 Justification of the Study Design

The objectives of QHD00008-DFI15130 will be to assess the safety and immunogenicity (as assessed by HAI GMTs and seroconversion rates at 28 days post-vaccination) of QIV-HD when administered SC and IM compared with the local QIV-SD.

The control product is the local QIV-SD because it is the only seasonal influenza vaccine licensed in Japan.

In addition, the route of administration of seasonal influenza vaccine is SC in Japan, whereas IM in the US and Canada. Therefore, the QIV-HD will be administered by SC or IM method in this study.

The investigational QIV-HD has never been administered to Japanese subjects. However, given the acceptable safety data generated from the millions of doses of TIV-HD administered in the US and Canada and the fact that no changes will be made to the drug substance manufacturing process of QIV-HD compared to the TIV-HD process currently licensed in the US and Canada, the Sponsor considers that the risk/benefit ratio is appropriate for the conduct of a Phase I/II clinical study with QIV-HD with a small group included for an early safety data review.

Given the different volumes and administration routes of the QIV-HD and the local QIV-SD vaccines, QHD00008-DFI15130 will be a modified double-blind study in which only a designated administrator at each study site will know which vaccine has been administered to the subjects. The subjects and the Investigator/Sub-investigator in charge of the safety assessment will be blinded in order to decrease the potential bias in safety assessment.

5.1.3 Study Plan

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

Vaccination

All eligible subjects in Cohort 1 will be randomized to receive a single injection of either QIV-HD by IM route or QIV-HD by SC route at V1 (D0).

All eligible subjects in Cohort 2 will be randomized to receive a single injection of either QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route at V1 (D0).

Blood Sampling

All subjects will provide a pre-vaccination blood sample at V1 (D0) and a post-vaccination blood sample at V3 (D28 [+ 7 days]).

Collection of Safety Data

Subjects will be asked to notify the site immediately about any potential SAEs and AESIs 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 to D7), unsolicited AEs (D0 to V3), SAEs (D0 to V3), and AESIs (D0 to V3) in a diary card.

Subjects will return to the site at V2 (D8 [+ 2 days]). Staff will review the recorded solicited reactions and unsolicited AEs, and determine whether the subject experienced any SAEs and AESIs not yet reported.

Staff will review the safety data (V2 to V3) with subjects at V3 (D28 [+ 7 days]).

5.1.4 Visit Procedures

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

1. Explain the study to the subject, answer any of his/her questions and ensure that he/she has been informed of all aspects of the study that are relevant to his/her decision and obtain a written informed consent signed by the subject. The Investigator will sign and date the ICF. A person designated by the Investigator and under the Investigator's responsibility, will also sign and date the ICF if that person explains the study to the subject. The Investigator will then retain the original and give a 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. If the subject is not eligible, only the specific form entitled “Screening/Enrollment log” will state the subject identification, no CRB will be completed.
3. Collect relevant demographic information (e.g., date of birth and sex).
4. Collect significant medical history and record any planned hospitalization during the study in the source documents.
5. Obtain information about history of seasonal influenza vaccination and any possible reactions to this vaccination in the previous year.
6. Collect reportable concomitant medications (see Section 6.7).

7. Perform a targeted physical examination based on medical history and record oral temperature[a] in the medical chart.
8. Measure the height and the body weight of the subject.
9. Contact the IRT to assign to the subject a subject number and allocate a dose number (see Section 6.5).
10. Draw approximately 10 mL blood sample. 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.
11. Administer the corresponding vaccine to the subject intramuscularly or subcutaneously into the upper arm (intramuscularly into the deltoid area or subcutaneously into the posterior region).

    Note: The vaccine is prepared by the administrator (a designated study site staff member such as an Investigator/Sub-investigator or a nurse) and administered without the presence of any other study site staff members who may be an assessor for safety in subsequent visits. The subjects are also blinded with an eye mask during vaccine administration. The vaccine must be administered on the side opposite to that of the blood sampling.

    Note: The administrator records the injection side / dose number in the CRB and the injection site / route in the administration record. The detachable corresponding label is affixed in the administration record.
12. 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.
13. Provide the subject with a diary card to record any solicited reactions and AEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs.
14. Provide the subject with a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement[a], and instructions on how to use them.
15. Remind the subject to bring the diary card on V2.
16. Instruct on the need to promptly report any SAE and AESI that may occur at any time during the study.
17. Complete the relevant case report forms (CRFs) for this visit.

a Tympanic and temporal artery thermometers should not be used.

Visit 2 (D8 [+ 2 days] after vaccination): Collection of Safety Information

1. Collect and review the diary card since V1, including any solicited reactions and AEs, medications, or therapy that occurred since vaccination. The occurrence of any injection site reaction, systemic event/reaction, any SAE, and/or any AESI should have been reported in the diary card.

   Note: The assessor (Investigator/Sub-investigator who was not the administrator of the vaccine at V1) assesses the safety events.
2. Provide the subject with a diary card to record any AEs and review the directions for its use.
3. Remind the subject to do the following:
   - Bring the diary card on V3
   - Notify the site in case of an SAE and/or an AESI
4. Complete the relevant CRFs for this visit.

Visit 3 (D28 [+ 7 days] after vaccination): Collection of Safety Information and Blood Sample

1. Collect and review the diary card since V2, including any AEs, medications, or therapy that occurred since vaccination. The occurrence of any systemic event, any SAE, and/or any AESI should have been reported in the diary card.

   Note: The assessor (Investigator/Sub-investigator who was not the administrator of the vaccine at V1) assesses the safety events.
2. Draw approximately 10 mL blood sample.

   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.
3. Contact the IRT to inform the subject's status.
4. Complete the relevant CRFs for this visit and the study termination record.

Follow-up of subjects with Related AEs or with AEs That Led to Study Discontinuation:

A 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.

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

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[a] to LVLS[b]:	15 September 2017 to 30 November 2017
Planned inclusion period - FVFS to FVLS[c]:	15 September 2017 to 26 October 2017
Planned end of study:	30 November 2017
Planned date of final clinical study report:	14 July 2018

a FVFS: first visit, first subject
b LVLS: last visit, last subject
c FVLS: first visit, last subject

5.1.6 Early Safety Data Review

The safety of the investigational product will be continuously monitored by the Sponsor. Early safety data review (ESDR) will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration.

An initial safety review for this study is planned when the first 10 subjects (Cohort 1, 5 subjects for QIV-HD by IM route and 5 subjects for QIV-HD by SC route) have been vaccinated and have provided safety data for D0-D7 post-vaccination, using the data collection methods described in the clinical study protocol. During this review, enrollment of subjects in Japan will be paused. Following a satisfactory safety review, enrollment of subjects will resume.

The safety data collected will be entered into the CRB, and will be summarized and reviewed by the Sponsor. The site will remain blinded except for the site's designated unblinded administrator. The review of Cohort 1's safety data for D0-D7 post- vaccination will occur in an unblinded manner by the Sponsor at a planned Safety Management Team (SMT) meeting.

It is understood that this review is based on preliminary data that have not been subject to validation and database lock. (The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined ESDR will continue unchanged.)

The following safety parameters will be assessed as part of the ESDR review in an unblinded manner by the SMT. They will be collected during a period of 7 days after the vaccination:

- Immediate reactions
- Solicited injection site and systemic reactions
- Unsolicited AEs
- SAEs
- AESIs

The detection/fulfillment of any of the following safety signals may put the study on a temporary hold:

- One SAE (including serious AESIs) considered as related to the vaccination by the Investigator and Sponsor
- One death considered as related to vaccination by the Investigator and Sponsor
- At least 40% of subjects of a study group experiencing a Grade 3 solicited injection site reaction(s) within 7 days after vaccination and persisting at least 48 hours (reactions not explained by any other possible etiology)
- At least 40% of subjects of a study group experiencing a Grade 3 solicited systemic reaction(s) within 7 days after vaccination and persisting at least 48 hours (reactions not explained by any other possible etiology)
- At least 20% of total subjects of Cohort 1 experiencing a Grade 3 unsolicited, non-serious reaction (s) within 7 days after vaccination and persisting at least 48 hours and reported as related by the investigator (reactions not explained by any other possible etiology)

If any of the above criteria are met, a decision will be made by the SMT as to whether enrollment in the study will be allowed to resume.

Apart from the ESDR review, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in the country where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects and should assure appropriate therapy and follow-up.

Throughout the course of the study, additional internal SMT meetings may be convened to conduct blinded analyses of safety data.

5.2 ENROLLMENT AND RETENTION OF STUDY POPULATION

5.2.1 Recruitment Procedures

Before the start of the study, the 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 (e.g., letters, pamphlets, posters) are submitted to the Sponsor prior to submission to the IEC/IRB for approval.

5.2.2 Informed Consent Procedures

The Investigator should fully inform the Subject of all pertinent aspects of the clinical study including the written information given approval/favorable opinion by the ethics committee

(IEC/IRB). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a subject's participation in the clinical study, the written ICF should be signed, name filled in and personally dated by the subject. A copy of the signed and dated written ICF will be provided to the subject.

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.

The ICF used by the investigator for obtaining the subject's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IEC/IRB) for approval/favorable opinion.

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 in order to be eligible for study enrollment:

I 01. Aged ≥65 years on the day of inclusion

I 02. Informed consent form has been signed and dated

I 03. Able to attend all scheduled visits and to comply with all study procedures

5.2.5 Exclusion Criteria

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

E 01. Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

E 02. Receipt of any vaccination with live vaccines within the past 27 days preceding the study vaccination or any vaccination with inactivated vaccines within the past 6 days preceding the study vaccination, or planned receipt of any vaccine prior to V3

E 03. Previous vaccination against influenza (in the preceding 6 months) with either the study vaccine or another vaccine

E 04. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E 05. 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)

E 06. Known systemic hypersensitivity to eggs, chicken proteins, or any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the study or to a vaccine containing any of the same substances

E 07. Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on Investigator's judgment

E 08. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E 09. Alcohol or substance abuse that, in the opinion of the Investigator might interfere with the study conduct or completion.

E 10. Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[a]

E 11. 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 (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

E 12. Personal or family history of Guillain-Barré syndrome

E 13. 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)

E 14. Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥37.5°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided

E 15. History of convulsions

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

If the subject has a primary physician who is not the Investigator, the site urges the subjects to contact this physician to inform him/her of the subject's participation in the study.

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

medical history (reported as diagnosis) including conditions for which the subject is or has been followed by a physician or conditions 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 purpose of this data is to assist later in the interpretation of safety data collected during the study.

The reporting of signs and symptoms is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and if the information is collected, it will not be coded.

5.2.7 Contraindications for Subsequent Vaccinations

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

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 (withdrawal) without the subject's permission
- At the request of the subject (dropout)

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant noncompliance with the protocol, based on the Investigator's judgment

The reason for a withdrawal or dropout should be clearly documented in the source documents and on 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 at V2 and/or V3, documented reasonable effort (i.e., 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 CRB and 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 CRB 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 9.1.1.
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 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 (e.g., deviation of the Inclusion/Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection, or error in the vaccine administration). • If the subject received the restricted treatments indicated in Section 6.7). • The subject 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	To be used: • When the subject indicated unwillingness to continue in the study • When the subject made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., 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, a protocol deviation, or loss of eligibility.

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.

5.3 SAFETY EMERGENCY CALL

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor for advice on study related medical question or problem. If the Sponsor 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 Sponsor's contact, as needed. The toll-free contact information for the Call Center is provided in the clinical study protocol (see Names and addresses).

This process does not replace the need to report an SAE. The investigator/Sub-investigator is still required to follow the protocol defined process for reporting SAEs to the Sponsor (see Section 10).

5.4 MODIFICATION OF THE STUDY AND PROTOCOL

All appendices attached hereto and referred to herein are made part of this clinical study protocol.

The Investigator should not implement any deviation from, or changes of the clinical study protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IEC/IRB and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical study subjects, or when the change(s) involves only logistical or administrative aspects of the study. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical study protocol.

Any amendment to the clinical study protocol requires written approval/favorable opinion by the IEC/IRB prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical study protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IEC/IRB approval/favorable opinion concerning the revised ICF prior to implementation of the change and subject signature should be re-collected if necessary.

5.5 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

5.5.1 By the Sponsor

The sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio
- Subject enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IP, means, and information necessary to perform the clinical study and has not included any subject after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator, delegated staff with any provision of the clinical study protocol, and breach of the applicable laws and regulations or breach of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP)
- The total number of subjects is included earlier than expected

In any case the Sponsor will notify the Investigator of its decision by written notice.

5.5.2 By the investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical study.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IEC/IRB and regulatory authorities should be informed according to applicable regulatory requirements.

6 VACCINES ADMINISTERED

6.1 IDENTITY OF THE INVESTIGATIONAL PRODUCT

6.1.1 Identity of Study Product

The investigational QIV-HD is a split virion quadrivalent influenza vaccine (60 µg HA/strain) containing virus strains chosen by WHO / VRBPAC for the 2017–2018 NH 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 single-dose syringe contains a total of 240 µg HA antigen per 0.7 mL dose provided in sterile suspension for IM or SC injection.

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 determined based on WHO / VRBPAC recommendations for the 2017–2018 NH influenza season.

Active substances:

- A/Michigan/45/2015 (H1N1) strain 60 µg HA
- A/Hong Kong/4801/2014 (H3N2) strain 60 µg HA
- B/Brisbane/60/2008 strain 60 µg HA
- B/Phuket/3073/2013 strain 60 µg HA

Excipients:

- Buffered saline solution quantity sufficient to appropriate volume
- Octylphenol Ethoxylate (Triton X-100®) not more than 350 µg

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

Batch number: To be determined

6.1.1.2 Preparation and Administration

The investigational QIV-HD is prepared by the administrator (a designated study site staff member such as an Investigator/Sub-investigator or a nurse) and administered intramuscularly or subcutaneously into the upper arm (intramuscularly into the deltoid area or subcutaneously into

the posterior region) by the administrator without the presence of any other study site staff members who may be an assessor for safety in subsequent visits.

The subjects are blinded with eye mask during 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 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 seasonal influenza vaccination.

6.1.2 Identity of Control Product

The control product is the local QIV-SD ([redacted]) manufactured by the [redacted].

QIV-SD is a split virion quadrivalent influenza vaccine (15 µg HA/strain) containing virus strains chosen by NIID for the 2017–2018 NH 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 single-dose syringe contains a total of 60 µg HA antigen per 0.5 mL dose provided in sterile suspension for SC injection.

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 QIV-SD vaccine contains the following components:

Strains to be determined based on NIID (Japan National Institute of Infectious Diseases) for the 2017–2018 NH influenza season.

- A/(H1N1)-like strain 15 µg HA
- A/(H3N2)-like strain 15 µg HA
- B/(B from primary lineage)-like strain 15 µg HA

- B/(B from alternate lineage)-like strain 15 µg HA
- Buffered saline solution quantity sufficient to appropriate volume

Batch number: To be determined

6.1.2.2 Preparation and Administration

The control product is administered subcutaneously into the upper arm (posterior region).

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 seasonal influenza vaccination.

6.2 IDENTITY OF OTHER PRODUCT(S)

Not applicable.

6.3 PRODUCT LOGISTICS

6.3.1 Labeling and Packaging

Investigational product will be supplied with investigational labeling and packaging. Control product will be supplied with the manufacturer's labeling and investigational packaging. Each single dose of investigational product will be identified by a unique dose number on the label and on the carton, while the control product will be identified by a unique dose number on the carton. The carton will have a detachable label for the sites to attach to the source documents. See the procedures for the product management for additional label detail.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Sponsor's monitoring staff will contact the Investigator or a designee in order 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 procedures for the product management, including checking that the cold chain was maintained during shipment (i.e., 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 Sponsor representative, and request authorization from Sponsor to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this 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 procedures for the product management) 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 Sponsor representative for further instructions.

6.3.2.3 Product Accountability

The 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 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.

The Sponsor's monitoring staff will verify the study site's product accountability records against the record in the CRBs and the communication from the IRT.

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the Sponsor 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 (e.g., 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 procedures for the product management.

6.3.4 Disposal of Unused Products

Unused or wasted products will be returned to the Sponsor in accordance with the instructions in the procedures for the product management. 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 study is designed as a modified double-blind study as follows:

- The Investigator/Sub-investigator in charge of safety assessment and the study staff who collect the safety data will not know which vaccine was administered or the route of administration
- The unblinded administrator, who is a separate designated study site staff member (e.g., an Investigator/Sub-investigator or a nurse), will administer the vaccine
- The subjects will be blinded with an eye mask during administration
- The laboratory personnel who analyze the blood samples will not know which vaccine was administered

The Investigator/Sub-investigator in charge of safety assessment will not be present during the vaccination but will be available on site in case of emergency (e.g., anaphylactic shock).

Dose number will be used to identify each vaccine for the purpose of randomization, vaccination, and the recording of vaccine administered. Dose numbers will be randomly assigned to QIV-HD and QIV-SD. The IRT vendor will be responsible for providing the treatment group identification and dose 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 IRT operation manuals. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sponsor 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 Sponsor through an internal system for reporting to Health authorities in the case of an SAE as described in ICH E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (i.e., 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 Global Pharmacovigilance & Epidemiology (GPE) 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 Sponsor 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.

6.5 RANDOMIZATION AND ALLOCATION PROCEDURES

For the randomization of dose numbers, the sponsor or designee will supply a computer generated randomization list, which will be used for the labeling and packaging.

For Cohort 1, subjects who meet the inclusion/exclusion criteria and sign the ICF (subjects aged 65 years and older) will be randomly assigned to one of 2 study groups (QIV-HD by IM route or QIV-HD by SC route) in a 1:1 ratio by block randomization.

On the day of enrollment for Cohort 2 subjects, those subjects who meet the inclusion/exclusion criteria and sign the ICF (subjects aged 65 years and older) will be randomly assigned to one of 3 study groups (QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route) in a 1:1:1 ratio by block randomization, stratified according to age (<75, ≥75), sex, and site.

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 vaccine dose number and have the site administrator confirm it. Dose numbers will be recorded on the source documents and CRBs. The full detailed procedures for group allocation are described in the IRT operation manuals. If the subject is not eligible to participate in the study, then the information will only be recorded on the screening/enrollment 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 392000100005 is the fifth subject enrolled in Center Number 1 in Japan (392 being Japan country code).

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

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 the 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 given to each subject, and the disposal of unused or wasted doses

6.7 CONCOMITANT MEDICATION

Ongoing medication

At the time of enrollment, ongoing medications including other therapies (e.g., 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 concomitant medication will be limited to specific categories of medication 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 to the end of the study (D28 [+ 7 days]).

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

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (e.g., antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs])
- Category 2: medications impacting or that may have an impact on the immune response (e.g., other vaccines, blood products, 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 (e.g., steroids/corticosteroids)
- Category 4: the statin family of anti-hyperlipidemia medications (e.g., atorvastatin, rosuvastatin, simvastatin, pravastatin, and fluvastatin)

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

- Trade name or generic 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
- Start and stop dates

Dosage and administration route will not be recorded.

Homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded.

Medication(s) given in response to an AE will be captured in the "Action Taken" Section of the AE CRF only. No details will be recorded on the concomitant medication(s) CRF unless the medication(s) received belongs to one of the prelisted categories. Medication(s) will not be coded.

Restricted treatments during the study period

- Immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks)
- Immune globulins, blood or blood-derived products
- Any other vaccines

7 MANAGEMENT OF SAMPLES

Blood samples for the assessment of antibody responses will be collected at V1 (D0, pre-vaccination) and at V3 (D28 [+ 7 days]). See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 SAMPLE COLLECTION

At V1 and V3, 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; will verify the assigned subject's number on the pre-printed label that contains that subject's number and sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 SAMPLE PREPARATION

Detailed instructions on how to prepare blood samples for assessment of antibody response are contained in the sample handling procedures 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 1 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.

The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. These tubes are pre-labeled with adhesive labels that identify the study code, the subject's number and the sampling stage or visit number.

The subject's number and 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 Sponsor's monitoring staff must be notified. See the sample handling procedures for further details.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Sponsor's monitoring staff. 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 International Air Transport Association (IATA) 602 regulations.

Samples will be shipped to Global Clinical Immunology (GCI) at Sanofi Pasteur. The address is provided in the sample handling procedures.

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 at least 5 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

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

Sponsor will supply the study sites with protocols, ICFs, CRBs, diary cards, 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 the Sponsor. If a computer is provided by the Sponsor, 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 the Sponsor, indicating the quantity required. Contact information is provided in the clinical study protocol (see Names and addresses).

9 ENDPOINTS AND ASSESSMENT METHODS

9.1 SAFETY

9.1.1 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 subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to 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 action 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 condition worsens in frequency or intensity, or if in the assessment of the treating physician 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 (e.g., 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[d]

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.

d Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These 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 (AR):

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)

Unexpected Adverse Reaction (UAR):

An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product).

The following additional definitions are used by the Sponsor:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the CRB. The assessment of these AEs post-vaccination is mandatory. A solicited event is defined by a combination of:

- Symptom and
- Onset post-vaccination

e.g., injection site pain between D0 and D7 post-vaccination, or headache between D0 and D7.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRB and considered as related to the product administered.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of symptom and/or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D7 is a solicited reaction (i.e., prelisted in the 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 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 site, e.g., erythema that is localized but that is not at the injection site.

Adverse Events of Special Interest (AESIs):

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 (e.g., regulators) might also be warranted.

9.1.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, maximum 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, maximum intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions and systemic reactions occurring up to 7 days (D0 through D7) 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 (D0 through D28) after vaccination

- Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the study (D0 through V3)
- Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the study (D0 through V3)

9.1.3 Safety Assessment Methods

At V1, the Investigator or a delegate will perform a targeted physical examination based on medical history.

At V2 and V3, the Investigator or a delegate may perform a targeted physical examination, as necessary, and will ask the subject about any solicited reactions and unsolicited AEs recorded in the diary card, 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.

9.1.3.1 Immediate Post-Vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination surveillance 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 and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10.

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

After vaccination, subjects will be provided with a safety diary card, 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 diary card on the day of vaccination and for the next 7 days (i.e., D0 to D7) 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 (e.g., 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

Table 1 and Table 2 present, respectively, the solicited injection site reactions and solicited systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 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
Data analysis term (MedDRA preferred term [PT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	injection site bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized.	Presence of a redness including the approximate point of needle entry.	Swelling at or near the injection site. Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling.	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.
Intensity scale[a]	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	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

a 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 2 - Solicited Systemic Reactions: Terminology, Definitions, and Intensity Scales

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Shivering
Data analysis term (MedDRA preferred term [PT])	Pyrexia	Headache	Malaise	Myalgia	Chills
Diary Card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills
Definition	Fever is defined by a temperature of ≥38.0°C (≥100.4°F).	A headache is pain or discomfort in the head, or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling.
Intensity scale[a]	Grade 1: ≥38.0°C to ≤38.4°C, or ≥100.4°F to ≤101.1°F Grade 2: ≥38.5°C to ≤38.9°C, or ≥101.2°F to ≤102.0°F Grade 3: ≥39.0°C, or ≥102.1°F	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

a 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 (in degrees Celsius), preferably always at the same time. The optimal time for measurement is the evening, when body temperature is highest. Temperature is also to be measured at the time of any apparent fever. The highest observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is oral. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic and temporal artery thermometers must not be used.

9.1.3.3 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 diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from inclusion until 28 (+ 7) days 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 Death/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 (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE. 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 1 and Table 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.

  - 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 9.1.3.5.

- Action taken for each event (e.g., 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 and elapsed time)

- Whether the AE was AESI
- Whether the AE caused study discontinuation

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.

9.1.3.4 Adverse Events of Special Interest

AESIs will have the same detailed information collected as SAEs (collected throughout the study). These include (13):

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

9.1.3.5 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[a]:

Not related – The AE is clearly/most probably caused by other etiologies such as subject's 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 injection site AEs (solicited and unsolicited) and all solicited systemic reactions 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.

AEs 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.

a ICH Guidelines, Clinical Safety Data Management E2A

9.2 IMMUNOGENICITY

9.2.1 Immunogenicity Endpoints

The endpoints for the evaluation of immunogenicity are:

- GMT of HAI at D0 and D28
- Individual Geometric Mean Titer Ratio (GMTR) of HAI at D28/D0
- Seroconversion rate (percentage of subjects with HAI titer <10 [1/dil] at D0 and post-injection titer ≥40 [1/dil] at D28, or HAI titer ≥10 [1/dil] at D0 and a ≥4-fold increase in HAI titer [1/dil] at D28)
- Seroprotection rate (percentage of subjects with HAI titer ≥40 [1/dil]) at D0 and D28

9.2.2 Immunogenicity Assessment Methods

Anti-Influenza Virus Antibody Titration by Inhibition of Hemagglutination

Assays will be performed by the Sanofi Pasteur laboratory (GCI, Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility. The address is provided in the sample handling procedures.

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 test 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 two independent assay runs, and the 2 values, which cannot differ by more than 1 two-fold dilution, are reported. The HAI 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. If the first/lowest serum dilution exhibits hemagglutination, the serum antibody titer is reported as <10 (1/dil). If the last/highest serum dilution exhibits complete inhibition of hemagglutination, the serum antibody titer is reported as ≥10 240 (1/dil).

In this study, QIV-HD will be compared to a local QIV-SD, and it is possible that the two vaccines contain different strains based on comparison of strains among Sanofi Pasteur QIV-HD (based on WHO / VRBPAC recommendations) and a local QIV-SD (based on NIID). Sanofi Pasteur plans on performing the HAI testing using both the QIV-HD and QIV-SD strains as test antigens for all the subjects, irrespective of the vaccine received. For example, if QIV-HD is comprised of a, b, c and d strains and QIV-SD is comprised of a, b, c and "d-like" strains (3 common and 1 "-like strain"), the proposed testing strategy would require HAI testing of sera from all subjects (irrespective of the vaccine received) with a, b, c, d and "d-like" strain test antigens in order to evaluate the comparability between the "-like strains" in this study.

9.3 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 within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor 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 (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Death/Safety Complementary Information CRFs.

10.1 INITIAL REPORTING BY THE INVESTIGATOR

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the CRB; the system will automatically send a notification to the Sponsor after approval of the Investigator within the CRB or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the Sponsor address that appears on the clinical study protocol (see Names and addresses). Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical study are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the CRB as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, subject status, etc.) should be sent (by fax or e-mail) to the Sponsor within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the CRB system does not work.
- Report the SAE information to the site IRB immediately.

If there is a need for urgent consultation, the Investigator is to contact the Sponsor. If the Sponsor 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 (e.g., outcome, precise description of medical history, results of the investigation). All relevant information must be

included directly in the AE CRF and the appropriate Death/Safety Complementary Information CRFs. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the Sponsor.

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 (e.g., 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 9.1.3.5.

Following this, the Pharmacovigilance Global Safety Expert of Sanofi Pasteur 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 Reporting procedure.

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

11 DATA COLLECTION AND MANAGEMENT

11.1 DATA COLLECTION AND ELECTRONIC CASE REPORT BOOK COMPLETION

Individual safety diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.1.3. These diary cards will include prelisted terms and intensity scales (see Table 1 and Table 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.

At specified intervals, the Investigator or an authorized designee will interview the subjects to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card 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 CRB, 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 in order to track all modifications and to 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

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) will be integrated into the Sponsor's centralized GPE 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 Clinical Study Director of Sanofi, the Pharmacovigilance Global Safety Expert and the RMO of Sanofi Pasteur. Follow-up information concerning a completed case will be entered into the GPE database, and a new version of the case will be created.

The information from the GPE 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 Sponsor CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and/or consistency checks will be systematically applied in order 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 GPE Department has been reconciled, the database will be released for statistical analysis.

11.3 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

11.4 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, with the 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 the database lock. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

12.1.1 Hypotheses and Statistical Methods for Objectives

12.1.1.1 Hypotheses

Safety

No hypotheses are to be tested.

Immunogenicity

No hypotheses are to be tested.

12.1.1.2 Statistical Methods

Safety

Safety results will be described for subjects in safety analysis set who received QIV-HD IM, QIV-HD SC, or QIV-SD SC. Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and AESIs will be summarized. The main parameters will be described with 95 % CI based on the Clopper-Pearson method (14).

- Unsolicited systemic AEs occurring within 30 minutes of injection (immediate unsolicited AEs)
- Solicited injection site reactions (pain, erythema, swelling, induration, and bruising) occurring within 7 days after the day of injection (D0 to D7) according to presence, time to onset, number of days of occurrence, maximum intensity (Grade 1, Grade 2, or Grade 3) and action taken. When more than 1 intensity level is reported within a time period, the highest intensity will be used.
- Solicited systemic reactions (fever, headache, malaise, myalgia, and shivering) occurring within 7 days after the day of injection (D0 to D7) according to presence, time to onset, number of days of occurrence, maximum intensity (Grade 1, Grade 2, or Grade 3) and

action taken. When more than 1 intensity level is reported within a time period, the highest intensity will be used.

- Unsolicited AEs occurring within 28 days after the day of injection by system organ class (SOC) and PT, time to onset, duration, maximum intensity (Grade 1, Grade 2, and Grade 3), and relationship to vaccination (for systemic AEs only).
- All SAEs that occur throughout the study by SOC and PT, time to onset, seriousness criteria, outcome and relationship to vaccination.
- All AESIs reported throughout the study by SOC and PT and relationship to vaccination.

Immunogenicity

Immunogenicity in terms of GMTs, seroconversion, and seroprotection rates will be summarized for each strain. The 95% CIs for the GMTs will be calculated using normal approximation of log-transformed titers. The GMT ratios of each QIV-HD group (IM or SC) to QIV-SD group will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The differences in the seroconversion rates between each QIV-HD group (IM or SC) and QIV-SD group will be computed along with the 2-sided 95% CIs by the Newcombe-Wilson method without continuity correction (15). In addition, the immunogenicity analyses will be performed by subgroups of age (<75, ≥75), and sex (male, female). Additional parameters may be displayed as appropriate. Details of the above analyses will be described in the SAP.

12.2 ANALYSIS SETS

Three analysis sets will be used: the Full Analysis Set, the Per-protocol Analysis Set, and the Safety Analysis Set.

12.2.1 Full Analysis Set

The full analysis set (FAS) will include all randomized subjects who received at least one dose of the study vaccine and had a post-vaccination blood sample HAI result for at least one strain. Subjects will be analyzed according to the vaccine group to which they were randomized.

12.2.2 Safety Analysis Set

The safety analysis set (SafAS) is defined as those subjects who have received study vaccine[a]. 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).

a for which safety data are scheduled to be collected

12.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specific 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 provide the post-dose serology sample at V3 in the proper time window (i.e., 28 to 35 days after vaccination) or a post-dose serology sample (V3) was not drawn

Subject received a protocol-restricted therapy / medication / vaccine (prohibited therapies / medications / vaccines should have been indicated in Section 6.7)

In addition to the criteria listed above, subjects will also be excluded from the PPAS if their HAI serology sample at V3 did not produce a valid test result for all strains.

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 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 (for example, the disposition, the demographics or baseline characteristics).

The safety analyses will be performed on the SafAS.

The immunogenicity analyses will be performed on the PPAS and the FAS. The main immunogenicity analyses will be conducted on Cohort 2 for the PPAS. Immunogenicity analyses will also be conducted on Cohort 2 for the FAS and on all 175 subjects. More details will be described in the SAP.

12.3 HANDLING OF MISSING DATA AND OUTLIERS

12.3.1 Safety

No replacement will be done.

Nevertheless, missing relationship will be considered as related at the time of statistical analysis. No search for outliers will be performed. In all subject listings, partial and missing data will be clearly indicated as missing. Details will be described in the SAP.

12.3.2 Immunogenicity

In order to appropriately manage replicate values for analysis purpose, the individual GMT of all values will be computed for each blood sample after managing extreme values as described. The computed value is then considered the titer for that particular blood sample.

- If a titer is <LLOQ, then the computed value, LLOQ/2, will be used
- If a titer is ≥LLOQ and <ULOQ (or ≤ULOQ), then the titer itself will be used
- If a titer is ≥ULOQ (or >ULOQ), then computed value, ULOQ, will be used.

Any other replacement to be applied to specific endpoints will be described in the SAP. No test or search for outliers will be performed.

No replacement will be done for missing values. Based on the previous TIV-HD and QIV-SD trials in this population, the amount of missing immunogenicity data is expected to be ≤5% in this study. Usually in vaccine trials, it seems generally reasonable to assume missing immunogenicity data are missing completely at random (MCAR) (16). Indeed, it is highly unexpected that the dropout (or any other reason for missing data) could be linked to the immune response of the subject. Therefore, confirming the results of the PPAS for the primary analysis with the FAS would be satisfactory in terms of sensitivity analysis.

12.3.3 Efficacy

Not applicable.

12.4 INTERIM / PRELIMINARY ANALYSIS

No interim/preliminary analyses are planned. There will be 1 statistical analysis conducted after the end of the study (D28).

12.5 DETERMINATION OF SAMPLE SIZE AND POWER CALCULATION

There is no statistical powered hypothesis test for sample size calculation.

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 Edinburgh revision of 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, diary cards, medical and hospital records, screening/enrollment 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 diary card, the Investigator or study coordinator will obtain verbal clarification from the subject, enter the response into the ”investigator’s comment” page of the diary card or source document, and transfer the information to the CRB.

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 later 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.

a Unless the electronic medical records are determined to be appropriate at site selection, in which case they are acceptable on their own.

13.3 CONFIDENTIALITY OF DATA AND ACCESS TO SUBJECT RECORDS

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

Sponsor personnel (or designates), the IECs/IRBs, and regulatory agencies require direct access to all study records, and will treat these documents in a confidential manner.

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.

13.4 MONITORING, AUDITING, AND ARCHIVING

13.4.1 Monitoring

Before the start of the study (i.e., 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 clinical 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 clinical research associates on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRB completion instructions for entering data into the CRB, and the guidelines for detailed study procedures such as the product management, sample handling procedures and IRT operation manuals.

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 (e.g., protocol violations, 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

For the purpose of ensuring compliance with the clinical study protocol, good clinical practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, the investigator will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

13.4.3 Archiving

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical study.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical study completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

13.4.4 Responsibilities of the Investigator(s)

The Investigator is required to ensure compliance with all procedures required by the clinical study protocol and with all study procedures provided by the Sponsor (including security rules).

The Investigator agrees to provide reliable data and all information requested by the clinical study protocol (with the help of the CRB, Query form or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the subject's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical study in accordance with the clinical study protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical study protocol and all necessary information.

13.4.5 Responsibilities of the Sponsor

The Sponsor of this clinical study is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical study as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the CRBs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical study.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and subject compliance with clinical study protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IP allocation, subject compliance with the IP regimen, IP accountability, concomitant therapy use and quality of data.

13.5 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical studies under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the Ethics IECs/IRBs or health authorities in countries requiring this document.

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 study visits and procedures.

13.7 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical study, including, but not limited to, the clinical study protocol, personal data in relation to the subjects, the CRBs, the Investigator's Brochure, and the results obtained during the course of the clinical study, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical study protocol and other necessary documentation to the ethics committee (IEC/IRB) is expressly permitted, the IEC/IRB members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical study.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical study, to the exclusion of any use for their own or for a third party's account.

13.8 PROPERTY RIGHT

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Sub-investigator not to mention any information or the product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical study in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

13.9 PUBLICATION POLICY

Data derived from this study are the exclusive property of the Sponsor and Sanofi Pasteur. Any publication or presentation related to the study must be submitted to the Sponsor and 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, the Sponsor and Sanofi Pasteur shall be offered an association with all such publications, it being understood that the Sponsor and Sanofi Pasteur are entitled to refuse the association.

The Sponsor and 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 the Sponsor and 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.

The review of Sponsor and Sanofi Pasteur can be expedited to meet publication guidelines.

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15 SIGNATURE PAGES

DFI15130-QHD00008 Appendix 1 Protocol

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	12-May-2017 08:44 GMT+0200
[redacted]	Clinical Approval	12-May-2017 11:10 GMT+0200
[redacted]	Regulatory Approval	12-May-2017 15:58 GMT+0200