NCT04498832

AMENDED CLINICAL STUDY PROTOCOL 01

Immunogenicity and Safety of High-Dose Quadrivalent Influenza Vaccine (SP0178) Administered by Intramuscular Route versus Standard-Dose Quadrivalent Influenza Vaccine by Subcutaneous Route in Subjects 60 Years of Age and Older in Japan

Phase III, randomized, modified double-blind, active-controlled, multi-center study evaluating the immunogenicity and safety of QIV-HD administered intramuscularly in healthy subjects 60 years of age and older in Japan

Product Code / Study number:	SP0178 / QHD00010-EFC15150
Development Phase:	Phase III
Sponsor:	Sanofi K.K. 3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1488, Japan
Investigational Product:	High-Dose Quadrivalent Influenza Vaccine, (Zonal Purified, Split Virus) 2020-2021 Strains (QIV-HD)
Form / Route:	Suspension / Intramuscular injection
Indication For This Study:	Single dose for individuals 60 years of age and older
Manufacturer:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA

Version Number:	1.0	EudraCT and/or	Not applicable
		IND Number(s)	Not applicable
		WHO universal study number:	U1111-1225-1085
Date:	24-Apr-2020	Total number of pages:	84

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.
STUDY MEDICAL MANAGER	Name: Address: Tel: Fax: E-mail:	[redacted]
LOCAL STUDY MANAGER (Monitoring Team's representative)	Name: Address: Tel: Fax: E-mail:	[redacted]
GLOBAL STUDY MANAGER	Name: Address: Tel: Fax: E-mail	[redacted]
OTHER EMERGENCY TELEPHONE NUMBERS	Company: Address: Tel:	[redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendement	Date, version
Amended Clinical Study Protocol 01	All	24-Apr-2020, Version 1.0 (electronic 1.0)
Original Protocol	All	25-Apr-2019, Version 1.0 (electronic 1.0)

OVERALL RATIONALE FOR THE AMENDMENT

The reason for this amendment is to update the information because the start date of this study has been changed. In addition, an exclusion criterion was added considering the impact of the coronavirus disease 2019 (COVID-19) pandemic.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Name and addresses of, Section 3 Investigators and study organization	The name of the global study manager and the role of study medical manager were changed.	Updated due to the role review and the change of persons in charge.
Synopsis (Planned study period), Section 5.1.5 Planned study calendar	The planned study calendar was updated.	Updated due to the change in the study start date.
Synopsis (Exclusion criteria), Section 5.2.5 Exclusion criteria	The following exclusion criterion (E16) was added: Any condition that in the opinion of the Investigator could interfere with the evaluation of the vaccine (e.g., under investigation or monitoring for possible COVID-19).	Added considering the impact of COVID-19 pandemic.
Table of study procedures, Section 5.1.4 Visit procedures	Shingles vaccination history was added as information to be obtained and collected.	Added in order to evaluate the uptake of the shingles vaccine in this study population since a new shingles vaccine for individuals 50 years of age and older was launched in Japan.
Section 1.1 Background, Section 1.2 Background of the investigational product, Section 5.1.2 Justification of the study design, Section 14 References list	The information about the background of this study and the investigational product was updated.	Updated according to the current situation.

Section # and Name	Description of Change	Brief Rationale
Section 6.7 Concomitant medication and other therapies	The description that medications will not be coded was deleted.	Medications will be coded because of the PMDA requirements for an electronic study data submission.
Section 9.2.2.3.2 Reactogenicity (solicited reactions from Day 0 to Day 7 after vaccination) Table 1, Table 2	The intensity scale for diary card/eDC was added to that for Injection site pain, Headache, Malaise, Myalgia and Shivering.	Updated in alignment with the current version of the Sanofi Pasteur Safety Guidelines.
Throughout	The investigational products and their active substances were updated.	Updated according to the virus strains for the 2020-2021 NH influenza season.
Throughout	Minor editing, typographical corrections, and wording standardization.	To clarify or update in alignment with the current version of the Sponsor's clinical study protocol template.

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SYNOPSIS

Company:	Sanofi K.K.
Investigational Product:	High-Dose Quadrivalent Influenza Vaccine, (Zonal Purified, Split Virus) 2020-2021 Strains (QIV-HD)
Active Substance(s):	A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1) strain, A/Hong Kong/2671/2019 IVR-208 (H3N2) strain, B/Washington/02/2019 wt virus strain, B/Phuket/3073/2013 wt virus strain

Title of the Study:	Immunogenicity and Safety of High-Dose Quadrivalent Influenza Vaccine (SP0178) Administered by Intramuscular Route versus Standard-Dose Quadrivalent Influenza Vaccine by Subcutaneous Route in Subjects 60 years of age and older in Japan
Development Phase:	Phase III
Coordinating Investigator	Not Applicable
Study Sites:	This will be a multi-center study conducted at approximately 10 to 15 study sites in Japan. Investigators and sites are listed in the lists of investigators, study centers, and sponsor's personnel involved in the study.
Planned Study Period:	First visit, first subject: 21 October 2020 Last visit, last subject: 19 January 2021
Study Design, Schedule of Study Procedures, and Methodology:	QHD00010-EFC15150 will be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in approximately 2100 healthy adults 60 years of age and older to evaluate the immunogenicity and safety of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) route. A local standard-dose quadrivalent influenza vaccine (QIV-SD) administered by subcutaneous (SC) route will serve as a control arm. Interactive response technology (IRT) will be used to randomly assign subjects to either of the 2 study groups and to assign subject numbers in each of the groups. <u>Vaccination</u> All eligible subjects will be randomized to receive a single injection of either QIV-HD (IM route) or QIV-SD (SC route) at Visit (V) 01 (Day [D] 0). <u>Blood sampling</u> All subjects will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V02 (D28 [+7 days]) for hemagglutination inhibition (HAI) testing. <u>Collection of safety data</u> Subjects will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study. All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic adverse events (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 V02), serious adverse events (SAEs) including adverse events of special interest (AESIs*) (D0 to V02) in a diary card.

	Study staff will contact subjects by phone at D8 post-vaccination to identify whether the subject experienced any SAEs not yet reported and will remind the subjects to bring the completed diary card with them to V02. Study staff will review the D0 to V02 safety data with subjects at V02. Electronic data capture (EDC) will be used for the collection of data. ***Note**: AESIs will be captured as SAEs. These include new onset of Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.
Interruption of the Study:	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), or the governing regulatory authorities in Japan where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.
Primary Objective(s):	**Immunogenicity** • To demonstrate that QIV-HD induces an immune response (as assessed by HAI geometric mean titers [GMTs] and seroconversion rates) that is superior to responses induced by QIV-SD for the 4 virus strains at 28 days post-vaccination in all subjects.
Primary Endpoint(s):	**Immunogenicity** • HAI antibody (Ab) titers obtained on D28 • Seroconversion (titer <10 [1/dilution {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)
Secondary Objective(s):	**Immunogenicity** • To describe the immune response induced by QIV-HD and QIV-SD by HAI measurement method in all subjects. **Safety** • To describe the safety profile of all subjects in each study group
Secondary Endpoint(s):	**Immunogenicity** • HAI Ab titers obtained on D0 and D28 • Individual HAI titers ratio 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) • Percentage of subjects with titers ≥40 (1/dil) at D0 and D28 **Safety** Safety will be described for all subjects: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, 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 event led to early termination from the study, of SAEs throughout the study. • Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the study.
Planned Sample Size:	A total of approximately 2100 subjects are planned to be enrolled and randomized in a 1:1 ratio as follows: • Group 1 (QIV-HD, IM): n = 1050 • Group 2 (QIV-SD, SC): n = 1050
Duration of Participation in the Study:	The duration of each subject's participation will be approximately 28 days (D0 through D28 [+7 days]).
Investigational Product:	High-Dose Quadrivalent Influenza Vaccine, (Zonal Purified, Split Virus) 2020-2021 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) / the United States Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2020-2021 NH influenza season. **Active Substances:** • A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1) strain 60 µg hemagglutinin (HA) • A/Hong Kong/2671/2019 IVR-208 (H3N2) strain 60 µg HA • B/Washington/02/2019 wt virus strain 60 µg HA • B/Phuket/3073/2013 wt virus strain 60 µg HA **Excipients:** • Buffered saline solution quantity sufficient (qs) 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, injected into the upper arm (deltoid area)
Batch Number:	TBD
Control Product:	[redacted] (Influenza HA Vaccine, [redacted]) Local Standard-Dose Inactivated Quadrivalent Influenza Vaccine, 2020-2021 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 to be determined by Ministry of Health, Labour and Welfare (MHLW) for the 2020-2021 NH influenza season.

	Active substances: • A/(H1N1)-like strain 15 µg HA • A/(H3N2)-like strain 15 µg HA • B/(Victoria lineage)-like strain 15 µg HA • B/(Yamagata lineage)-like strain 15 µg HA **Excipients:** Buffered saline solution qs to appropriate volume
Route:	SC, injected into the upper arm (posterior region)
Batch Number:	TBD
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: I 01. Aged ≥60 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 V02 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 E 16. Any condition that in the opinion of the Investigator could interfere with the evaluation of the vaccine (e.g., under investigation or monitoring for possible coronavirus disease 2019 [COVID-19])
Statistical Methods:	The per-protocol analysis set (PPAS) and full analysis set (FAS) will be used for the main immunogenicity analyses. Conclusions will be made based on the FAS results. The safety analysis set (SafAS) will be used for all safety analyses. There will be one statistical analysis conducted after the end of the study (D28). **Primary Objective** Immunogenicity – Superiority A superiority approach will be used to compare post-vaccination GMTs and seroconversion rates between QIV-HD and QIV-SD groups for each strain using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses. The definitions of superiority correspond to statistical superiority where 1 is used as the threshold for the ratio of GMTs and 0 is used as the threshold for difference of seroconversion rates. Superiority as defined in the primary objective is based on the following individual hypotheses: $$H_0^s : \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} \le 1 \Leftrightarrow \log_{10}(GMT_{QIV-HD}^s) - \log_{10}(GMT_{QIV-SD}^s) \le \log_{10}(1) = 0$$ $$H_A^s : \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} > 1 \Leftrightarrow \log_{10}(GMT_{QIV-HD}^s) - \log_{10}(GMT_{QIV-SD}^s) > \log_{10}(1) = 0$$ $$H_0^s : \pi_{QIV-HD}^s - \pi_{QIV-SD}^s \le 0$$ $$H_A^s : \pi_{QIV-HD}^s - \pi_{QIV-SD}^s > 0$$ where • s: strain • π : The seroconversion rate If superiority is demonstrated for post-vaccination GMTs and seroconversion rates in the 4 strains, then the immunogenicity of QIV-HD will be considered as superior to QIV-SD. The statistical methodology will be based on the use of the 2-sided 95% confidence intervals (CIs) of the ratio of post-vaccination GMTs and difference in seroconversion rates between the QIV-HD and QIV-SD groups. The 95% CIs will be calculated by normal approximation of log-transformed titers for GMTs and by the Wilson score method without continuity correction, quoted by Newcombe, for seroconversion rates. **Secondary Objective** Immunogenicity – Descriptive Analyses The GMTs in terms of Ab titers obtained at the pre-vaccination (V01) and post-vaccination (V02), and seroconversions will be summarized with their 95% CIs using the same methods for the primary objectives. The percentages of subjects with titers ≥40 (1/dil) and the corresponding 95% CIs (Clopper-Pearson method) will be performed for pre-vaccination (V01) and post-vaccination immunogenicity (V02). The geometric mean of individual titer ratios (GMTRs) will be calculated for post-vaccination immunogenicity (V02) over the baseline immunogenicity (V01) with the corresponding 95% CIs (assuming normal approximation of log-transformed values). Reverse

cumulative distribution curves against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (V02). Additional parameters may be displayed as appropriate.

In addition, the immunogenicity analyses in terms of GMTs, seroconversion rates, and the percentages of subjects with titers ≥40 (1/dil) will be performed by age (i.e., 60 to 64, 65 to 74, and 75 years of age and older; 60 to 64 and 65 years of age and older), sex, previous influenza vaccination status, and baseline seropositivity status. Details of the above analyses will be described in the statistical analysis plan (SAP).

Safety – Descriptive Analyses

Safety results will be analyzed descriptively for subjects in SafAS who received QIV-HD or QIV-SD. Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and AESIs will be summarized. The main parameters will be described with 95% CIs (Clopper-Pearson method).

Calculation of Sample Size

A total of approximately 2100 adults 60 years of age and older will be enrolled. A sample size of 2100 is determined based on an overall power of 90% controlled with one-sided 0.025 type I error for demonstrating superiority in the primary objective for all 4 strains for both the HAI GMTs and seroconversion rates comparing QIV-HD versus QIV-SD groups. The margins for superiority are defined as 1 for GMTs and 0 for seroconversion rates. All of the statistical assumptions used in the sample size calculation are presented below.

Statistical Assumptions for the sample size calculation

Statistical Criteria	Assumption
Allocation ratio	1:1 between the QIV-HD and QIV-SD group
Overall power	More than 90%
Type I error	One-sided 0.025 on each strain for each endpoint
Expected GMT ratio	1.6 for all 4 strains
Standard deviation for the log titers (in log10 scale)	0.7 for all 4 strains
Expected seroconversion rates	40% for 2 strains with an increase of 17% in the QIV-HD group and 50% for another 2 strains with an increase of 8% in the QIV-HD group
Attrition rate	5% in FAS

TABLE OF STUDY PROCEDURES

Phase III Study, 2 Visits, 1 Telephone Call, 1 Vaccination, 2 Blood Samples, 28 Days' Duration per Subject

Visit/Contact	**Visit 1 (V01)**	**D8 Telephone Call**	**Visit 2 (V02)**
Study timelines (days)	0	8	28
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		
History of pneumococcal vaccination & shingles vaccination	X		
History of influenza infection[a]	X		
Reportable concomitant medications	D0-V02		
Physical examination[b]	X		
Height	X		
Body weight	X		
Contact interactive response technology	X		X
Randomization/allocation of subject number and unique dose number	X		
Blood sampling (BL), 10 mL	BL0001[c]		BL0002
Vaccination	X		
Immediate surveillance (30 min)	X		
Diary card provided[d]	X		
Recording of solicited injection site & systemic reactions	D0-D7		
Follow-up phone call		X[e]	
Collection of unsolicited AEs	D0-V02		
Diary card collected and reviewed			X
Study termination record			X
Collection of SAEs (including AESIs)[f]	To be reported at any time during the Study		

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

a History of influenza infection in the previous year

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

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

d Subjects will use this diary card to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D0 to D7 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02.

e During this phone call, study staff will find out whether the subject experienced any SAEs and AESIs not yet reported and will remind the subjects to bring the completed diary card to V02.

f AESIs will be captured 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

Ab	antibody
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
CDM	Clinical Data Management
CI	confidence interval
COVID-19	coronavirus disease 2019
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
D	Day
DP	drug product
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
GMT	geometric mean titer
GMTR	geometric mean of individual 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
IME	important medical event

IND	investigational new drug (application)
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
LVLS	last visit, last subject
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
NH	Northern Hemisphere
NIID	Japan National Institute of Infectious Diseases
NSAID	non-steroidal anti-inflammatory drug
PMDA	Pharmaceuticals and Medical Devices Agency
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
qs	quantity sufficient
RBC	red blood cell
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SMM	Study Medical Manager
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
ULOQ	upper limit of quantification
UN	United Nations
US	United States
V	Visit

VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 INTRODUCTION

1.1 BACKGROUND

This study will evaluate the immunogenicity and safety of high-dose quadrivalent influenza vaccine (hereafter referred to as QIV-HD) administered by intramuscular (IM) route in subjects 60 years of age 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 non-productive cough, influenza can also cause severe malaise lasting for several days. Individuals in high-risk groups (e.g., adults 65 years of age and older and persons with underlying medical conditions) are at high 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 remains the most effective means of preventing influenza and the complications associated with the disease. The World Health Organization (WHO) and the Advisory Committee on Immunization Practices (ACIP) in the United States (US) recommends annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (1) (3). Routine influenza vaccination for adults 65 years of age and older and adults 60 to 64 years of age with respiratory, cardiac, renal disease, or human immunodeficiency virus (HIV) has also been recommended in Japan since 2001 under the Preventative Vaccination Law (4).

The immune response to standard-dose (SD) influenza vaccines (15 micrograms [µg] hemagglutinin [HA] per strain) is sub-optimal in adults 65 years of age and older compared to healthy young adults (5). A strategy to improve protection against influenza in adults 65 years of age and older is to increase the antigen dose (6). Sanofi Pasteur has developed a quadrivalent influenza vaccine high-dose (QIV-HD) containing 60 µg of HA of each of 4 virus strains (A/H1N1, A/H3N2, and 1 B strain from each of the Victoria and the Yamagata lineages).

QIV-HD has been developed based on the experience gained with Sanofi Pasteur's trivalent influenza vaccine high-dose (TIV-HD) which contains 60 µg of HA of each of 3 virus strains and is manufactured in the United States (US). TIV-HD was licensed by Sanofi Pasteur under the name Fluzone® High Dose for use in adults 65 years of age and older in the US in 2009 (7), Canada in 2015 (8), Australia in 2017 (9), Brazil in 2018, and the United Kingdom in 2019.

TIV-HD generated superior immune responses (10) (study FIM05) and improved vaccine efficacy (VE) (11) (study FIM12) compared to a trivalent influenza vaccine standard-dose (TIV-SD) in clinical studies conducted in adults 65 years of age and older. FIM12 was a large-scale, multi-center efficacy trial which demonstrated that TIV-HD was 24.2% (95% confidence interval [CI], 9.7 to 36.5) more effective in preventing laboratory-confirmed influenza illness against any

circulating strain compared to TIV-SD, or in other words, one in 4 breakthrough cases of influenza could be prevented if TIV-HD was used instead of TIV-SD in this population.

Several retrospective studies, in over 8 influenza seasons and in more than 24 million individuals 65 years of age and older, confirmed the superior protection offered by TIV-HD compared to TIV-SD against complications of influenza such as pneumonia and influenza hospitalization (13.4% [95% CI, 7.3% to 19.2%, p<0.001]), cardio-respiratory hospitalizations (17.9% [95% CI, 14.9% to 20.9%, p<0.001]) and all–cause hospitalization (8.1% [95% CI, 5.9% to 10.3%, p<0.001]); although the impact may vary per season (12) (13) (14) (15) (16) (17) (18) (19) (20) (21).

Based on approximately 26 500 subjects who were exposed to TIV-HD through its clinical development program or in post-marketing surveillance (ie, more than 137 million doses distributed), the safety profile of TIV-HD in humans has been shown to be well tolerated with no safety concerns.

QIV-HD is produced using the same drug substance (DS) and drug product (DP) manufacturing processes as TIV-HD except for the DP formulation step, which includes the addition of a second influenza B strain at the same HA content as the other 3 strains (60 µg HA/strain/dose). This results in a slightly higher fill volume to provide a delivered dose of 0.7 mL.

In November 2019, QIV-HD was licensed in adults 65 years of age and older in the US. In April 2020, QIV-HD also received a positive opinion from the European Union health authority with marketing authorizations granted by Norway, France, and Latvia as of 21 April 2020. Moreover, QIV-HD has been submitted for licensure in adults 65 years of age and older in Canada (July 2019), Australia (July 2019), South Korea (January 2020), and Switzerland (March 2020).

Thus, the goal of the QIV-HD project is to also license QIV-HD for adults 60 years of age and older in Japan.

1.2 BACKGROUND OF THE INVESTIGATIONAL PRODUCT

Sanofi Pasteur's TIV-HD, containing 60 µg HA of each of the 3 virus strains (4-times more 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 in 2009, Canada in 2015, Australia in 2017, Brazil in 2018, and the United Kingdom in 2019 in order to improve the effectiveness of the influenza vaccine in adults 65 years of age and older (22). The improvement in efficacy of TIV-HD vaccine when compared with TIV-SD was demonstrated in a large scale, multi-center study (FIM12), which enrolled 31,989 adults 65 years of age 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 vaccine 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 vaccine was used instead of the 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 (23). This efficacy study concluded that the high-dose vaccine is safe, induces significantly higher antibody (Ab)

responses, and provides superior protection against laboratory-confirmed influenza illness compared to the TIV-SD among adults 65 years of age 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 (24). To overcome the problem of B strain selection and further improve protection against the 2 seasonal influenza B virus strains recommended each influenza season, Sanofi Pasteur has developed a QIV-HD containing 1 Victoria lineage B strain and 1 Yamagata lineage B strain in addition to the two influenza A strains. QIV-HD is produced using the same drug substance process as the licensed TIV-HD; for the drug product, the licensed TIV-HD manufacturing process was modified slightly to increase the fill volume in order to include the 2nd influenza B strain at the same HA content as the other 3 strains (60 µg HA/strain/dose).

A Phase III immunogenicity bridging study (QHD00013) was conducted in adults 65 years of age and older during the 2017-2018 influenza season and demonstrated the non-inferiority of the hemagglutination inhibition (HAI) antibody responses between QIV-HD and TIV-HD (25). Furthermore, QHD00013 demonstrated that the addition of a 2nd B strain to TIV-HD did not interfere with the immune response to the other vaccine components or adversely affect the safety profile of the vaccine; in order to demonstrate the added value of the 2nd B strain in QIV-HD, superiority of antibody responses to each B-strain in QIV-HD compared with the TIV-HD that does not contain the corresponding B strain was also demonstrated. Based on the comparability of responses to the TIV and QIV formulations, QIV-HD is expected to be more efficacious than SD influenza vaccines in preventing influenza disease in adults 65 years of age and older.

Japan has one of the largest aging populations in the world with a 2019 estimate of 35 million adults 65 years of age and older, comprising more than one-fourth of the total population. By 2040, the proportion of adults 65 years of age and older is expected to be 35% of the total population, according to Ministry of Internal Affairs and Communications statistics (26).

In Japan, during the 2017-2018 and 2018-2019 influenza season, adults 60 years of age and older represented 64% and 65% of influenza-related hospitalizations, respectively (27). Furthermore, in 2017 and 2018, adults 65 years of age and older accounted for 95% and 93% of influenza-related deaths, respectively (28) (29).

Since adults 65 years of age and older and adults 60 to 64 years of age with comorbidities are at increased risk from influenza and its complications, the Ministry of Health, Labour and Welfare has incorporated the seasonal influenza vaccine into the National Immunization Program for these at-risk groups. Since 2001, the influenza vaccine has been introduced into the routine vaccination schedule for adults 65 years of age and older and adults 60 to 64 years of age with respiratory, cardiac, or renal disease, or infected with HIV (4). With a growing population of adults 60 years of age 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 as currently only QIV-SD vaccine is available in Japan. A cost-effectiveness ratio for the influenza vaccination was 516,332 yen per year of life saved for 100,000 adults 65 years of age and older in one study (30).

Therefore, in order to license QIV-HD and bring a new innovative influenza vaccine that provides improved immunogenicity to an increasing aging population in Japan, a Phase I/II study (QHD00008) was conducted in Japan during the 2017-2018 NH influenza season to be followed by a Phase III study (QHD00010) to be conducted in the 2020-2021 NH influenza season.

QHD00008 was a Phase I/II, randomized, modified double-blind, multi-center study of the safety and immunogenicity of QIV-HD administered by either subcutaneous (SC) route or IM route, and a local QIV-SD by SC route. QHD00008 enrolled 175 Japanese adults, 65 years of age and older, and generated safety and immunogenicity (as assessed by HAI geometric mean titers [GMTs] and seroconversion rates at 28 days post-vaccination) of QIV-HD when administered SC or IM compared with the local QIV-SD ([redacted]). The results of this study were used for the assumptions in the sample size calculation for QHD00010.

1.3 POTENTIAL BENEFITS AND RISKS

1.3.1 Potential Benefits to Subjects

All subjects participating in Study QHD00010-EFC15150 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 2020-2021 influenza season.

Subjects who will receive QIV-HD will be vaccinated against the influenza strains A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1), A/Hong Kong/2671/2019 IVR-208 (H3N2), B/Washington/02/2019 wt virus (B/Victoria lineage), and B/Phuket/3073/2013 wt virus (B/Yamagata lineage) chosen and recommended by World Health Organization (WHO) / the United States Vaccines and Related Biological Products Advisory Committee (VRBPAC). 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 Ministry of Health, Labour and Welfare (MHLW) for the composition of QIVs for the 2020-2021 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 TIV-HD (Fluzone High Dose)

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

Events reported spontaneously during post-approval use of TIV-HD and may occur in subjects receiving QIV-HD are:

- Blood and Lymphatic System Disorders: thrombocytopenia, lymphadenopathy
- Immune System Disorders: anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)
- 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), paresthesia
- Vascular Disorders: vasculitis, vasodilation
- Respiratory, Thoracic and Mediastinal Disorders: dyspnea, wheezing, throat tightness, oropharyngeal pain, rhinorrhea
- Skin and Subcutaneous Tissue Disorders: Steven-Johnson syndrome
- General Disorders and Administration Site Conditions: asthenia, chest pain
- Gastrointestinal Disorders: vomiting

1.4 RATIONALE FOR THE STUDY

QHD00010 will be a Phase III, randomized, modified double-blind, active-controlled, multicenter study of the immunogenicity and safety of QIV-HD administered by IM route in comparison to

the local QIV-SD in Japan ([redacted]) administered by SC route as influenza vaccines in Japan. Based on the QHD00008 results which showed that QIV-HD administered IM was more immunogenic than QIV-HD administered SC and showed a similar safety profile as the licensed Japanese QIV-SD comparator, QIV-HD will be given by IM route in the QHD00010. QHD00010 is planned to be conducted during the 2020-2021 NH influenza season in approximately 2100 adults 60 years of age and older to generate additional immunogenicity and safety data. The primary objective of QHD00010 will be to evaluate the superiority of the immune response generated by the QIV-HD compared to the local QIV-SD (as assessed by HAI GMTs and seroconversion rates at 28 days post-vaccination). The secondary objectives in QHD00010 will be to describe the immunogenicity and safety of QIV-HD.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE(S)

- To demonstrate that QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to responses induced by QIV-SD for the 4 virus strains at 28 days post-vaccination in all subjects.

The endpoint(s) for the primary objective(s) are presented in Section 9.1.1.

2.2 SECONDARY OBJECTIVE(S)

Immunogenicity

- To describe the immune response induced by QIV-HD and QIV-SD by HAI measurement method in all subjects.

Safety

- To describe the safety profile of all subjects in each study group

The endpoint(s) for the secondary objective(s) are presented in Section 9.2.

3 INVESTIGATORS AND STUDY ORGANIZATION

This study will be conducted in approximately 10 to 15 centers in Japan.

Details of the study centers and the Investigators at each center are provided in the list of Investigators and centers involved in the study.

An internal Safety Management Team (SMT) will assess safety data after vaccination.

Sanofi Pasteur's laboratory (Global Clinical Immunology [GCI], Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility will be used for the assessment of immunogenicity endpoints.

The Sponsor's Study Medical Manager (the SMM, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted] Local Medical Operation, Sanofi K. K.

4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the Sponsor must submit this clinical study protocol to the Health Authorities (Competent Regulatory Authority) and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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 IRB/IEC 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 IRB/IEC 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 IRB/IEC 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 IRB/IEC should be informed as soon as possible. They 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 IRB/IEC and to Health Authorities (Competent Regulatory Authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the study's outcome 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

QHD00010-EFC15150 will be a Phase III, randomized, modified double-blind, active controlled, multi-center study to be conducted in approximately 2100 healthy adults 60 years of age and older to assess the immunogenicity and safety of QIV-HD administered by IM route in comparison to the local QIV-SD administered by SC route as a control arm.

Interactive response technology (IRT) will be used to randomly assign subjects to either of the 2 study groups and to assign subject numbers in each of the groups.

A total of approximately 2100 subjects are planned to be enrolled and randomized in a 1:1 ratio as follows:

- Group 1 (QIV-HD by IM route): n = 1050
- Group 2 (QIV-SD by SC route): n = 1050

An unblinded administrator at each site will administer the vaccine.

All subjects will provide a pre-vaccination (baseline) blood sample at Visit (V) 01 (Day [D] 0) and a post-vaccination blood sample at V02 (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 V02. Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected throughout the study (D0 through V02).

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

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

5.1.2 Justification of the Study Design

The objectives of QHD00010-EFC15150 will be to assess the immunogenicity (as assessed by HAI GMTs and seroconversion rates at 28 days post-vaccination) and safety of QIV-HD administered by IM route compared with the local QIV-SD administered by SC route.

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

Given the different volumes and administration routes of the QIV-HD and the local QIV-SD vaccines, QHD00010-EFC15150 will be a modified double-blind study in which only designated study staff 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.

The risk / benefit ratio is appropriate for the conduct of a Phase III clinical study with QIV-HD without an early safety data review for the following reasons:

- There were no safety issues identified from the Phase I/II study (QHD00008-DFI15130) which enrolled 175 Japanese adults 65 years of age and older, and evaluated the QIV-HD formulation administered by SC route or IM route compared with the local QIV-SD administered by SC route.
- There were no safety issues identified from the Phase III (QHD00013) US study which enrolled 2670 adults, 65 years and older, and evaluated the QIV-HD formulation administered by IM route compared with the licensed TIV-HD also administered by IM route. This study successfully supported the licensure of QIV-HD in the US in November 2019. In April 2020, QIV-HD also received a positive opinion from the European Union health authority with marketing authorizations granted by Norway, France, and Latvia as of 21 April 2020.
- The QIV-HD vaccine assessed in QHD00010-EFC15150 is manufactured using the same drug substance manufacturing process as the currently licensed TIV-HD manufacturing process.
- There is a large vaccine safety database generated following significant post-marketing use of TIV-HD (more than 137 million doses distributed since 2009).

5.1.3 Study Plan

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

Vaccination

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

Blood Sampling

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

Collection of Safety Data

Subjects will be asked to notify the site immediately about any potential SAEs including 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 V02), SAEs including AESIs (D0 to V02) in a diary card.

Study staff will contact subjects by phone at D8 post-vaccination to identify whether the subject experienced any SAEs not yet reported and will remind the subjects to bring the completed diary card with them to V02.

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

5.1.4 Visit Procedures

Visit 1 (Day 0): 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., age and sex).
4. Collect significant medical history and record any planned hospitalization during the study in the source documents.
5. Obtain and collect information about history of influenza infection and history of seasonal influenza vaccination and any possible reactions to this vaccination in the previous year.
6. Obtain and collect information about history of pneumococcal vaccination and shingles vaccination.
7. Collect reportable concomitant medications (see Section 6.7).
8. Perform a targeted physical examination based on medical history and record oral temperature[1] in the medical chart.
9. Measure the height and the body weight of the subject.
10. Contact the IRT to assign to the subject a subject number and allocate a dose number (see Section 6.5).

[1] Tympanic and temporal artery thermometers should not be used.

11. 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 attempts to collect blood are unsuccessful (3 attempts), then the subject is still to be included in the study and vaccinated.

12. 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 an unblinded study staff (a designated administrator such as an Investigator/Sub-investigator, a nurse, or a designated pharmacist) and administered by the unblinded administrator (a designated study staff such as an Investigator/Sub-investigator or nurse) without the presence of any other study staff who may be an assessor for safety in subsequent visits. The subjects are also blinded with an eye mask or other appropriate methods 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.

13. Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any AE in the CRB.
14. 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.
15. Provide the subject with a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement[2], and instructions on how to use them.
16. Remind the subject to bring the diary card on V02.
17. Instruct on the need to promptly report any SAE and AESI that may occur at any time during the study.
18. Complete the relevant (electronic) case report forms (CRFs) for this visit.

Day 8 Telephone Call (8 days [+ 2 days] after Visit 1)

Note: If Day 8 Telephone Call falls on a weekend or a holiday, the telephone call may be made on the following business day.

[2] Tympanic and temporal artery thermometers should not be used.

1. Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10.1 for reporting it.
2. Remind the subject to do the following:
   - Complete the D0–D7 pages of the diary card.
   - Complete the remaining pages of the diary card, and bring them to V02.
   - Notify the site in case of an SAE and/or an AESI.

Visit 2 (28 days [+7 days] after Visit 1): Collection of Safety Information and Blood Sample

1. Collect and review the diary card since V01, 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 V01) assesses the safety events.
2. Draw approximately 10 mL blood sample.

   Note: If the attempts to collect blood 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/Vaccination Discontinuation:

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

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

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[3] to LVLS[4]: 21 October 2020 to 19 January 2021

Planned inclusion period - FVFS to FVLS[5]: 21 October 2020 to 15 December 2020

Planned end of study: 19 January 2021

Planned date of final clinical study report: 29 January 2022

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 IRB/IEC for approval.

5.2.2 Informed Consent Procedures

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the subject of all pertinent aspects of the clinical study including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). 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.

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 (IRB/IEC) for approval/favorable opinion.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented. In case of study suspension due to safety concerns, study subjects will be informed of this study suspension and the reason for it. Once it is confirmed that it is safe for the study to continue, study subjects will be asked to confirm their agreement to continue the study.

[3] FVFS: first visit, first subject
[4] LVLS: last visit, last subject
[5] FVLS: first visit, last subject

5.2.3 Screening Criteria

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

5.2.4 Inclusion Criteria

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

I 01. Aged ≥60 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 V02

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[6]

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

[6] The components of QIV-HD are listed in Section 3.2 of IB. The components of comparator product are listed in the composition section of package insert.

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[7]

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

E 16. Any condition that in the opinion of the Investigator could interfere with the evaluation of the vaccine (e.g., under investigation or monitoring for possible coronavirus disease 2019 [COVID-19])

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRB. The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

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

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

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. Its purpose is to assist in the later interpretation of safety data collected during the study.

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable since only one dose of vaccine will be administered in this 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 request of the subject (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for V02, 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 source documents.

5.2.10 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.2.2.1.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the investigator and returned unsigned, and the subject or his/her family did not give any other news and did not come to any following visit.
Protocol Deviation	To be used when 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 or a protocol deviation.

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

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 how to address any 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 (refer to Section 10).

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

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

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

5.4.1 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;
- Non-compliance of the Investigator or Sub-investigator, delegated site staff with any provision of the clinical study protocol, and breach of the applicable laws and regulations or breach of the International Council for Harmonisation (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.

5.4.2 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 IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

6 PRODUCTS ADMINISTERED

6.1 IDENTITY OF THE INVESTIGATIONAL PRODUCT(S)

6.1.1 Identity of Study Product(s)

The investigational QIV-HD is a split virion QIV (60 µg HA/strain) containing virus strains determined based on WHO / US VRBPAC recommendations for the 2020-2021 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 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 to be determined based on WHO / US VRBPAC recommendations for the 2020-2021 NH influenza season.

Active substances:

- A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1) strain 60 µg HA
- A/Hong Kong/2671/2019 IVR-208 (H3N2) strain 60 µg HA
- B/Washington/02/2019 wt virus strain 60 µg HA
- B/Phuket/3073/2013 wt virus strain 60 µg HA

Excipients:

- Buffered saline solution quantity sufficient (qs) 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 an unblinded administrator (a designated study staff such as an Investigator/Sub-investigator, or a nurse), or the designated pharmacist and administered intramuscularly into the upper arm (deltoid area) by the unblinded administrator

without the presence of any other study staffs who may be an assessor for safety in subsequent visits.

The subjects are blinded with eye mask or other appropriate methods 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, vasovagal, or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

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

6.1.2 Identity of Control Product(s)

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

QIV-SD is a split virion QIV (15 µg HA/strain) containing virus strains determined by Ministry of Health, Labour and Welfare (MHLW) for the 2020-2021 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 by MHLW for the 2020-2021 NH influenza season.

Active substances:

- A/(H1N1)-like strain 15 µg HA
- A/(H3N2)-like strain 15 µg HA

- B/(Victoria lineage)-like strain 15 µg HA
- B/(Yamagata lineage)-like strain 15 µg HA

Excipients:

- Buffered saline solution qs 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

The IP 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 IP 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 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 the Sponsor to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a site staff 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 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(s) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRB.

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

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the 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 the 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 designated study staff (e.g., an Investigator/Sub-investigator or a nurse), will administer the vaccine. The unblinded administrator needs to keep himself/herself blinded until the key code is released from the sponsor, even after the database lock for the CRB.
- The subjects will be blinded with an eye mask or other appropriate methods during administration.
- The laboratory personnel who analyze the blood sample will not know which vaccine was administered.

The Investigator/Sub-investigator in charge of the 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 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 (GPV) representative.

The IEC/IRB must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site's study records and in the Sponsor's 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.

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and sign the ICF will be randomly assigned to either of the 2 study groups (QIV-HD by IM route or QIV-SD by SC route) in a 1:1 ratio by block randomization, stratified according to age (i.e., 60 to 64, 65 to 74, and 75 years of age and older), and site.

Study 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 qualified study personnel

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

6.7 CONCOMITANT MEDICATION AND OTHER THERAPIES

At the time of enrollment, ongoing medications and 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 ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of vaccination 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 Ab 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 and immune globulins, 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 (1, 2, 3, or 4)
- Start and stop dates

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

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the prelisted categories.

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 Ab responses will be collected at V01 (D0, pre-vaccination) and at V02 (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 V01 and V02, 10 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the site staff performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label, and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 SAMPLE PREPARATION

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the 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 one hour and a maximum of 24 hours in order to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

After centrifugation, 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, 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.

Sample collection by a logistics vendor 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 logistic vendor. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to GCI at Sanofi Pasteur. The address is provided in the sample handling procedures.

7.4 FUTURE USE OF STORED BIOLOGICAL SAMPLES FOR RESEARCH

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

The Sponsor will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, 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, site 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 PRIMARY ENDPOINTS AND ASSESSMENT METHODS

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoint(s) for the evaluation of immunogenicity are:

- HAI Ab titers obtained on D28
- 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)

9.1.1.2 Immunogenicity Assessment Methods

Anti-Influenza Virus Ab Titration by Inhibition of Hemagglutination

Assays will be performed by the Sanofi Pasteur's 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 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 GMT between the 2 values is calculated at the time of statistical analysis. The lower limit of quantification (LLOQ) is set at the lowest dilution used in the assay, 1:10. Titers below this level are reported as <10 (1/dil). If the highest / last serum dilution used in the assay exhibits complete inhibition of hemagglutination, the serum Ab titer will be reported as ≥10240 (1/dil).

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 VRBPAC recommendations) and a local QIV-SD (based on NIID recommendation). The Sponsor 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" strains), 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.

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 SECONDARY ENDPOINTS AND ASSESSMENT METHODS

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

- HAI Ab titers obtained on D0 and D28
- Individual HAI titers ratio 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)
- Percentage of subjects with titers ≥40 (1/dil) at D0 and D28

9.2.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 9.1.1.2.

9.2.2 Safety

9.2.2.1 Safety Definitions

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

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with

this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (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[8]
- Requires inpatient hospitalization or prolongation of existing hospitalization[9]
- Results in persistent or significant disability / incapacity[10]
- Is a congenital anomaly / birth defect

[8] 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.
[9] 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.
[10] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

- Is an important medical event (IME)

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

Adverse Reaction (AR):

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

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

The following additional definitions are used by the Sponsor:

Immediate Event/Reaction:

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

Solicited Reaction:

A solicited reaction is an “expected” AR (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB.

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

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

The assessment of these reactions by the investigator is mandatory.

Unsolicited AE / AR:

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

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

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

9.2.2.2 Safety Endpoints

The secondary endpoint(s) for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, 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 event led to early termination from the study, of SAEs throughout the study.
- Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the study.

9.2.2.3 Safety Assessment Methods

At V01, the Investigator or a delegate will perform a targeted physical examination based on medical history.

At V02, 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.

9.2.2.3.1 Immediate Post-vaccination Observation Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the CRB, as follows:

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

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

After vaccination, subjects will be provided with a 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 through 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

Subjects will be contacted by telephone 8 days (+2 days) after vaccination to remind them to record all safety information in the diary card.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, site staff will continue

calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 1and Table 2 present, respectively, the injection site reactions and 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
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Intensity scale[a]	CRB: Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Diary card/eDC: Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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 and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

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

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

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

9.2.2.3.3 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 days (+ 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 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). 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[11]
- 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

[11] 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.

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 IP (for unsolicited systemic AEs)

The Investigator will assess the causal relationship between the AE and the IP as either "Not related" or "Related", as described in Section 9.2.2.3.5.

- Action taken for each AE (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, elapsed time, and relationship to study procedures)

- Whether the AE caused study discontinuation

9.2.2.3.4 Adverse Events of Special Interest

AESIs will be captured as SAEs (collected throughout the study). These include new onset of (31):

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

9.2.2.3.5 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[12]:

[12] ICH Guidelines, Clinical Safety Data Management E2A

Not related – The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable).

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

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

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.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 OBSERVATIONAL ENDPOINTS AND ASSESSMENT METHODS

There are no observational objectives in this 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 IPs. It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, physical autopsy report if performed) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 REPORTING BY THE INVESTIGATOR

In the case of a 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 the notification to the Sponsor after approval by the Investigator within the CRB or after a standard delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical study protocol. 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 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 medication, subject status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.
- A back-up plan is used (using paper flow) when the CRB system does not work.

Back-up plan

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) in the CRB to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical study protocol.
- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. 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 source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further documentation should be sent to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the subject and considered by the Investigator to be caused by the IP with a reasonable possibility, should be reported to the monitoring team.

10.2 GUIDELINES FOR REPORTING ADVERSE EVENTS OF SPECIAL INTEREST

For AESI, the Sponsor is to be informed immediately (i.e., within 24 hours), as per SAE notification guidelines described in Section 10.1, even if a seriousness criterion is not met, using the corresponding pages of the CRF (to be sent) or screens in the CRB.

10.3 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 Safety Complementary Information CRFs. An e-mail alert will be sent automatically to Sponsor. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by Sponsor.

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

10.4 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 IP(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.

10.5 ASSESSMENT OF CAUSALITY

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.2.2.3.5.

Following this, the Global Safety Officer 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).

10.6 REPORTING SAES TO HEALTH AUTHORITIES AND INDEPENDENT ETHICS COMMITTEES/INSTITUTIONAL REVIEW BOARDS

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

The Sponsor 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 study protocol.

11 DATA COLLECTION AND MANAGEMENT

11.1 DATA COLLECTION AND CASE REPORT BOOK COMPLETION

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.2.2.3. 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 CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

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

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

11.2 DATA MANAGEMENT

Management of SAE Data

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms

and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer of Sanofi Pasteur, and SMM of Sanofi Pasteur and Sanofi.K.K. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

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

Management of Clinical and Laboratory Data

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

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the 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 to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

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

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

11.3 DATA REVIEW

A blind review of the data is anticipated through the data review process led by CDM.

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.

Statistical analysis for immunogenicity will be performed using the results from strains to be determined based on WHO / US VRBPAC recommendations contained in the QIV-HD and the strains to be determined by MHLW contained in the QIV-SD.

12.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

12.1.1.1 Hypotheses

Immunogenicity

A superiority approach will be used to compare post-vaccination GMTs and seroconversion rates between QIV-HD and QIV-SD groups for each strain using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses. The definitions of superiority correspond to statistical superiority where 1.0 is used as the threshold for the ratio of GMTs and 0 is used as the threshold for difference of seroconversion rates. Superiority as defined in the primary objective is based on following individual hypothesis:

$$H_0^s: \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} \leq 1 \Leftrightarrow \log_{10}(GMT_{QIV-HD}^s) - \log_{10}(GMT_{QIV-SD}^s) \leq \log_{10}(1) = 0$$
$$H_A^s: \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} > 1 \Leftrightarrow \log_{10}(GMT_{QIV-HD}^s) - \log_{10}(GMT_{QIV-SD}^s) > \log_{10}(1) = 0$$

$$H_0^s: \pi_{QIV-HD}^s - \pi_{QIV-SD}^s \leq 0$$
$$H_A^s: \pi_{QIV-HD}^s - \pi_{QIV-SD}^s > 0$$

where

- s: strain
- π: the seroconversion rate

If the superiority is demonstrated for both post-vaccination GMTs and seroconversion rates in the 4 strains, then the immunogenicity of QIV-HD will be considered as superior to QIV-SD.

12.1.1.2 Statistical Methods

Immunogenicity

Assuming that log10 transformation of the data follows a normal distribution, the log10 (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMTs.

The statistical methodology will be based on the use of the 2-sided 95% CIs of the ratio of post-vaccination GMTs and difference in seroconversion rates between the QIV-HD group and QIV-SD group. The 95% CIs will be calculated by normal approximation of log-transformed titers for GMTs and by the Wilson score method without continuity correction, quoted by Newcombe, for seroconversion rates (32). The margins used for superiority hypotheses testing are 1.0 for GMTs and 0% for seroconversion rates.

The superiority objective will be achieved if the superiority is demonstrated for all of the 4 strains for both GMTs and seroconversion rates. For the objective, it is planned to use the HAI assay results using the strains contained in the QIV-SD determined by the MHLW for all subjects. The per-protocol analysis set (PPAS) and full analysis set (FAS) will be used for the immunogenicity analyses. Conclusion will be made based on the FAS results.

Sensitivity analyses will be also performed according to the following analyses for the ratios of post-vaccination GMTs and the differences in the seroconversion rates in the FAS and PPAS:

- Analysis of covariance (ANCOVA) with treatment group and age group (60 to 64, 65 to 74, and 75 years of age and older) of the stratification factor as fixed effects, and pre-vaccination value (V01) as a covariate for ratio of GMTs.
- Cochran-Mantel-Haentzel method stratified on age group (60 to 64, 65 to 74, and 75 years of age and older) of the stratification factor for difference in seroconversion rates.

12.1.2 Hypotheses and Statistical Methods for Secondary Objective(s)

12.1.2.1 Hypotheses

Safety

No hypotheses are to be tested.

Immunogenicity

No hypotheses are to be tested.

12.1.2.2 Statistical Methods

Safety

Safety results will be analyzed descriptively for subjects in the safety analysis set (SafAS) who received QIV-HD or QIV-SD. Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and AESIs will be summarized. The main parameters will be described with 95% CIs (Clopper-Pearson method) (33).

- Unsolicited systemic AEs occurring within 30 minutes of injection (immediate unsolicited AEs)
- Solicited injection site reactions (pain, erythema, swelling, induration, and brusing) 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), action taken, and whether the reaction led to early termination from the study. 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), action taken, and whether the reaction led to early termination from the study. 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, or Grade 3), relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study.
- All SAEs that occur throughout the study by SOC and PT, time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study.
- All AESIs reported throughout the study by SOC and PT and relationship to vaccination.

Immunogenicity

The GMTs in terms of Ab titers obtained at the pre-vaccination (V01) and post-vaccination (V02) and seroconversions will be summarized with their 95% CIs using the same methods for the primary objectives. The percentages of subjects with titers ≥40 (1/dil) and the corresponding 95% CIs (Clopper-Pearson method) will be performed for pre-vaccination (V01) and post-vaccination immunogenicity (V02). The geometric mean of individual titer ratios (GMTRs) will be calculated for post vaccination immunogenicity (V02) over the baseline immunogenicity (V01) with the corresponding 95% CIs (assuming normal approximation of log-transformed values). Reverse cumulative distribution curves against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (V02). Additional parameters may be displayed as appropriate.

In addition, the immunogenicity analyses in terms of GMTs, seroconversion rates, and percentages of subjects with titers ≥40 (1/dil) will be performed by age (i.e., 60 to 64, 65 to 74, and 75 years of age and older; 60 to 64, 65 years of age and older), sex, previous influenza

vaccination status, and baseline seropositivity status. Details of the above analyses will be described in the SAP.

12.1.3 Statistical Methods for Observational Objective(s)

12.2 ANALYSIS SETS

Three analysis sets will be used: the FAS, the PPAS, and the SafAS.

12.2.1 Full Analysis Set

The 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 SafAS is defined as those subjects who have received the study vaccine[13]. All subjects will have their safety analyzed according to the vaccine they actually received.

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

12.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample at V02 in the proper time window (i.e., 28 to 35 days after vaccination) or a post-dose serology sample (V02) was not drawn
- Subject received a protocol- prohibited therapy / medication / vaccine (restricted therapies / medications / vaccine are 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 V02 did not produce a valid test result for all strains (i.e., results for all antigens are missing). In any case, the PPAS definition will be finalized before the database lock.

[13] For which safety data are scheduled to be collected.

12.2.4 Other Analysis Set(s)

Not applicable.

12.2.5 Populations Used in Analyses

All subjects with data in the CRB will be taken into account in the description of the population (e.g., the disposition, the demographics, or baseline characteristics). The safety analyses will be performed on the SafAS. The immunogenicity analyses will be performed on the FAS and PPAS, and the conclusion will be made based on the results of the FAS.

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 <upper limit of quantification (ULOQ), then the titer itself will be used.
- If a titer is ≥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, QIV-HD, and QIV-SD studies in this population, the amount of missing immunogenicity data is expected to be ≤5% in this study. Usually in vaccine studies, it seems generally reasonable to assume missing immunogenicity data are missing completely at random (MCAR) (34). 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 one statistical analysis conducted after the end of the study (D28).

12.5 DETERMINATION OF SAMPLE SIZE AND POWER CALCULATION

A total of approximately 2100 adults 60 years of age and older will be enrolled. A sample size of 2100 is determined based on an overall power of 90% controlled with one-sided 0.025 type I error for demonstrating superiority in the primary objective for all 4 strains for both the HAI GMTs and seroconversion rates comparing QIV-HD versus QIV-SD groups. The margins for the superiority are defined as 1.0 for GMTs and 0 for seroconversion rates. All the statistical assumptions used in the sample size calculation are presented in Table 3.

Table 3 – Statistical Assumptions for the Sample Size Calculation

Statistical Criteria	Assumption
Allocation ratio	1:1 between the QIV-HD and QIV-SD
Overall power	>90%
Type I error	One-sided 0.025 on each strain for each endpoint
Expected GMT ratio	1.6 for all strains
Standard deviation for the log titers (in log10 scale)	0.7 for all strains
Expected seroconversion rates	40% for 2 strains with an increase of 17% in the QIV-HD group and 50% for another 2 strains with an increase of 8% in the QIV-HD group
Attrition rate	5% in FAS

13 ETHICAL AND LEGAL ISSUES AND INVESTIGATOR/SPONSOR RESPONSIBILITIES

13.1 ETHICAL CONDUCT OF THE STUDY / GOOD CLINICAL PRACTICE

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

13.2 SOURCE DATA AND SOURCE DOCUMENTS

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, 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[14] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

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

13.3 CONFIDENTIALITY OF DATA, DATA PROTECTION, AND ACCESS TO SUBJECT RECORDS

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with the Sponsor. Sponsor personnel (or designates), the IECs / IRBs, and regulatory agencies, including Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA), 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.

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

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the General Data Protection Regulation. Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

The race of each subject will be collected in this study because these data are required for submissions for licensure in countries which require an analysis of results by race.

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

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

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

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

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 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 Sponsor's monitoring staff on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB, 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 deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

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

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

13.4.2 Audits and Inspections

For the purpose of ensuring compliance with the clinical study protocol, GCP 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 is 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, he/she 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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after the end of the clinical study unless local regulations or institutional policies require a longer retention period.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical Study completion or discontinuation. No records may be destroyed during the retention period without the written approval of the Sponsor.

No records may be transferred to another location or party without written notification to the Sponsor.

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 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 CRF, discrepancy resolution form , or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to the 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 CRFs. 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 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 CRFs, the IB, 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 IRB/IEC is expressly permitted, the IRB/IEC 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.

13.6 PROPERTY RIGHTS

All information, documents and IP 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 site 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.

13.7 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 IEC/IRB or regulatory authorities in countries requiring this document.

13.8 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 is 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 Sponsor's and Sanofi Pasteur's reviews can be expedited to meet publication guidelines.

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Signature Page

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