NCT04537234

Immunogenicity and Safety of a High-Dose Quadrivalent Influenza Vaccine in Subjects 65 Years of Age and Older in Taiwan

Phase III, randomized, modified double-blind, active-controlled, multi-center study describing the immunogenicity and safety of high-dose quadrivalent influenza vaccine (QIV-HD) and standard-dose quadrivalent influenza vaccine (QIV-SD) administered by the intramuscular route in subjects 65 years of age and older in Taiwan

Clinical Study Protocol

Health Authority File Number(s):	Not applicable
WHO Universal Trial Number (UTN):	U1111-1238-1970
Study Code:	QHD00023
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur SA 14 Espace Henry Vallée, 69007 Lyon, France
Investigational Product:	Quadrivalent Influenza Vaccine (split virion, inactivated) High-Dose (QIV HD)
Form / Route:	Suspension for injection in pre-filled syringe / Intramuscular
Indication For This Study:	Active immunization in adults 65 years of age and older for the prevention of influenza disease
Manufacturer:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Principal Investigators	This is a multi-center study with multiple investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Sponsor's Responsible Medical Officer:	[redacted]
Local Medical Officer	[redacted]

Project Manager and Study Leader	[redacted]
Global Safety Officer:	[redacted]
Clinical Trial Manager:	[redacted]
Version and Date of the Protocol:	Version 1.0 dated 14 October 2019

History of Protocol Versions

Not applicable as this is the first version of the protocol.

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	High-Dose Quadrivalent Influenza Vaccine, (Zonal Purified, Split Virus) 2020-2021 Strains (QIV-HD)
Active Substance(s):	A/(H1N1), A/(H3N2), B (Victoria Lineage), B (Yamagata Lineage)

Title of the Study:	Immunogenicity and Safety of a High-Dose Quadrivalent Influenza Vaccine in Subjects 65 Years of Age and Older in Taiwan
Development Phase:	Phase III
Study Sites:	This will be a multi-center study conducted at approximately 2-3 sites in Taiwan. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Q3 2020 to Q4 2020
Study Design, Schedule of Study Procedures, and Methodology:	QHD00023 will be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in approximately 200 healthy adults 65 years of age and older to evaluate the immunogenicity and safety of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) route. A local standard-dose quadrivalent influenza vaccine (AdimFlu-S (QIS) also referred to as QIV-SD in this protocol) administered by IM route will serve as a control arm. Interactive response technology (IRT) will be used to randomly assign subjects to one of the 2 study groups and to assign subject numbers for all subjects. <u>Vaccination</u> All eligible subjects will be randomized to receive a single injection of either QIV-HD (IM route) or AdimFlu-S (QIS) (IM route) at Day (D) 0. An unblinded administrator at each site will administer the vaccine. <u>Blood sampling</u> All subjects will provide a pre-vaccination (baseline) blood sample at Visit (V) 01 (D0) and a post-vaccination blood sample at V02 (D28 [+7 days]) for hemagglutination inhibition (HAI) testing. <u>Collection of safety data</u> 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). Solicited reactions will be collected up to 7 days after vaccination, and AEs will be collected up to D28. Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs*) will be collected throughout the study (D0 through approximately D28). Subjects will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study. Staff will review the D0 to D28 safety data with subjects at V02.

	Electronic data capture (EDC) will be used for the collection of data. *Note: AESIs will be considered as SAEs. These include of Guillain-Barré syndrome (GBS), 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 IECs/IRBs (Independent Ethics Committees/Institutional Review Boards), or the governing regulatory authorities in Taiwan 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) (CROs) 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.
Objective(s):	***Immunogenicity*** • To describe the immune response induced by QIV-HD and AdimFlu-S (QIS) by HAI measurement method in all subjects. ***Safety*** • To describe the safety profile of all subjects in each study group
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*** • Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Occurrence of solicited, ie, pre-listed in the subject's diary and electronic case report form (eCRF), injection site and systemic reactions occurring up to 7 days after vaccination • Occurrence of unsolicited (spontaneously reported) AEs up to 28 days after vaccination • Occurrence of SAEs, including AESIs, throughout the study period Other endpoints recorded or derived as described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), time of onset, duration, number of days of occurrence, intensity, relationship to vaccine, whether the AE led to early termination from the study, seriousness, or outcome.

Planned Sample Size:	A total of approximately 200 subjects are planned to be enrolled and randomized in a 1:1 ratio as follows: • QIV-HD Group: n = 100 • QIV-SD Group: n = 100
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) / US, Food and Drug Administration, Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2020-2021 Northern Hemisphere (NH) influenza season.* **Active Substances:** • A/(H1N1) 60 microgram (µg) HA • A/(H3N2) 60 µg HA • B/(Victoria Lineage) 60 µg HA • B/(Yamagata Lineage) 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:	Local standard-dose quadrivalent influenza vaccine (split virion), 2020-2021 Strains, provided in a pre-filled single-dose syringe (AdimFlu-S (QIS)), manufactured by AdImmune Corporation)
Form:	Suspension
Composition:	Each 0.5 mL dose of AdimFlu-S (QIS) will contain: *Strains to be determined based on World Health Organization (WHO) recommendations for the 2020-2021 NH influenza season.* **Active Substances:** • A/(H1N1) 15 µg HA • A/(H3N2) 15 µg HA • B/(Yamagata Lineage) 15 µg HA • B (Victoria lineage) 15 µg HA **Excipients:** • Sodium chloride • Disodium hydrogen phosphate • Potassium dihydrogen phosphate

Route:	IM, injected into the upper arm (deltoid area)
Batch Number:	TBD
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Aged ≥ 65 years on the day of inclusion 2) Informed consent form has been signed and dated 3) Able to attend all scheduled visits and to comply with all study procedures
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) 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 2) Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine prior to Visit 2 3) Previous vaccination against influenza (in the preceding 6 months) with either the study vaccine or another vaccine 4) Receipt of immune globulins, blood or blood-derived products in the past 3 months 5) 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) 6) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the study or to a vaccine containing any of the same substances 7) Thrombocytopenia, bleeding disorder, or receipt of anticoagulants that based on Investigator's judgment contraindicate intramuscular vaccination 8) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 9) Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion 10) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion 11) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided 12) Personal or family history of Guillain-Barré syndrome (GBS) 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)

<table>
<tr><td></td><td>14) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse) of the Investigator or employee with direct involvement in the proposed study</td></tr>
<tr><td>Statistical Methods:</td><td>No hypotheses for immunogenicity and safety are planned. All analyses are descriptive.
<u>Immunogenicity – Descriptive Analyses</u>
Immunogenicity results will be evaluated by vaccine group. The main parameters will be evaluated with 95% confidence intervals (CIs).
The per protocol analysis set (PPAS) will be used for the main immunogenicity analyses.
<u>Safety – Descriptive Analyses</u>
Safety results will be analyzed descriptively by vaccine groups. 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.
The safety analysis set (SafAS) will be used for all safety analyses.
Calculation of the 95% CIs will be done using:
• the normal approximate method for GM of titers and GM of titer ratios
• the exact binomial distribution for percentages (Clopper Pearson method)

Calculation of Sample Size
The sample size is not based on any hypothesis testing. The number of subjects is designed to provide supportive immunogenicity and safety data on the study vaccine when administered in adults 65 years of age and older in Taiwan. The sample size of 200 subjects was arbitrarily chosen to comply with local requirements.
There was no power assessment as the analyses will be descriptive.
With a sample size of 90 subjects evaluable (taking into account an estimated 10% drop-out), the immunogenicity assessment in terms of percentages of subjects will have 95% CI widths of less than 22% in QIV-HD group (as shown in the table below).
Table: 95% Confidence intervals for proportions (Exact method)
<table>
<tr><th>n/N</th><th>% subjects observed</th><th>95% CI</th></tr>
<tr><td>45/90</td><td>50.0%</td><td>(39.3; 60.7)</td></tr>
<tr><td>50/90</td><td>55.6%</td><td>(44.7; 66.0)</td></tr>
<tr><td>60/90</td><td>66.7%</td><td>(55.9; 76.3)</td></tr>
<tr><td>70/90</td><td>77.8%</td><td>(67.8; 85.9)</td></tr>
<tr><td>80/90</td><td>88.9%</td><td>(8.05; 94.5)</td></tr>
<tr><td>85/90</td><td>94.4%</td><td>(87.5; 98.2)</td></tr>
</table></td></tr>
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Table of Study Procedures

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

Visit/Contact	**Visit 1**	**Visit 2**
Study timelines (days)	D0	D28
Time windows (days)	NA	[+7 days]
Informed consent	X	
Inclusion/exclusion criteria	X	
Collection of demographic data	X	
Medical history	X	
History of seasonal influenza vaccination§	X	
Reportable concomitant medications	X	X
Physical examination*	X	
Contact IRT system for randomization, subject number, and unique dose number allocation	X	
Blood sampling (BL), 10 mL	BL0001†	BL0002
Vaccination	X	
Immediate surveillance (30 minutes)	X	
Diary card provided‡	X	
Recording of solicited injection site & systemic reactions	D0-D7	
Collection of unsolicited adverse events	D0-D28	
Diary card collected and reviewed		X
Study termination record		X
Collection of SAEs (including AESIs)**	To be reported at any time during the study	

Abbreviations: AE, adverse event; AESI, adverse event of special interest; D, Day; SAE, serious adverse event.

§Previous influenza vaccination history should be collected for the previous year

* Clinical or medically-driven physical examination based on medical history will be performed at V01. Clinical or medically driven physical examination may also be performed at V02, as necessary.

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

‡ Subjects will use this diary card to record information about solicited reactions from D0 to D7, as well as unsolicited AEs, SAEs, and AESIs from D0 to D28 after vaccination.

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

List of Abbreviations

µg	Microgram
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling
CDE	Center for Drug Evaluation
CDM	Clinical Data Management
CI	confidence interval
CRA	clinical research associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	case report forms
CRO	contract research organization
D	day
dil	dilution
DP	drug product
DS	drug substance
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good clinical practice
GPV	Global PharmacoVigilance
HA	hemagglutinin
HAI	hemagglutination inhibition
ICF	informed consent form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
IM	Intramuscular
IME	important medical event
IRB	Institutional Review Board
IRT	interactive response technology
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NH	Northern Hemisphere

PMSL	Project Manager Study Leader
PPAS	per-protocol analysis set
PT	preferred term
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
SAS	Statistical analysis system
SMT	Safety management team
SOC	system organ class
TBD	to be determined
TFDA	Taiwan Food and Drug Administration
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
TMF	Trial master file
V	Visit
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 Introduction

1.1 Background

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. Individuals in high-risk groups (eg, adults 65 years of age and older and persons with underlying medical conditions) are at high risk of influenza and its complications.

Vaccination currently represents the most effective medical intervention against influenza. The World Health Organization (WHO) recommends annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (1) (2). However, efficacy of the influenza vaccine is affected by the age, underlying conditions, and immune status of the vaccine recipient, as well as the match of the strains present in the vaccine and circulating in a population.

Influenza outbreaks are a serious public health threat in Taiwan. The Western Pacific region has one of the highest burdens of influenza related deaths, and a mortality rate of 9% has been reported in Taiwan (3) (4). These outbreaks are costly and strain public services. Furthermore, Taiwan has one of the most rapidly aging populations in the world. The population of adults 65 years of age and older in Taiwan in 2017 was estimated at 13.3% of the country's population and is expected to grow to at least 20% over the next decade (5). In 2017, adults 65 years of age and older accounted for 33.1% and 35.4%, for men and women, respectively, of the Taiwan National Health Insurance expenditures and approximately 44% of hospitalization costs. Despite influenza vaccine coverage rates in Taiwanese adults 65 years of age and older ranging from 40.79-49.2% between 2012 and 2017 (6), this population and its burden of influenza disease and complications has a significant impact on Taiwan's health care system (7) (8).

Since adults 65 years of age and older are at significantly increased risk of influenza infection and related complications, Taiwan's national mass vaccination campaign has designated this population as a priority group since 2001 and began to cover all adults over the age of 50 in 2016 (4). With a growing population of adults 65 years of age and older, an influenza vaccine that can better prevent influenza infection and its complications would have a significant public health impact (3).

1.2 Background of the Investigational Product

The immune response to standard dose influenza vaccines (15 µg hemagglutinin [HA] per strain) and protection are suboptimal in adults 65 years of age and older (9). One strategy to improve protection against influenza in this group is to increase the antigen dose (10). QIV-HD contains 60 µg HA of each of 4 virus strains (A/H1N1, A/H3N2, and one B strain from each of the Victoria and the Yamagata lineages) for a total of 240 µg of HA antigen per 0.7 milliliter (mL) dose.

QIV-HD has been developed based on the experience gained with Sanofi Pasteur's high-dose trivalent influenza vaccine (TIV-HD) containing 60 µg HA of each of 3 virus strains manufactured in the US. TIV-HD was licensed by Sanofi Pasteur under the name of Fluzone® High-Dose in the US (2009), Canada (2015), Australia (2017), Brazil (2018), and the United

Kingdom (2019) for use in adults 65 years of age and older. The improved efficacy of TIV-HD vaccine when compared with standard-dose trivalent influenza vaccine (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% 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, the relative efficacy of TIV-HD versus TIV-SD was 35.4% (95% CI, 12.5 to 52.5) in an analysis restricted to influenza cases caused by vaccine-similar strains (11). This efficacy study concluded that the TIV-HD is safe and provides superior protection against laboratory-confirmed influenza illness compared to the TIV-SD among adults 65 years of age and older.

Results of clinical studies conducted in subjects 65 years of age and older have shown that TIV-HD resulted in superior immune responses (12) and improved vaccine efficacy (11) compared to standard-dose trivalent influenza vaccine (TIV-SD) containing 15 µg HA of each of the virus strains. These data were confirmed by real world evidence in more than 23 million people (13) (14) (15) (16) (17) (18) (19) (20) (21) (22). TIV-HD demonstrated an improved benefit in the prevention of hospitalization related to influenza, pneumonia, cardio-respiratory events, and all cause when compared against standard dose influenza vaccines in post-licensure studies (11).

QIV-HD is produced using the same drug substance process as the licensed TIV-HD; for the drug product (DP), the TIV-HD manufacturing process was modified slightly to increase the fill volume (0.7 mL for QIV-HD versus 0.5 mL for TIV-HD) in order to include the 2nd influenza B strain at the same HA content as the other 3 strains (60 µg HA/strain/dose).

The objective of the clinical development of QIV-HD was to demonstrate that QIV-HD is able to induce robust immune responses to 4 influenza strains (A/H1N1, A/H3N2, and 2 B strains (one each from the Yamagata and Victoria lineages) and be a useful replacement for TIV-HD by offering the possibility of protection against both B lineages simultaneously, without compromising vaccine safety.

Thus, a Phase III clinical study (QHD00013) was conducted in the US in adults 65 years of age and older during the 2017-2018 NH influenza season (23). QHD00013 demonstrated the non-inferior immunogenicity of QIV-HD compared to the TIV-HD for all strains. Moreover, each B strain in QIV-HD induced an immune response that was superior to the response induced by the TIV-HD that did not contain the corresponding B strain. QIV-HD was also found to be safe and well tolerated and showed comparable reactogenicity (solicited injection site reactions and solicited systemic reactions) to TIV-HD.

In addition, a Phase II descriptive safety and immunogenicity study (QHD00008) was conducted in adults 65 years of age and older in Japan during the 2017-2018 NH influenza season. QHD00008 described the safety and immunogenicity of QIV-HD in the Japanese population. Vaccination with QIV-HD (either via the intramuscular [IM] or the subcutaneous route) was found to be safe and well tolerated, with no safety concerns identified. The SC route of administration for QIV-HD was evaluated because administering influenza vaccines subcutaneously is the standard practice in Japan. Solicited reactions were more frequently reported in subjects vaccinated with QIV-HD via the SC route than in subjects vaccinated with

QIV-HD via the IM route or with the standard-dose quadrivalent influenza vaccine (QIV-SD) via the SC route. QIV-HD (administered via the IM or SC route) was more immunogenic than QIV-SD for all 4 strains. QIV-HD administered via the IM route was more immunogenic than the QIV-HD administered via the SC route. QHD00008 supports further clinical development in Japan and establishes further safety profile of QIV-HD in the East Asian population.

In conclusion, the QIV-HD has been shown to be as immunogenic as the licensed TIV-HD and with a similar safety profile in adults 65 years and older. In addition, QIV-HD provides coverage against influenza B of both lineages simultaneously compared to the TIV-HD.

As the QIV-HD formulation was proven to be non-inferior to the TIV-HD formulation in Study QHD00013, the efficacy for QIV-HD against lab-confirmed influenza cases as well as the better effectiveness against influenza complications assessed by reduction of hospitalization is likely to be comparable to that of TIV-HD.

As of September 2019, QIV-HD has been submitted for licensure in the US (January 2019), EU (April 2019), Canada (July 2019), and Australia (July 2019).

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects participating in Study QHD00023 will receive influenza vaccination with either the investigational QIV-HD or the control vaccine QIV-SD. All subjects will therefore be vaccinated against the influenza viruses recommended by the WHO for the 2020-2021 NH influenza season. Thus, these older adults may be protected against those strains and be less likely to catch influenza or develop complications from an influenza infection during the respective influenza season.

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

1.3.2 Potential Risks to Subjects

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

QIV-HD is safe and well tolerated in this population. However, as with any vaccine, the QIV-HD vaccine may cause side effects in certain people, and QIV-HD may have more local reactions than with the use of QIV-SD.

Expected Adverse Events

The safety of QIV-HD is based on adverse reactions (ARs) that were recorded following vaccination with QIV-HD during study QHD00013 (1777 adults 65 years of age and older) and ARs reported during clinical development and post-marketing experience with TIV-HD.

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

The following reactions have been also observed:

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

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

Other Potential Adverse Events

In addition to the expected adverse events (AEs), the following additional AEs have been spontaneously reported during the post-marketing use of TIV-HD (24) or during clinical trials conducted on TIV-HD, and may occur in people receiving QIV-HD:

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

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

- *Skin and Subcutaneous Tissue Disorders*: Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions*: asthenia, chest pain

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

Refer to the package inserts of the marketed QIV-SD vaccine (AdimFlu-S (QIS)) for information regarding potential risks.

1.4 Rationale for the Study

Vaccination remains the most effective means of preventing influenza infection and complications associated with the disease (25). However, the effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age, underlying conditions, and immune competence of the vaccine recipient and on the similarity between the virus strains present in the vaccine and the strains circulating in the community. The immune response to standard-dose influenza vaccines (15 µg HA per strain) is sub-optimal in adults 65 years of age and older compared to healthy young adults (26). One strategy to combat the observed decreased immune response to influenza vaccination in adults 65 years of age and older is to increase the antigen dose in the vaccine (27). Therefore, Sanofi Pasteur developed the QIV-HD vaccine containing 60 µg HA of each of 4 virus strains for a total of 240 µg of HA antigen per dose for licensure in adults aged 65 years and older and thus eliminating the issue of having to choose a strain from only one B lineage for the seasonal TIV-HD and the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage.

Results of QHD00023 will allow the registration of QIV-HD by the Taiwan Food and Drug Administration (TFDA) for use in adults 65 years of age and older. The design of this trial was agreed by the Center for Drug Evaluation (CDE) during a formal consultation meeting on 22 August 2019.

2 Study Objectives

Immunogenicity

To describe the immune response induced by QIV-HD and AdimFlu-S (QIS) 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 primary objective(s) are presented in Section 9.

3 Investigators and Study Organization

This study will be conducted in approximately 2-3 centers in Taiwan. Details of the study centers and the Investigators at each center are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal safety management team (SMT) will perform an analysis of safety data at the end of the study. An ad hoc analysis can be done by the SMT at any time during the conduct of the study if necessary.

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

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form (ICF), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

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

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

QHD00023 will be a Phase III, randomized, modified double-blind, active-controlled, multi-center study. The study will be conducted during the 2020-2021 NH influenza season in 200 adults 65 years of age and older in Taiwan. The objective of this study is to describe the immunogenicity and safety of QIV-HD administered by IM route. A locally licensed QIV-SD (AdimFlu-S (QIS)) administered by IM route will serve as a control arm. AdimFlu-S (QIS) was approved for use by the Taiwan Food and Drug Administration (TFDA) in 2017. AdimFlu-S (QIS) is a split vaccine and contains 15 µg HA of each of 4 virus strains (A/H1N1, A/H3N2, and one B strain from each of the Victoria and the Yamagata lineages) for a total of 60 µg of HA antigen per 0.5 mL dose (28). Starting in 2019, Taiwan's mass vaccination campaign will switch from a TIV-SD vaccine to a QIV-SD vaccine (6).

5.1.2 Justification of the Study Design

The primary objective of QHD00023 is to compare the immune response induced by QIV-HD (as assessed by HAI GMTs and seroconversion rates) to a local licensed QIV-SD (AdimFlu-S (QIS)) and to describe the safety of QIV-HD.

Given the acceptable safety data generated from over 1800 subjects vaccinated with the QIV-HD in the US (Phase III QHD00013 study) and Japan (Phase I/II QHD00008 study), and the fact that the safety profile of TIV-HD in humans has been shown to be well tolerated with no safety concerns in 25,564 subjects who received at least one dose of TIV-HD in the clinical development studies and observational studies as well as after 10 years of post-marketing surveillance with more than 115 million doses distributed, neither an early safety data review nor Independent Data Monitoring Committee is planned for this trial.

The QHD00023 study will be a modified double-blind study with an unblinded designated vaccine preparer(s)/administrator(s) used at each study site. The designated vaccine preparer(s)/administrator(s) will be unblinded given that the QIV-HD and QIV-SD vaccines have different dose volumes (0.7 mL for QIV-HD and 0.5 mL for QIV-SD). Neither the subject nor the investigator nor the study staff will know which vaccine will be administered (the syringes will be masked to maintain the blind of the subjects and other members of the clinical site). The unblinded designated vaccine preparer(s)/administrator(s) will not be involved in any of the blinded study assessments (eg, immunogenicity, safety). The Investigators (or delegates) in charge of safety assessment, the trial staff who collect the safety data, and the laboratory personnel who analyze the blood samples will not know which product was administered.

The design of this trial was agreed upon by the CDE during a formal consultation meeting on 22 August 2019.

5.1.3 Study Plan

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

Vaccination

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

Blood Sampling

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

Collection of Safety Data

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

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

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

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

5.1.4 Visit Procedures

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

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

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

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

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

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

5) Obtain & collect information about history of seasonal influenza vaccination for at least the previous year.

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

7) Perform and document a clinical or medically-driven physical examination per standard site-specific immunization practices and record oral temperature[a] in the medical chart.

8) If the subject satisfies all eligibility criteria, contact the IRT to assign to the subject a 12-digit subject number and allocate a treatment number (see Section 6.5).

9) Draw an approximately 10 mL blood sample (This blood sample should be drawn before vaccination). Process the blood sample as specified in the "Management of Samples" section (see Section 7).
   Note: If the subject withdraws consent before blood sampling (before any invasive procedure has been performed), do not vaccinate the subject. The subject should be terminated from the study.
   Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), the subject should be given the opportunity for another attempt, even on another day within the enrollment period. When the subject can be included in the study, the same inclusion number as the one assigned initially will be used, and inclusion and exclusion criteria will be re-checked. If ultimately a blood sample cannot be obtained, the reason will be recorded in the CRF. In this case, the subject will not be vaccinated and will be withdrawn from the study, but the

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

electronic CRF will be created. The subject's number will not be re-allocated to another subject.

10) An unblinded designated administrator should apply a piece of opaque tape over the syringe to obscure the contents prior to administration of the vaccine and administer the appropriate study vaccine by IM injection into the region of the deltoid muscle. The vaccine must be administered on the side opposite to that of blood sampling.
Note: Complete information on vaccine administration can be found in the operating guidelines.

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

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

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

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

15) Instruct the subject on the need to promptly report any SAE that may occur at any time during the study.

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

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

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

2) Perform a clinical or medically-driven physical examination, as necessary, based on medical history.

3) Collect reportable concomitant medications (see Section 6.7)

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

5) Complete the termination record of the CRF for all subjects.

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

Unless a subject refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or

becomes chronic (even after the end of the subject's participation in the study) if *either* of the following is true:

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

5.1.5 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject): September 2020 to November 2020

Planned inclusion period - FVFS to FVLS (first visit, last subject): September 2020 to October 2020

Planned vaccination period: September 2020 to October 2020

Planned end of study (last visit, last subject): November 2020

Planned date of final clinical study report: August 2021

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Subjects may be recruited from the general population. The sites will ensure that any advertisements used to recruit subjects (letters, pamphlets, posters, etc.) are submitted to Sanofi Pasteur prior to submission to the IEC / IRB for approval.

5.2.2 Informed Consent Procedures

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

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

The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

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

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

5.2.3 Screening Criteria

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

5.2.4 Inclusion Criteria

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

1) Aged ≥ 65 years on the day of inclusion
2) Informed consent form has been signed and dated
3) Able to attend all scheduled visits and to comply with all study procedures

5.2.5 Exclusion Criteria

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

1) 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
2) Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine prior to Visit 2
3) Previous vaccination against influenza (in the preceding 6 months) with either the study vaccine or another vaccine
4) Receipt of immune globulins, blood or blood-derived products in the past 3 months
5) 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)
6) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the study or to a vaccine containing any of the same substances
7) Thrombocytopenia, bleeding disorder, or receipt of anticoagulants that based on Investigator's judgment contraindicate intramuscular vaccination
8) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
9) Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion

10) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion

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

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

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)

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

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 case report book (CRB). The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

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

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

5.2.8 Conditions for Withdrawal

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

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

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (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 9.1.2.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the investigator and returned unsigned, and the subject did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is not an SAE or AE. • 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 (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

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

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

If the subject's status at the end of the study is "Withdrawal by Subject", the site will attempt to contact them except if they specified that they do not want to be contacted again and it is documented in the source document.

5.3 Modification of the Study and Protocol

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

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs will either be notified of or will approve administrative amendments depending on local regulations

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

5.4 Interruption of the Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in Taiwan 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 applicable regulatory requirements. The Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.

6 Products Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product (QIV-HD)

The investigational QIV-HD is a split virion quadrivalent influenza vaccine (60 µg HA/strain) containing virus strains chosen by the WHO (Vaccines and Related Biological Products Advisory Committee [VRBPAC] in the US) for the NH 2020-2021 influenza season. The vaccine contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages). Each pre-filled syringe contains a total of 240 µg HA antigen per 0.7 mL dose provided in sterile suspension for IM injection.

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 vaccine contains the following components:

(*Strains to be determined based on WHO / US, Food and Drug Administration, VRBPAC recommendations for the 2020-2021 NH influenza season.):*

Active substances:

- A/(H1N1) 60 µg HA
- A/(H3N2) 60 µg HA
- B/(Victoria lineage) 60 µg HA
- B/(Yamagata lineage) 60 µg HA

Excipients:

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

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

6.1.1.2 Preparation and Administration

The vaccine is provided in a pre-filled single-dose syringe and should be shaken before use. The vaccine is to be administered intramuscularly into the deltoid muscle of the upper arm. If the vaccine is injected in the arm, it should be on the opposite arm from which blood was drawn before vaccination.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration,

whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

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

6.1.1.3 Dose Selection and Timing

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

6.1.2 Identity of Control Product (Licensed QIV-SD)

Local QIV-SD (split virion), 2020-2021 Strains, provided in a pre-filled single-dose syringe (AdimFlu-S (QIS)), manufactured by AdImmune Corporation.

(Strains to be determined based on World Health Organization (WHO) recommendations for the 2020-2021 NH influenza season).

6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

Active substances:

- A/(H1N1) 15 µg HA
- A/(H3N2) 15 µg HA
- B/(Victoria lineage) 15 µg HA
- B/(Yamagata lineage) 15 µg HA

Excipients:

- Sodium chloride
- Disodium hydrogen phosphate
- Potassium dihydrogen phosphate

6.1.2.2 Preparation and Administration

Adimflu-S (QIS) will be prepared and administered according to the manufacturer's package insert (28).

6.1.2.3 Dose Selection and Timing

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

6.2 Identity of Other Product(s)

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

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

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

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

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

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

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

6.3.2.3 Product Accountability

The vaccination study staff 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 CRF. If applicable, information may also be entered into the subject's vaccination card.

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

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

6.3.3 Replacement Doses

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

6.3.4 Disposal of Unused Products

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

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigators will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

Given the different volumes of the QIV-HD and the local QIV-SD vaccines, QHD00023 will be a modified double-blind study in which an unblinded administrator will apply a piece of opaque tape over the syringe to obscure the contents. The Investigator/Sub-investigator or staff involved in the safety assessment will be blinded in order to decrease the potential bias in safety assessment.

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

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a

subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code breaking CRF is to be completed.

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

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

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

6.5 Randomization and Allocation Procedures

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and sign the ICF will be randomly assigned to the QIV-HD Group or the QIV-SD Group in a 1:1 ratio, 100 subjects per group.

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

Subject numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 158000100005 is the fifth subject enrolled in Center Number 1 in Taiwan (158 being the Taiwan country code).

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

6.6 Treatment Compliance

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

- All vaccinations will be administered by qualified study personnel

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

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

6.7 Concomitant Medications and Other Therapies

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

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

Reportable medications will be collected in the CRB from the day of vaccination to the end of the solicited and unsolicited follow-up period.

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

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

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

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

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

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

7 Management of Samples

Blood samples for the assessment of antibody (Ab) responses will be collected at Visit 1 (D0, pre-vaccination) and at Visit 2 (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 Visits 1 and 2, 10 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 Sample Preparation

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

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

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

7.3 Sample Storage and Shipment

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

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

Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

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

7.4 Future Use of Stored Biological Samples for Research

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

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

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, 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 Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

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

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

9 Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The 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

9.1.1.2 Immunogenicity Assessment Methods

9.1.1.2.1 Hemagglutination Inhibition Assay

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

Anti-Influenza Virus Ab Titration by Inhibition of Hemagglutination

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

Test serum samples and quality control sera (sheep, ferret, and/or human sera) are incubated with Sigma Type III neuraminidase from vibrio cholerae to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins is then performed by incubating the test serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures are centrifuged and the supernatants containing the treated sera are collected for testing. Ten two-fold dilutions (starting at 1:10) of the treated test serum samples and quality control sera are incubated with a previously titrated influenza antigen at a concentration of 4 hemagglutination unit (HAU)/25 µL. Influenza antigen is not added to the serum control wells containing only serum and RBCs. The mixture is then incubated and a RBC suspension is added. Following incubation, the results are read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. The lower limit of quantitation (LLOQ) is set at the lowest dilution used in the assay, 1:10. Titers below this level are reported as < 10 (1/dilution [dil]). If the highest / last serum dilution used in the assay exhibits complete inhibition of hemagglutination, the serum Ab titer will be reported as ≥ 10240 (1/dil).

9.1.2 Safety

9.1.2.1 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 (eg, asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on subject / event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death

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

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

Adverse Reaction:

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

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

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (eg, injection site pain or headache occurring between D0 and D7 post-vaccination)

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.

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

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

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

Unsolicited AE / AR:

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

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

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

9.1.2.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after vaccination
- Occurrence of solicited, ie, pre-listed in the subject's diary and electronic case report form (eCRF), injection site and systemic reactions occurring up to 7 days after vaccination
- Occurrence of unsolicited (spontaneously reported) AEs up to 28 days after vaccination
- Occurrence of SAEs, including AESIs, throughout the study period

Other endpoints recorded or derived as described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), time of onset, duration, number of days of occurrence, Grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

9.1.2.3 Safety Assessment Methods

At Visit 2, the Investigator or a delegate will perform a clinical or medically-driven physical examination and will ask the subject about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.1.2.3.1 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.

9.1.2.3.2 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 (ie, Day 0 through Day 7) until resolution:

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

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

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

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

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

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

* For the subjective reaction of pain, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness 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 9.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Shivering**
MedDRA preferred term [PT]	Pyrexia	Headache	Malaise	Myalgia	Chills
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event (AE) that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Shivering
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

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

Important notes for the accurate assessment of temperature:

Subjects are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the 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.

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

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

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

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

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

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

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

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

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

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.1.2.3.5.

- Action taken for each AE (eg, medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

9.1.2.3.4 Adverse Events of Special Interest

AESIs will be captured as SAEs (collected throughout the study). These include (29):

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

9.1.2.3.5 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:

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

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

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

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

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

10 Reporting of Serious Adverse Events

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

10.1 Initial Reporting by the Investigator

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

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

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

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

- By fax, to the following number: 570-957-2782

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address:

  Global PharmacoVigilance, Sanofi Pasteur
  Discovery Drive
  Swiftwater, PA 18370

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

If there is need for urgent consultation, the Investigator is to contact the RMO.

10.2 Follow-up Reporting by the Investigator

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

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

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

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

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.1.2.3.5.

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

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

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

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

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

11 Data Collection and Management

11.1 Data Collection and CRB 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 9.1.2.3 . These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Subjects will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects on how to correctly use these tools.

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

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

Management of Clinical and Laboratory Data

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

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

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

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

11.3 Data Review

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

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

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

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

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

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

12.1.1 Hypotheses and Statistical Methods for Immunogenicity Objective

12.1.1.1 Hypotheses

No statistical hypotheses will be tested. All analyses will be descriptive.

12.1.1.2 Statistical Methods

The following parameters will be presented by vaccine group with their 95% Confidence Interval (CI):

1. GM of titers on D0 and D28
2. GM of titer ratio D28/D0
3. Rate of subjects with titer ≥ 10 [1/dil] on D0 and D28
4. Rate of subjects with titer ≥ 40 [1/dil] on D0 and D28
5. Seroconversion or significant increase rate from D0 to D28

Geometric Mean and 95% CI Computation
Assuming that log10 transformation of the measurements follows a normal distribution, at first, the mean and 95% CI will be calculated on $\log_{10}$ measurements using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, in order to provide GMs and their 95% CIs. The 95% CIs will be computed using the normal approximate method for GMs, and the exact binomial distribution for percentages (Clopper-Pearson's method, quoted by Newcomb (30). HAI (1/dil) Ab titers against each strain will be graphically represented by a Reverse Cumulative Distribution Curve for each vaccine group by visit.

Additional analyses may be added in the Statistical Analysis Plan.

12.1.2 Hypotheses and Statistical Methods for Safety Objective

12.1.2.1 Hypotheses

No statistical hypotheses will be tested. All analyses will be descriptive.

12.1.2.2 Statistical Methods

Safety results will be analyzed descriptively for subjects in SafAS who received one of the vaccines. 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) (30).

- Unsolicited systemic AEs occurring within 30 minutes of injection (immediate unsolicited AEs)
- Solicited injection site reactions (pain, erythema, swelling, induration, and bruising) occurring within 7 days after the day of injection (D0 to D7) according to presence, time to onset, maximum intensity, number of days of occurrence, and action taken.
- 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, maximum intensity, number of days of occurrence, and action taken.
- Unsolicited AEs occurring within 28 days after injection by system organ class (SOC) and PT, relationship, maximum intensity, time to onset, and duration
- All SAEs that occur throughout the study by SOC and PT, seriousness criteria, time to onset, outcome, and relationship
- All AESIs reported throughout the study by SOC and PT and relationship

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

The full analysis set (FAS) is defined as the subset of randomized subjects who received 1 the study vaccine and had a post-vaccination blood sample. Subjects will be analyzed according to the vaccine group to which they were randomized.

12.2.2 Safety Analysis Set

The safety analysis set (SafAS) is defined as those subjects who have received the study vaccine and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received.

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

12.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide the post-dose serology sample at V2 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited medication / vaccine
- Subject with no post-vaccination HAI results for all 4 strains

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

12.2.4 Populations Used in Analyses

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

The immunogenicity analyses from the HAI assay will be performed on the PPAS and on the FAS.

The safety analyses will be performed on the SafAS.

12.3 Handling of Missing Data and Outliers

12.3.1 Immunogenicity

In order to appropriately manage replicate values for analysis purposes, the individual geometric mean 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 quantitation (ULOQ) (or ≤ ULOQ), then the titer itself will be used.

- If a titer is ≥ ULOQ (or > ULOQ), then computed value, ULOQ, will be used.

Any other replacement to be applied to specific endpoints will be described in the SAP.

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

12.3.2 Safety

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

12.4 Interim / Preliminary Analysis

No interim analyses are planned.

12.5 Determination of Sample Size and Power Calculation

The sample size is not based on any hypothesis testing. The number of subjects is designed to provide supportive immunogenicity and safety data on the study vaccine when administered in adults 65 years of age and older in Taiwan. The sample size of 200 subjects was arbitrarily chosen to comply with local requirements.

There was no power assessment as the analyses will be descriptive.

With a sample size of 90 subjects evaluable (taking into account an estimated 10% drop-out), the immunogenicity assessment in terms of percentages of subjects will have 95% CI widths of less than 22% in QIV-HD group (as shown in the table below).

Table 12.1: 95% Confidence intervals for proportions (Exact method)

n/N	% subjects observed	95% CI
45/90	50.0%	(39.3; 60.7)
50/90	55.6%	(44.7; 66.0)
60/90	66.7%	(55.9; 76.3)
70/90	77.8%	(67.8; 85.9)
80/90	88.9%	(8.05; 94.5)
85/90	94.4%	(87.5; 98.2)

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 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 study coordinator will obtain verbal clarification from the subject, enter the response into the "investigator's comment" page of the diary card, and transfer the information to the CRB.

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

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

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

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

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the investigational site, it is the responsibility of the investigator, with the subjects consent, to obtain those records if needed.

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

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

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

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

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

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)

- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

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

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

13.4.2 Audits and Inspections

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

13.4.3 Archiving

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

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

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

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

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

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

13.7 Publication Policy

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

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

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

14 Reference List

1 Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med. 1995;123(7):518-27.

2 Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2007;(2):CD001269.

3 Yang MC, Tan ECH, Su JJ. Cost-effectiveness analysis of quadrivalent versus trivalent influenza vaccine in Taiwan: A lifetime multi-cohort model. Hum Vaccin Immunother. 2016;13(1):81-9.

4 Su CP, Tsou TP, Chen CH, Lin TY, Chang SC. Seasonal influenza prevention and control in Taiwan-Strategies revisited. J Formos Med Assoc. 2019;118(3):657-63.

5 National Development Council. Population Projections for the R.O.C. (Taiwan): 2018~2065 [homepage on the Internet]. [Updated 2019 Aug 30, Accessed 2019 Oct 08]. Available at: https://www.ndc.gov.tw/en/cp.aspx?n=2E5DCB04C64512CC&s=002ABF0E676F4DB5.

6 Taiwan Centers for Disease Control. Available at https://www.cdc.gov.tw/?aspxerrorpath=/rwd/english

7 National Health Insurance Administration, Taiwan. Available at: https://www.nhi.gov.tw/Content_List.aspx?n=F352CF91F8505CA3&topn=CDA985A80C0DE710

8 Chung JY, Hsu CC, Chen JH, Chen WL, Lin HJ, Guo HR, et al. Geriatric influenza death (GID) score: a new tool for predicting mortality in older people with influenza in the emergency department. Sci Rep. 2018;8(1):9312.

9 Greenberg DP, Robertson CA, Noss MJ, Blatter MM, Biedenbender R, Decker MD. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. Vaccine. 2013;31(5):770-6.

10 Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017;5(9):738-46.

11 DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371(7):635-45.

12 Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis. 2009;200(2):172-80.

13 Izurieta, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis. 2015;15(3):293-300.

14 Shay DK, Chillarige Y, Kelman J, Forshee RA, Foppa IM, Wernecke M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare

beneficiaries in preventing post influenza deaths during 2012-2013 and 2013-2014. J Infect Dis. 2017;215(4):510-7.

15 Richardson DM, Medvedeva EL, Roberts CB, Linkin DR. Comparative effectiveness of high-dose versus standard-dose influenza vaccination in community-dwelling veterans. Clin Infect Dis. 2015;61(2):171-6.

16 Young-Xu Y, van Aalst R, Mahmud SM, Rothman KJ, Snider JT, Westreich D,et al. Relative vaccine effectiveness of high-dose versus standard-dose influenza vaccines among veterans health administration patients. J Infect Dis. 2018;217(11):1718-27.

17 Robison SG, Thomas AR. Assessing the effectiveness of high-dose influenza vaccine in preventing hospitalization among seniors, and observations on the limitations of effectiveness study design. Vaccine. 2018;36(45):6683-7.

18 Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among Elderly Persons in the United States, 2017-2018. J Infect Dis. 2019;220(8):1255-64.

19 Young-Xu Y, Snider JT, van Aalst R, Mahmud S, Thommes E, Lee J, et al. Analysis of relative effectiveness of high-dose versus standard-dose influenza vaccines using an instrumental variable method. Vaccine. 2019;37(11):1484-90.

20 Young-Xu Y, Snider JT, van Aalst R, Mahmud SM, Thommes EW, Lee JKH, et al. Analysis of relative effectiveness of high-dose versus standard-dose influenza vaccines using an instrumental variable method. Vaccine. 2019;37(11):1484-90.

21 Lu Y, Chillarige Y, Izurieta HS, Wei Y, Xu W, Lu M, et al. Effect of age on relative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries aged ≥ 65 years. J Infect Dis. 2019;220(9):1511-20.

22 Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: A systematic review and meta-analysis. Exp Rev Vaccines. 2018;17(5):435-43.

23 Chang LJ, Meng Y, Janosczyk H, Landolfi V, Talbot HK. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥ 65 years of age: A phase 3 randomized clinical trial. Vaccine. Vaccine. 2019 Sep 16;37(39):5825-5834.

24 Fluzone High-Dose prescribing information. Swiftwater, Pennsylvania, USA, Sanofi Pasteur Inc. June 2018.

25 Grohskopf LA, Sokolow LZ, Broder KR, Olsen SJ, Karron RA, Jernigan DB, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2016-17 Influenza Season. MMWR Recomm Rep. 2016;65(RR-5):1-54.

26 Goodwin K, Viboud C, Simonsen L.Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006;24(8):1159-69.

27 Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2006;3:CD004876.

28 AdimFlu-S (QIS) [package insert]. Adimmune Corporation. Taichung City, Taiwan.

29 Brighton Collaboration Website. https://www.brightoncollaboration.org/case-definitions. Accessed 08 October 2019.

30 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17:857-72.

15 Signature Page

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