NCT number: NCT03282240

Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine Administered by Intramuscular Route in Subjects Aged 65 Years and Older

Phase III, randomized, modified double-blind, active-controlled, multi-center trial evaluating the safety and immunogenicity of QIV-HD in healthy subjects aged 65 years and older in the United States

Clinical Trial Protocol

Health Authority File Number:	BB-IND #: 17556
WHO Universal Trial Number (UTN):	U1111-1183-5556
Trial Code:	QHD00013
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017–2018 Strains (QIV-HD)
Form / Route:	Liquid / Intramuscular
Indication For This Study:	Single dose for individuals aged 65 years and older
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted] [redacted] Tel: [redacted] Fax: This is a multi-center trial 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] [redacted] [redacted], Sanofi Pasteur Inc. Tel: [redacted] Fax:

Pharmacovigilance Global Safety Expert:	[redacted], [redacted] [redacted], Sanofi Pasteur Inc. Tel: [redacted] Fax:
Clinical Trial Manager:	[redacted] [redacted], Sanofi Pasteur Inc. Tel: [redacted] Fax:
Version and Date of the Protocol:	Version 4.0 dated 20 July 2017

History of Protocol Versions

Table 1: Previous versions of the protocol

Version	Date	Comments
1.0	09 February 2017	Version not approved by the IEC/IRB
2.0	09 May 2017	Version not approved by the IEC/IRB. Change needed to be made immediately after document was approved by CTL.
3.0	15 May 2017	Version submitted to IEC/IRB

Table of Contents

List of Tables

Synopsis

Company:	Sanofi Pasteur
Investigational Product:	High-Dose Influenza Vaccine Quadrivalent, 2017-2018 Northern Hemisphere Formulation (QIV-HD)
Active Substances:	A/(H1N1)-like strain, A/(H3N2)-like strain, B (B from primary lineage)-like strain, B (B from alternate lineage)-like strain

Title of the Trial:	Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine Administered by Intramuscular Route in Subjects Aged 65 Years and Older
Development Phase:	Phase III
Coordinating Investigator:	[redacted], [redacted] [redacted], [redacted], [redacted]
Trial Centers:	This will be a multi-center trial conducted at approximately 36 sites in the United States. Investigators and sites are listed in the "List of Investigators, Trial Centers, and Sponsor's Personnel Involved in the Trial" document.
Planned Trial Period:	First visit, first subject: 01 September 2017 Last contact, last subject: 04 April 2018
Trial Design and Methodology:	QHD00013 will be a randomized, modified double-blind, active-controlled, multi-center trial to be conducted in 2616 healthy subjects aged 65 years and older to assess the safety and immunogenicity of the high-dose quadrivalent influenza vaccine (QIV-HD) compared to one of the high-dose trivalent influenza vaccines (TIV-HDs) containing either the B strain from the primary lineage (TIV-HD1, which will be the licensed vaccine [Fluzone® High-Dose] for the 2017-2018 Northern Hemisphere [NH] influenza season) or the B strain from the alternate lineage (TIV-HD2, which will be an investigational TIV-HD containing an alternate B strain). An unblinded administrator at each site will administer the vaccine. All subjects will provide a pre-vaccination (baseline) blood sample at Day (D) 0 and a post-vaccination blood sample at Visit (V) 02 (D28 [+7 days]) for hemagglutination inhibition (HAI) testing. A randomized subset of these subjects (Expanded Immunogenicity Subset) from each group (100 subjects per study group) will be selected for seroneutralization (SN) testing. Solicited reactions will be collected up to 7 days after vaccination, and unsolicited adverse events (AEs) will be collected up to V02, which is the active phase of the trial (V01 to V02 [D0-D28]). Serious adverse events (SAEs) and adverse events of special interest (AESIs*) will be collected throughout the trial (D0 through approximately D180 [6-month follow-up period]). *Note: AESIs will be captured as SAEs. These include new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis. Interactive response technology (IRT) will be used to randomly assign subjects to one of the 3 trial groups and to assign subject numbers in each of the groups. Electronic data capture (EDC) will be used for the collection of data.

Early Safety Data Review:	This trial will not include an early review of safety data (i.e., no early safety review[s] of preliminary data occurring at pre-determined milestones defined in the protocol with pause in enrollment). However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Institutional Review Boards (IRBs), or the governing regulatory authorities in the country where the trial is taking place. If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the trial subjects and should assure appropriate therapy and follow-up.
Primary Objective:	***Immunogenicity*** To demonstrate that QIV-HD induces an immune response (as assessed by HAI geometric mean titers [GMTs] and seroconversion rates) that is non-inferior to responses induced by the TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects.
Primary Endpoints:	***Immunogenicity*** • HAI antibody (Ab) titers obtained on D28 • Seroconversion (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28)
Secondary Objectives:	***Immunogenicity*** 1) To demonstrate that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects. 2) To describe the immune response induced by QIV-HD, TIV-HD1, and TIV-HD2 by HAI measurement method in all subjects. 3) To describe the immune response 28 days after vaccination by virus SN measurement method in a randomized subset of subjects from each study group. ***Safety*** To describe the safety profile of all subjects in each trial group.
Secondary Endpoints:	***Immunogenicity Assessment by HAI (for all subjects)*** • 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) • Seroprotection (titer ≥ 40 [1/dil]) at D0 and D28

	Immunogenicity Assessment by SN (for the Expanded Immunogenicity Subset) Neutralizing Ab titers will be measured for each influenza strain with the SN method in a randomly selected subset of subjects from each study group. They will be obtained on D0 and D28. • Individual neutralization test (NT) Ab titer on D0 and D28 • Individual NT Ab titer ratio (fold increase in serum NT post-vaccination relative to D0) at D28 • Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28 • Fold-increase in NT Ab titer [post/pre] ≥2 and ≥ 4 at D28 • Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0 and D28 ***Safety*** Safety will be described for all subjects: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the trial, of solicited (prelisted in the subject's diary card and Case Report Book [CRB]) injection site reactions and systemic reactions occurring up to 7 days after vaccination. • Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the trial, of unsolicited AEs up to 28 days after vaccination. • Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the trial, of SAEs throughout the trial. • Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the trial.
Planned Sample Size:	A total of 2616 subjects are planned to be enrolled and randomized in a 4:1:1 ratio, as shown in Table S1.

<table>
<tr><td></td><td>S1: QHD00013 Planned Sample Size
<table>
<tr><td></td><td>QIV-HD</td><td colspan="2">TIV-HDs</td><td>Total Subjects Enrolled</td></tr>
<tr><td></td><td>QIV-HD</td><td>TIV-HD1 (licensed TIV-HD)</td><td>TIV-HD2 (investigational TIV-HD with alternate B strain)</td><td></td></tr>
<tr><td>Subjects to be Enrolled*</td><td>1744</td><td>436</td><td>436</td><td>2616</td></tr>
<tr><td>Expanded Immunogenicity Subset†</td><td>100</td><td>100</td><td>100</td><td>300</td></tr>
</table>
*Safety data and serum samples for HAI testing will be collected for all subjects.
† A randomized subset of subjects from each group will be selected for SN testing.</td></tr>
<tr><td>Schedule of Trial Procedures:</td><td>Vaccination
All eligible subjects will be randomized to receive a single injection of either the QIV-HD vaccine or one of the TIV-HD vaccines at 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 trial.
All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the CRB.
Subjects will record information about solicited reactions (D0-D7), unsolicited AEs (D0-V02), SAEs (D0-V02), and AESIs (D0-V02) in a diary card. Subjects will record information about SAEs (V02-D180 phone call) and AESIs (V02-D180 phone call) in a memory aid.
Staff will contact subjects by phone at D8 post-vaccination to identify whether the subject experienced any SAEs not yet reported and will remind the subjects to bring the completed diary card with them to V02.
Staff will review the D0 to V02 safety data with subjects at V02.
Subjects will continue to collect information on SAEs and AESIs in a memory aid (from V02-D180). Staff will contact subjects by telephone at D180 (+14 days) post-vaccination to review the memory aid and to identify the occurrence of any SAEs that had not yet been reported.</td></tr>
<tr><td>Duration of Participation in the Trial:</td><td>The duration of each subject’s participation will be approximately 6 months (D0 through D180).</td></tr>
</table>

Investigational Product:	High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017–2018 Strains (QIV-HD)
Form:	Liquid; essentially clear and slightly opalescent in color
Composition:	Each 0.7 mL dose of QIV-HD will contain: *Strains are based on World Health Organization (WHO) / Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2017-2018 NH influenza season.* ***Active substances:*** • A/Michigan/45/2015 (H1N1) strain — 60 µg HA • A/Hong Kong/4801/2014 (H3N2) strain — 60 µg HA • B/Brisbane/60/2008 strain — 60 µg HA • B/Phuket/3073/2013 strain — 60 µg HA ***Excipients:*** • Buffered saline solution — quantity sufficient (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.
Route:	Intramuscular (IM), injected into the upper arm area
Batch Number:	TBD
Control Product 1:	High-dose trivalent inactivated influenza vaccine (licensed Fluzone® High-Dose, TIV-HD1)
Form:	Liquid; essentially clear and slightly opalescent in color
Composition:	Each 0.5 mL dose of TIV-HD1 will contain: *Strains are based on WHO/ VRBPAC recommendations for the 2017-2018 NH influenza season.* ***Active Substances:*** • A/Michigan/45/2015 (H1N1) strain — 60 µg HA • A/Hong Kong/4801/2014 (H3N2) strain — 60 µg HA • B/Brisbane/60/2008 strain — 60 µg HA ***Excipients:*** • Buffered saline solution — qs to appropriate volume • Octylphenol Ethoxylate (Triton X-100®) — NMT 250 µg Preservative is not used in the manufacture of licensed TIV-HD1.
Route:	IM, injected into the upper arm area
Batch Number:	TBD

Control Product 2:	High-dose trivalent inactivated influenza vaccine (Investigational TIV-High-Dose with alternate B strain, TIV-HD2)
Form:	Liquid; essentially clear and slightly opalescent in color
Composition:	Each 0.5 mL dose of TIV-HD2 will contain: *Strains are based on WHO / VRBPAC recommendations for the 2017-2018 NH influenza season.* ***Active Substances:*** • A/Michigan/45/2015 (H1N1) strain 60 µg HA • A/Hong Kong/4801/2014 (H3N2) strain 60 µg HA • B/Phuket/3073/2013 strain 60 µg HA ***Excipients:*** • Buffered saline solution qs to appropriate volume • Octylphenol Ethoxylate (Triton X-100®) NMT 250 µg Preservative is not used in the manufacture of TIV-HD2.
Route:	IM, injected into the upper arm area
Batch Number:	TBD
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial 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 trial procedures
Exclusion Criteria	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Participation at the time of trial enrollment (or in the 4 weeks preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 2) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to V02 3) Previous vaccination against influenza (in the preceding 6 months) with either the trial 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 vaccines used in the trial or to a vaccine containing any of the same substances

	7) Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on investigator's judgment 8) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 9) Alcohol or substance abuse that, in the opinion of the investigator, might interfere with the trial 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) Identified as an Investigator or employee of the Investigator or trial center with direct involvement in the proposed trial, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed trial 12) Personal or family history of 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) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the trial until the condition has resolved or the febrile event has subsided
Statistical Methods:	The statistical analyses will be performed in 2 steps: 1) The first step will be the analysis of the main HAI immunogenicity and safety results obtained on data collected within approximately 28 days following vaccination (from D0 to V02). The study blind will be broken at that time. 2) The second step will be assessing the remaining objectives of the study. No statistical adjustment for the interim analysis is necessary because there are no planned repeat analyses of the same hypotheses. The Per-Protocol analysis set (PPAS) and Full analysis set (FAS) will be used for the immunogenicity analyses. The Safety analysis set (SafAS) will be used for all safety analyses. For the purposes of the statistical methods section, the 4 virus strains in the QIV-HD trial groups and the TIV-HD trial groups will be labeled as follows: • A/Michigan/45/2015 (H1N1) strain A1 • A/Hong Kong/4801/2014 (H3N2) strain A2 • B/Brisbane/60/2008 strain B1 • B/Phuket/3073/2013 strain B2

	Primary Objective Immunogenicity *Non-inferiority of QIV-HD to TIV-HD1 and/or TIV-HD2* The immunogenicity of QIV-HD will be compared to that of TIV-HD1 and / or TIV-HD2. For each A strain, the comparison will be made with the pooled TIV-HD groups. For each B strain, the comparison will be made with the TIV-HD group containing the corresponding B strain. For each strain, a non-inferiority approach will be used to compare the post-vaccination GMTs and the seroconversion rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis: • $H_0^s : \frac{GMT^s_{QIV\_HD}}{GMT^s_{TIV\_HD}} \leq \frac{1}{1.5}$ $\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) \leq -log_{10}(1.5)$ $H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV\_HD}} > \frac{1}{1.5}$ $\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) > -log_{10}(1.5)$ • $H_0^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} \leq -0.1$ $H_A^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} > -0.1$ with: • s: strain in {A1, A2, B1 and B2} • If s in {A1 and A2}, TIV-HD represents the pooled TIV-HD1 and TIV-HD2 groups • If s = B1, TIV-HD represents the TIV-HD1 group • If s = B2, TIV-HD represents the TIV-HD2 group • π: The seroconversion rate
	The statistical methodology will be based on the use of the 2-sided 95% confidence intervals (CIs) of the ratio of post-vaccination GMTs and difference in seroconversion rates between QIV-HD and TIV-HD groups. The 95% CIs will be calculated by normal approximation of log-transformed titers for GMTs and by the Newcombe-Wilson score method without continuity correction for seroconversion rates. The margins used for hypothesis testing are 1.5 for GMTs and 10% for seroconversion rates to demonstrate non-inferiority. The non-inferiority objective will be achieved only if it is demonstrated for 4 strains and for both GMTs and seroconversion rates. Analyses will be performed for both FAS and PPAS, but the conclusion will be made from PPAS results. A sensitivity analysis will be performed with adjustment on the pre-vaccination HAI titers.

	Secondary Objectives Immunogenicity *Superiority of QIV-HD to TIV-HD1 or TIV-HD2* The superiority analyses will be demonstrated in all subjects. For each B strain, the immunogenicity of QIV-HD will be compared to that of TIV-HD group which does not contain the corresponding B strain. A superiority approach will be used to compare post-vaccination GMTs and seroconversion rates between groups using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses: • $H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} \leq 1.5$ $\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) \leq log_{10}(1.5)$ $H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} > 1.5$ $\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) > log_{10}(1.5)$ • $H_0^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} \leq 0.1$ $H_A^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} > 0.1$ with: • s: strain in {B1 and B2} • If s = B1, TIV-HD represents the TIV-HD2 group • If s = B2, TIV-HD represents the TIV-HD1 group π: The seroconversion rate
	The statistical methodology will be based on the use of the 2-sided 95% CI of the ratio of post-vaccination GMTs and difference in seroconversion rates between the QIV-HD group and TIV-HD group. The 95% CIs will be calculated using normal approximation of log-transformed titers for GMTs and using the Newcombe-Wilson score method without continuity correction for seroconversion rates. For each strain, the 2-sided 95% CI should lie above 1.5 for GMTs and above 10% for seroconversion rates. The superiority objective will be achieved if the superiority is demonstrated for both B strains and for both GMTs and seroconversion rates. Analyses will be performed for both FAS and PPAS but the conclusion will be made from FAS results.

	Immunogenicity by HAI Method The percentages of subjects achieving seroprotection and the corresponding 95% CIs (Clopper-Pearson method) will be performed for pre-vaccination (V01) and post-vaccination immunogenicity (V02). The geometric mean titer ratios (GMTRs) will be calculated for post-vaccination immunogenicity (V02) over the baseline immunogenicity (V01) with the corresponding 95% CIs (assuming normal approximation of log-transformed values). Reverse cumulative distribution curves (RCDCs) against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (V02). Additional parameters may be displayed as appropriate. *Immunogenicity by SN Method* Immunogenicity in terms of GMTs, seroconversion, and percent of subjects with GMTs $\geq$ 1/40 [dil] will be summarized along with their 95% CIs for post-vaccination immunogenicity (V02) in the Expanded Immunogenicity Subset. The normal approximation of log-transformed titers will be applied to calculate the 95% CIs for GMTs. The 95% CIs will be calculated using Clopper-Pearson method for percentages. The geometric mean titer ratios (GMTRs) will be calculated for post-vaccination immunogenicity (V02) over the baseline immunogenicity (V01) with the corresponding 95% CIs (assuming normal approximation of log-transformed values). Reverse cumulative distribution curves (RCDCs) against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (V02). Additional parameters may be displayed as appropriate. *Safety* 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). ***Calculation of Sample Size*** A total of 2616 adults aged 65 years and older will be enrolled. A sample size of 2616 is determined based on an overall power of 90% for demonstrating non-inferiority for both the HAI GMTs and seroconversion rates comparing QIV-HD vs TIV-HD1 and / or TIV-HD2 for all 4 virus strains. The non-inferiority margins are defined as 1.5 for GMTs and 10% for seroconversion rates.
	Assumptions for the above calculations are: • The expected seroconversion rates for the 4 strains: 45% for A1 strain, 70% for A2 strain, and 40% for both B strains. • Assumed standard deviations for HAI GMTs are 0.63 for both A strains and 0.55 for both B strains. • An 8% attrition rate which provides approximately 2407 evaluable adults for immunogenicity analysis (PPAS). Based on current sample size, there is 55.4% power to detect the superiority of each B strain comparing QIV-HD groups versus either the TIV-HD1 or TIV-HD2 group in the secondary objective. It is based on an assumption of expected GMT ratio of 1.8 with a standard deviation of 0.55, seroconversion rate of 8% in the group without the B strain and 22% increase in the group with the B strain, and a 5% attrition rate in FAS. A subset of 300 subjects with 100 subjects from each study group will be randomly selected for SN testing.

Table of Study Procedures

Phase III Trial, 2 Visits, 2 Telephone Calls, 1 Vaccination, 2 Blood Samples, Approximately 180 Days Duration per Subject

Visit/Contact	**Visit 1**	**D8 Telephone Call**	**Visit 2**	**D180 Safety Follow-up Call**
Trial timelines (days)	D0	D08	D28	D180
Time windows (days)	NA	[+2D]	[+7D]	[+14D]
Informed consent	X			
Inclusion/exclusion criteria	X			
Demographic data	X			
History of seasonal influenza vaccination	X			
Medical history	X			
Reportable concomitant medications	X			
Physical examination*	X			
Randomization/allocation of subject number and unique dose number	X			
Blood sampling (BL), 10 mL	BL1†		BL2	
Vaccination	X			
Immediate surveillance (30 min)	X			
Diary card provided‡	X			
Recording of solicited injection site & systemic reactions	D0-D7			
Follow-up phone call		X§		X**
Collection of unsolicited AEs	D0-V02			
Diary card collected and reviewed			X	
Memory Aid provided††			X	
Memory Aid reviewed				X
Trial active phase termination record			X	
Reporting of SAEs and AESIs‡‡	To be reported at any time during the trial			

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

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

‡ Subjects will use this diary card to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D0 to D7 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to Visit (V) 02.

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

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

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

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

List of Abbreviations

Ab	antibody
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
CDM	Clinical Data Management
CI	confidence interval
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	Day
DS	drug substance
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	geometric mean
GMT	geometric mean titer
GPE	Global Pharmacovigilance & Epidemiology
GSE	Global Safety Expert
HA	hemagglutinin
HAI	hemagglutination inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology

LCLS	last contact, last subject
LLOQ	lower limit of quantification
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
NH	Northern Hemisphere
NMT	not more than
NT	neutralization test
PPAS	per-protocol analysis set
QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
QS	quantity sufficient
RMO	Responsible Medical Officer
RNA	ribonucleic acid
SAE	serious adverse event
SafAS	safety analysis set
SN	seroneutralization
SOC	system organ class
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
TMF	trial master file
ULOQ	upper limit of quantification
VRBPAC	Vaccines and Related Biological Products Advisory Committee
V	Visit
WHO	World Health Organization

1 Introduction

1.1 Background

This trial will evaluate the safety and immunogenicity of high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) route in subjects aged 65 years and older.

Influenza is a highly contagious, acute viral respiratory disease caused by influenza type A and type B viruses. Typically characterized by the rapid onset of fever, myalgia, sore throat, and non-productive cough, influenza can also cause severe malaise lasting for several days. Members of high risk groups (e.g., adults aged 65 years and older and persons with underlying medical conditions) are at high risk of influenza and its complications including primary viral pneumonia, secondary bacterial pneumonia, and/or exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and congestive heart failure (1) (2).

Vaccination currently represents the most effective medical intervention against influenza. The World Health Organization (WHO) (the Advisory Committee on Immunization Practices [ACIP] in the US) recommends annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (1) (3). The effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age and immune competence of the vaccine recipient.

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

In parallel, to reduce the risk of B-lineage mismatch and offer broader protection against seasonal influenza virus strains, Sanofi Pasteur has been transitioning the influenza vaccines portfolio from trivalent to quadrivalent formulations with the launch of Fluzone® Quadrivalent (a quadrivalent standard-dose influenza vaccine administered via IM route [hereafter referred to as QIV-SD] for persons aged 6 months and older, licensed in the US in 2013). In contrast to TIVs, which contain only one B-strain, the QIVs contain two B strains, one from each of the Victoria and Yamagata lineages, which have been co-circulating globally since the early 2000s. Thus, QIVs offer protection against both lineages simultaneously and reduce the risk of lack of protection against the alternate B lineage.

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

1.2 Background of the Investigational Product

Sanofi Pasteur's TIV-HD, containing 60 µg HA of each of the 3 virus strains (4-times more than the TIV-SD), for a total of 180 µg of HA antigen per dose, was developed and subsequently licensed by Sanofi Pasteur in the US in 2009 and Canada in 2015 in order to improve immune responses to the influenza vaccine in people 65 years of age and older (4). In a large scale, multicenter efficacy trial (FIM12) conducted during the 2011-2012 and 2012-2013 influenza seasons in the Northern Hemisphere (NH), TIV-HD was compared to TIV-SD in adults aged 65 years and older. This efficacy study concluded that TIV-HD is safe, induces significantly higher antibody (Ab) responses, and was 24.2% (95% confidence interval [CI], 9.7 to 36.5) more effective in preventing laboratory-confirmed influenza illness against any circulating strain compared to the TIV-SD vaccine, or in other words, one in four breakthrough cases of influenza could be prevented if TIV-HD were used instead of the TIV-SD vaccine in this population (5). Additionally, relative efficacy was 35.4% (95% CI, 12.5 to 52.5) in an analysis restricted to influenza cases caused by vaccine-similar strains.

Until recently, influenza vaccines contained a single influenza B strain. Two distinct genetic lineages of influenza B virus (the Victoria and the Yamagata lineages) have been co-circulating worldwide; both are responsible for influenza illnesses. However, the B strain included in seasonal influenza vaccines was not the dominant circulating B lineage (mismatched strains) in approximately 25% of the seasons between 2000 and 2013 (6). To overcome the problem of B-strain selection and improve protection of the population against seasonal influenza virus strains, Sanofi Pasteur has been transitioning the Fluzone influenza vaccine portfolio from trivalent to quadrivalent formulations. The quadrivalent formulations contain 1 Victoria lineage B strain and 1 Yamagata lineage B strain. Thus, the issue of having to choose a strain from only one B lineage for the seasonal influenza vaccine and the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage is eliminated (7).

An unmet need in adults aged 65 years and older is to improve protection of this population against the problem of B strain mismatch and it is for this purpose that Sanofi Pasteur is developing the QIV-HD vaccine, containing 60 µg HA of each of 4 virus strains for a total of 240 µg of HA antigen per 0.7 mL dose.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects participating in Study QHD00013 will receive a high-dose influenza vaccination. These subjects should benefit from coverage against influenza and may be less likely to catch influenza or develop complications during the 2017-2018 influenza season.

Subjects who will receive one of the controls (TIV-HD1 [the licensed vaccine containing the B strain from the primary lineage] or TIV-HD2 [the investigational vaccine containing the B strain from the alternate lineage) will be vaccinated against the influenza A/H1N1 and A/H3N2 strains, as well as a B-strain from the primary or alternate lineage, which are chosen by WHO / VRBPAC for TIVs for the 2017-2018 NH season.

Subjects who will receive the investigational vaccine (QIV-HD) will benefit from vaccination against the same influenza A strains contained in TIV-HD1 and TIV-HD2. In addition, these subjects will benefit from vaccination against the B strains from both the Victoria and Yamagata lineages chosen and recommended by WHO / VRBPAC for the composition of QIVs for the 2017-2018 NH season.

Regarding immunogenicity, the investigational QIV-HD is expected to induce an effective immune response against 4 influenza strains, comparable to the 3 strains covered by TIV-HD. Therefore, the investigational QIV-HD is likely to bring an increased benefit versus TIV-HD in terms of immunogenicity against influenza B virus and with a risk-benefit profile of QIV-HD that is expected to remain favorable, without any impact on its safety profile.

1.3.2 Potential Risks to Subjects

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

Possible Reactions to Blood Draw

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

Possible Reactions to Vaccination

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

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

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

Post-marketing experience with QIV-SD and TIV-HD has not identified any events other than those described below, which were spontaneously reported during the post-approval use of TIV-SD, for addition to the QIV-SD package insert (8).

The following events have been spontaneously reported during the post-approval use of TIV-SD and TIV-HD (9). These events are reported voluntarily from a population of uncertain size, consequently it is not always possible to reliably estimate the frequency of the events or establish a causal relationship to vaccine exposure. AEs were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to TIV-SD:

- *Blood and Lymphatic System Disorders*: thrombocytopenia, lymphadenopathy
- *Immune System Disorders*: anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)

Note: This type of reaction is rare and would most likely occur in persons with a severe reaction to influenza vaccine in the past.

- *Eye Disorders*: ocular hyperemia
- *Nervous System Disorders*: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- *Vascular Disorders*: vasculitis, vasodilation/flushing
- *Respiratory, Thoracic and Mediastinal Disorders*: dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- *Skin and Subcutaneous Tissue Disorders*: Steven-Johnson syndrome
- *General Disorders and Administration Site Conditions*: pruritus, asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders*: vomiting

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

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

1.4 Rationale for the Trial

While the large-scale, multi-center efficacy trial (FIM12) concluded that TIV-HD was safe, induced significantly higher Ab responses, and provided superior protection against laboratory-confirmed influenza illness compared to the TIV-SD vaccine in persons aged 65 years and older, a remaining unmet need in adults aged 65 years and older is to improve protection of this population against the circulating B-strain that may not be included in the trivalent vaccines. Therefore, Sanofi Pasteur is developing a 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.

2 Trial Objectives

2.1 Primary Objective

Immunogenicity

To demonstrate that QIV-HD induces an immune response (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion rates) that is non-inferior to

responses induced by the TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects.

The endpoints for the primary immunogenicity objective are presented in Section 9.1.1.1.

2.2 Secondary Objectives

Immunogenicity

1) To demonstrate that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects.
2) To describe the immune response induced by QIV-HD, TIV-HD1, and TIV-HD2 by HAI measurement method in all subjects.
3) To describe the immune response 28 days after vaccination by virus SN measurement method in a randomized subset of subjects from each study group.

The endpoints for the secondary immunogenicity objectives are presented in Section 9.2.1.1.1 for the HAI method and in Section 9.2.1.1.2 for the SN method.

Safety

To describe the safety profile of all subjects in each trial group.

The endpoints for the secondary safety objective are presented in Section 9.2.2.2.

3 Investigators and Trial Organization

This trial will be conducted in approximately 36 centers in the US. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the trial centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" document.

The Sponsor's Responsible Medical Officer (the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted], [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 trial. 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 trial to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the trial 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 Trial Design and Plan

5.1.1 Trial Design

QHD00013 will be a randomized, modified double-blind, active-controlled, multi-center trial to be conducted in 2616 healthy subjects aged 65 years and older to assess the safety and immunogenicity of the QIV-HD compared to one of the TIV-HDs containing either the B strain from the primary lineage (TIV-HD1, which will be the licensed vaccine [Fluzone High-Dose] for the 2017-2018 Northern Hemisphere [NH] influenza season) or the B strain from the alternate lineage (TIV-HD2, which will be an investigational TIV-HD containing an alternate B strain).

Subjects will be randomized into 3 groups as shown below:

- QIV-HD: N = 1744
- TIV-HD1: N = 436
- TIV-HD2: N = 436

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

An unblinded administrator at each site will administer the vaccine.

All subjects will provide a pre-vaccination (baseline) blood sample at Day (D) 0 and a post-vaccination blood sample at Visit (V) 02 (D28 [+7 days]) for HAI testing. A randomized subset of these subjects (Expanded Immunogenicity Subset) from each group (100 subjects per study group) will be selected for seroneutralization (SN) testing.

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

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

Interactive response technology (IRT) will be used to randomly assign subjects to one of the 3 trial groups and to assign subject numbers in each of the groups. Electronic data capture (EDC) will be used for the collection of data.

5.1.2 Justification of the Trial Design

The overall strategy for the QIV-HD project is to demonstrate clinically that the addition of a second influenza B strain to TIV-HD would not interfere with the immune response to other vaccine strains or adversely alter the safety profile of the vaccine in healthy adults aged 65 years and older.

The primary objective of QHD00013 is assess the safety of QIV-HD and to demonstrate that QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is non-inferior to responses induced by the licensed TIV-HD (TIV-HD1) and TIV-HD2 (containing the alternate B strain lineage).

In addition, demonstration of comparability between QIV-HD and the licensed TIV-HD, which is representative of the lots used in FIM12 (Sanofi Pasteur's Phase IIIb/IV efficacy trial comparing TIV-HD to the TIV-SD in adults aged 65 years and older), will be an indicator in terms of expected vaccine efficacy.

Given the different volumes in the QIV-HD and TIV-HD vaccines, QHD00013 will be a modified double-blind trial with an unblinded administrator used at each trial site. The administrator will not be involved in any of the blinded study assessments (e.g., safety).

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

- There were acceptable safety data generated from a Phase II study (QHD01) evaluating a different QIV-HD vaccine formulation than the QIV-HD that will be used in QHD00013, but which also contained 240 µg HA/dose.
- The QIV-HD vaccine assessed in QHD00013 is manufactured using the same drug substance (DS) manufacturing process as the currently licensed TIV-HD manufacturing process.
- There is a large vaccine safety database generated following significant post-marketing use of TIV-HD.
- It is to be noted that other licensed vaccines in the US with a dose volume greater than 0.5 mL include Twinrix®, Engerix®-B, Havrix®, Vaqta®, Imovax® Rabies, and Zostavax®.

5.1.3 Trial Plan

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

Vaccination

All eligible subjects will be randomized to receive a single injection of either the QIV-HD vaccine or one of the TIV-HD vaccines at 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 trial.

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.

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

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

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

5.1.4 Visit Procedures

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

1) Explain the trial to the subject, answer any of his / her questions and ensure that he / she has been informed of all aspects of the trial that are relevant to his / her decision and obtain a written informed consent signed by the subject. If the subject is illiterate, an independent witness/legal representative is required to sign the consent form.

   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. If the subject is not eligible, only the specific form entitled “Recruitment log” will state the subject identification, no CRB will be completed.

3) Collect relevant demographic information (e.g., date of birth and gender).

4) Obtain information about history of influenza vaccination in the previous year.

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

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

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

8) Call the IRT to assign to the subject a 12-digit subject number and allocate a medication number (see Section 6.5). At this time, some subjects will be assigned to the Expanded Immunogenicity Subset.

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

10) Administer the corresponding vaccine to the subject in the region of the upper arm muscle (the vaccine must be administered on the side opposite to that of the blood sampling).

11) Record the injection site / side / route / medication number in the CRB and affix the detachable corresponding label in the medical chart 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 diary card 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) Remind the subject to expect a telephone call 8 days after Visit 1.

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

17) Complete the relevant case report forms (CRFs) for this visit.

D8 Telephone Call 1 (8 days [+2 days] after Visit 1)

Note: If D8 [+2 days] falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Remind the subject to do the following:
   - Complete the D0–D7 pages of the diary card
   - Complete the remaining pages of the diary card and bring them to Visit 2
   - Notify the site in case of an SAE

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

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

1) Collect and review the diary card 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 should have been reported in the diary card.
2) Draw an approximately 10 mL blood sample for the titration of Abs. Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), the subject should be given the opportunity to return to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRB.
3) Provide the subject with a Memory Aid and review the directions for its use.
4) Remind the subject to expect a safety follow-up telephone call 180 days after Visit 1.
5) Remind the subject to report any SAE that may occur between Visit 2 and the 6-month follow-up call.
6) Complete the relevant CRFs for this visit.

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

1) Inquire whether the subject has received any vaccinations since the last contact (to be taken into account for the collection of information in the "Concomitant Vaccination" Section (see Section 6.7).
2) Inquire about new occurrences of SAEs and perform follow-up on SAEs.
3) Explain that this will be the last contact with the site for this trial (except for subjects with SAEs that need further follow-up, as stated below).

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

The exceptions for the final phone calls are:

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

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

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

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

5.1.5 Planned Trial Calendar

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

Planned trial period (active phase) - FVFS[a] to LVLS[b]: 01 SEP 2017 to 27 OCT 2017

Planned inclusion period - FVFS to FVLS[c]: 01 SEP 2017 to 22 SEP 2017

Planned end of trial (LCLS[d]): 04 APR 2018

Planned date of final clinical study report: 14 SEP 2018

5.1.6 Early Safety Data Review

This trial will not include an early review of safety data (i.e., no early safety review[s] of preliminary data occurring at pre-determined milestones defined in the protocol with pause in enrollment). However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IRBs, or the governing regulatory authorities in the country where the trial is taking place.

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

5.2 Enrollment and Retention of Trial Population

5.2.1 Recruitment Procedures

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

5.2.2 Informed Consent Procedures

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

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[a] FVFS: first visit, first subject

[b] LVLS: last visit, last subject

[c] FVLS: first visit, last subject

[d] LCLS: last contact, last subject (phone call at end of D180 follow-up period)

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 trial that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

If the subject is not able to read and sign the ICF, then it must be signed and dated by an impartial witness who is independent of the Investigator. A witness who signs and dates the consent form is certifying that the information in this form and any other written information had been accurately explained to and understood by the subject or his / her representative.

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 trial, 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 in order to be eligible for trial 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 trial procedures

5.2.5 Exclusion Criteria

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

1) Participation at the time of trial enrollment (or in the 4 weeks preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
2) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to V02
3) Previous vaccination against influenza (in the preceding 6 months) with either the trial 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 vaccines used in the trial or to a vaccine containing any of the same substances[a]
7) Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on investigator's judgment
8) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
9) Alcohol or substance abuse that, in the opinion of the investigator, might interfere with the trial 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[b]
11) Identified as an Investigator or employee of the Investigator or trial center with direct involvement in the proposed trial, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed trial
12) Personal or family history of 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) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the trial until the condition has resolved or the febrile event has subsided

5.2.6 Medical History

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

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[a] The components of the QIV-HD and TIV-HD vaccines are listed in the Investigator's Brochure.

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, autoimmune disorders, diabetes, psychiatric disorders or chronic infection.

The pertinent medical history for study purposes includes conditions belonging to the following categories:

1) Chronic co-morbid illnesses considered to increase the risk for influenza complications (including pre-specified diagnoses [e.g. respiratory, cardiac, blood, neurologic, kidney, and liver disorders] listed in the CRB and other significant chronic conditions, as judged by the investigator)
2) Other conditions (e.g., autoimmune disorders, tobacco use, residence at an assisted-living facility or nursing home within the last 6 months)

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 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 trial.

5.2.7 Contraindications for Subsequent Vaccination

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

5.2.8 Conditions for Withdrawal

Subjects will be informed that they have the right to withdraw from the trial at any time. A subject may be withdrawn from the study:

- At the request of the subject (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return 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 CRB and in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Trial

For any subject who discontinues the trial prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant

to the least significant (refer to the CRF Completion Instructions for additional details and examples):

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.2.2.1.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the investigator and returned unsigned, and the subject did not give any other news and did not come to any following visit.
Protocol Deviation	To be used when the subject signed the certified letter sent by the investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject	To be used: • When the subject indicated unwillingness to continue in the study • When the subject made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

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

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

If the subject's status at the end of the study is “Withdrawal by Subject”, the site will attempt to contact them for the D180 safety follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.3 Safety Emergency Call

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

This process does not replace the need to report an SAE. The investigator is still required to follow the protocol-defined process for reporting SAEs to the GPE Department (Please refer to Section 10).

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

5.4 Modification of the Trial and Protocol

Any amendments to this trial 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., that affect the conduct of the trial 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 or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. Administrative changes do not require IEC / IRB approval; however, the IEC / IRB must be notified whenever one is made.

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

5.5 Interruption of the Trial

The trial may be discontinued if new data about the investigational product resulting from this or any other trials become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, and / or the IECs / IRBs. If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the regulatory authorities, and the IECs / IRBs of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The Investigator shall promptly inform the trial subjects and assure appropriate therapy and / or follow-up for them.

6 Vaccines Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Trial 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 / VRBPAC for the NH 2017-2018 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.

When compared to the licensed TIV-HD, the production of QIV-HD uses the same DS and drug product manufacturing processes except for the DP formulation step, which includes the addition of a second influenza B-strain at the same concentration as the other 3 strains (60µg/strain/dose). This also results in a slightly higher fill volume. QIV-HD vaccine is thimerosal-free and prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.1.1 Composition

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

(*Strains are based on WHO / VRBPAC recommendations for the 2017-2018 NH influenza season.):*

Active substances:

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

Excipients:

- Buffered saline solution quantity sufficient (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.

Batch number: TBD

6.1.1.2 Preparation and Administration

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

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

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

6.1.1.3 Dose Selection and Timing

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

6.1.2 Identity of Control Product 1 (Licensed TIV-HD [TIV-HD1])

Fluzone High-Dose Influenza Vaccine (Zonal Purified, Subvirion) (TIV-HD1) is the licensed (in the US) injectable sterile suspension with trivalent inactivated Type A and B influenza split virus vaccine, provided in a pre-filled syringe. It is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.2.1 Composition

Each 0.5 mL dose of TIV-HD1 vaccine contains the following components:

(*Strains are based on WHO/VRBPAC recommendations for the 2017-2018 NH influenza season.):*

Active Substances:

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

Excipients:

- Buffered saline solution qs to appropriate volume
- Octylphenol Ethoxylate (Triton X-100®) NMT 250 µg

Preservative is not used in the manufacture of licensed TIV-HD1.

Batch number: TBD

6.1.2.2 Preparation and Administration

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

6.1.2.3 Dose Selection and Timing

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

6.1.3 Identity of Control Product 2 (Investigational TIV-HD [TIV-HD2])

The investigational TIV-HD (TIV-HD2) is a High-Dose Influenza Vaccine (Zonal Purified, Subvirion) injectable sterile suspension with trivalent inactivated Type A and B influenza split virus vaccine, provided in a pre-filled syringe. It is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.3.1 Composition

Each 0.5 mL dose of TIV-HD2 vaccine contains the following components:

(*Strains are based on WHO/VRBPAC recommendations for the 2017-2018 NH influenza season.):*

Active Substances:

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

Excipients:

- Buffered saline solution qs to appropriate volume
- Octylphenol Ethoxylate (Triton X-100®) NMT 250 µg

Preservative is not used in the manufacture of TIV-HD2.

Batch number: TBD

6.1.3.2 Preparation and Administration

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

6.1.3.3 Dose Selection and Timing

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

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

All products for this blinded trial will be administered by IM injection.

All study vaccines will be supplied with investigational labeling and packaging. Each single dose of investigational or control product will be identified by a unique medication number on the label and on the carton. 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 in order to determine the dates and times of delivery of products.

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

the product, alert the 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. 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 trial 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 person in charge of product management at the site will maintain records of product delivery to the trial site, product inventory at the site, the dose given to each subject, and the disposal of or return to the Sponsor of unused doses.

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

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

In case of any expected or potential shortage of product during the trial, 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 (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

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

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

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

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

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

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

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

The blind can be broken by the Investigator or a delegate through the IRT system as explained in the code-breaking procedures described in the 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 GPE Department through an internal system for reporting to Health Authorities in the case of an SAE as described in ICH E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (i.e., the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPE representative.

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

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

6.5 Randomization and Allocation Procedures

The study will be randomized, modified double-blinded for 3 vaccine groups. Table 6.1 shows the allocation of subjects to each vaccine group. No age stratification is applied here.

Table 6.1: Enrollment of subjects by vaccine groups and the expanded immunogenicity subsets

	QIV-HD	TIV-HDs		Total Subjects
	QIV-HD	TIV-HD1 (licensed TIV-HD)	TIV-HD2 (investigational TIV-HD with alternate B strain)	
Subjects to be Enrolled	1744	436	436	2616
Expanded Immunogenicity Subset†	100	100	100	300

*Safety data and serum for HAI testing will be collected for all subjects.

†A randomized subset of subjects from each group will be selected for SN testing.

For the subject list, block randomization is applied for all subjects within strata by sites. The allocation ratio for the 3 vaccine groups is 4:1:1. Subjects who meet the inclusion / exclusion criteria and sign an ICF will be randomly assigned to one of the groups via IRT. Subjects will also be randomly assigned into the Expanded Immunogenicity Subset for SN testing via IRT. The site administrator 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 subject number, the vaccine assignment, and have the site administrator confirm it. Subject numbers and dose numbers will be recorded on the source documents and CRBs. The full detailed procedures for randomization 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 840000100005 is the fifth subject enrolled in Center Number 1 in the US (840 being the US country code).

Subject numbers should not be reassigned for any reason.

For packaging list, dose numbers will be 7 digits long. Dose numbers are not used for packaging but only in the IRT system.

6.6 Treatment Compliance

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

- All vaccinations will be administered by qualified trial personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the trial site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including other therapies e.g., blood products, should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during trial participation.

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

Reportable medications will be collected in the CRB from the day of vaccination to the end of the 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. Four categories of reportable medications are defined:

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

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

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

Dosage and administration route will not be recorded. Homeopathic medications, topical and inhaled steroids, and topical, ophthalmic, and ear treatments will not be recorded.

The fact that a medication was 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 received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

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

7.1 Sample Collection

At Visits 1 and 2, 10 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity; will verify the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

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

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

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

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

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form

during the entire trial. 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 International Air Transport Association 602 regulations.

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 Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 5 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

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

8 Clinical Supplies

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

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

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

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

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

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

9.1.1.2 Immunogenicity Assessment Methods

Anti-Influenza Virus Ab Titration by Inhibition of Hemagglutination

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

Test serum samples and quality control sera (sheep, ferret, and/or human sera) are incubated with Sigma Type III neuraminidase from vibrio cholerae to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins is then performed by incubating the test serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures are centrifuged and the supernatants containing the treated sera are collected for testing. Ten two-fold dilutions (starting at 1:10) of the treated test serum samples and quality control sera are incubated with a previously titrated influenza antigen at a concentration of 4 hemagglutination unit (HAU)/25 µL. Influenza antigen is not added to the serum control wells containing only serum and RBCs. The mixture is then incubated and a RBC suspension is added. Following incubation, the results are read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample is titrated in two independent assay runs, and the 2 values, which cannot differ by more than 1 two-fold dilution, are reported. The GMT between the 2 values is calculated at the time of statistical analysis. The lower limit of quantitation (LLOQ) is set at the lowest dilution used in the assay, 1:10. Titers below this level are reported as < 10 (1/dil). If the lowest / first serum dilution used in the assay exhibits complete inhibition of hemagglutination, the serum Ab titer will be reported as < 10 (1/dil). If the highest / last serum dilution used in the assay exhibits complete inhibition of hemagglutination, the serum Ab titer will be reported as ≥ 10240 (1/dil).

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

9.2.1.1.1 Immunogenicity by HAI Method

The secondary endpoints for the evaluation of immunogenicity by HAI method 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)
- Seroprotection (titer ≥ 40 [1/dil]) at D0 and D28

9.2.1.1.2 Immunogenicity by SN Method

Neutralizing Ab titers will be measured for each influenza strain with the SN method in a randomly selected subset of subjects from each study group. They will be obtained on D0 and D28.

The secondary endpoints for the evaluation of immunogenicity by SN method are:

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

9.2.1.2 Immunogenicity Assessment Methods

9.2.1.2.1 Immunogenicity by HAI Method

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

9.2.1.2.2 Immunogenicity by SN Method

Influenza Virus Neutralization Test

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

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

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

9.2.2 Safety

9.2.2.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

Adverse Reaction:

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

(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)

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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 out-patient treatment with no hospitalization.

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

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

Unexpected Adverse Reaction:

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

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

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

- Symptom and
- Onset post-vaccination

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

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

Unsolicited AE / AR:

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

Injection Site Reaction:

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

Systemic AE:

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

Adverse Events of Special Interest (AESIs):

An AESI is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and

[a] All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (e.g., regulators) might also be warranted.

9.2.2.2 Safety Endpoints

The secondary endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the trial, of solicited (prelisted in the subject's diary card and CRB) injection site reactions and systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the trial, of unsolicited AEs up to 28 days after vaccination.
- Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the trial, of SAEs throughout the trial.
- Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the trial.

9.2.2.3 Safety Assessment Methods

At V01, the Investigator or a delegate will perform a clinical or medically-driven physical examination.

At V02, the Investigator or a delegate may perform a targeted clinical or medically-driven physical examination, as necessary, and will ask the subject about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit.

All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.2.2.3.1 Immediate Post-vaccination Surveillance Period

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

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked by "yes" and details collected).

- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10.

9.2.2.3.2 Reactogenicity (Solicited Reactions From D0 to D7After Vaccination)

After vaccination, subjects will be provided with a diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (i.e., D0 to D7) until resolution:

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

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

Subjects will be contacted by telephone 8 days (+2 days) after vaccination to remind them to record all safety information in the diary card and to find out if they have experienced any SAEs not yet reported.

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

Table 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the 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)	**Injection site pain**	**Injection site erythema**	**Injection site swelling**	**Injection site induration**	**Injection site bruising**
MedDRA PT	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.
Intensity scale*	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: ≥ 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

	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.				

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

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

CRB term (MedDRA lowest level term)	Fever	Headache	Malaise	Myalgia	Shivering
MedDRA PT	Pyrexia	Headache	Malaise	Myalgia	Chills
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills
Definition	Fever is defined by a temperature of ≥ 38.0°C/≥ 100.4°F	A headache is pain or discomfort in the head, or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling.
Intensity scale*:	Grade 1: ≥ 38.0°C to ≤ 38.4°C Grade 2: ≥ 38.5°C to ≤ 38.9°C Grade 3: ≥ 39.0°C Or	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	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	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	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

		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.	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.	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.	usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
	Grade 1: ≥100.4°F to ≤ 101.1°F Grade 2: ≥ 101.2°F to ≤ 102.0°F Grade 3: ≥ 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, 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Subjects are to measure body temperature once per day (in degrees Fahrenheit), 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 trial is oral. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic and temporal artery thermometers must not be used.

9.2.2.3.3 Unsolicited AEs

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

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

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

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

- Action taken for each AE (e.g., medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

9.2.2.3.4 Adverse Events of Special Interest

AESIs will be captured as SAEs (collected throughout the trial). These include (10):

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

9.2.2.3.5 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the product administered as either ***not related*** or ***related***, based on the following definitions[a]:

0: Not related – The AE is clearly / most probably caused by other etiologies such as subject's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination

[a] ICH Guidelines, Clinical Safety Data Management E2A

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

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

AEs likely to be related to the product, whether serious or not, that persist at the end of the trial 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 the "chronicity" establishment.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the trial.

10 Reporting of Serious Adverse Events

In order 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 (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Death/Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's GPE 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 Death/Safety Complementary Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPE mailbox, the CRA and the CTL with relevant SAE information details.

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

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

- By fax, to the following number: [redacted]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted]
- 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. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Death/Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPE Department and to the CRA. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPE 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 products or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

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

Following this, the Sponsor's Pharmacovigilance (PV) Global Safety Expert (GSE) 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 trial 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 ([redacted], [redacted]) 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 trial protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this trial by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.2.2.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Subjects will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects on how to correctly use these tools.

The D180 follow-up will be done by interviewing subjects over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A memory aid will be provided to the subjects at the preceding trial visit to help them record information on events occurring between this visit and the D180 follow-up.

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

At specified intervals, the Investigator or an authorized designee will interview the subjects to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical trial 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 trial 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 trial.

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 trial 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 trial personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry in order to track all modifications and to ensure database integrity.

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

11.2 Data Management

Management of SAE Data

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

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

Management of Clinical and Laboratory Data

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

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

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

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

11.3 Data Review

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

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical database data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor, US, with the 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. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

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

- A/Michigan/45/2015 (H1N1) strain A1
- A/Hong Kong/4801/2014 (H3N2) strain A2
- B/Brisbane/60/2008 strain B1
- B/Phuket/3073/2013 strain B2

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Immunogenicity

12.1.1.1.1 Hypotheses

The immunogenicity of QIV-HD will be compared to that of TIV-HD1 and / or TIV-HD2. For each A strain, the comparison will be made with the pooled TIV-HD groups. For each B strain, the comparison will be made with the TIV-HD group containing the corresponding B strain.

For each strain, a non-inferiority approach will be used to compare the post-vaccination GMTs and the seroconversion rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis:

- $H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} \leq \frac{1}{1.5}$
  $\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) \leq -log_{10}(1.5)$

$$H_A^s : \frac{GMT_{QIV-HD}^s}{GMT_{TIV-HD}^s} > \frac{1}{1.5}$$
$$\Leftrightarrow log_{10}(GMT_{QIV\_HD}^s) - log_{10}(GMT_{TIV\_HD}^s) > -log_{10}(1.5)$$

- $H_0^s : \pi_{QIV-HD}^s - \pi_{TIV-HD}^s \leq -0.1$

  $H_A^s : \pi_{QIV-HD}^s - \pi_{TIV-HD}^s > -0.1$

with:

- s: strain in {A1, A2, B1 and B2}
- If s in {A1 and A2}, TIV-HD represents the pooled TIV-HD1 and TIV-HD2 groups
- If s = B1, TIV-HD represents the TIV-HD1 group
- If s = B2, TIV-HD represents the TIV-HD2 group
- π: The seroconversion rate

12.1.1.1.2 Statistical Methods

Assuming that log_{10} transformation of the data follows a normal distribution, the log_{10} (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of geometric means (GMs).

The statistical methodology will be based on the use of the 2-sided 95% CI of the ratio of post-vaccination GMTs and difference in seroconversion rates between QIV-HD and TIV-HD groups. The 95% CIs will be calculated by normal approximation of log-transformed titers for GMTs and by the Newcombe-Wilson score method without continuity correction for seroconversion rates. The margins used for non-inferiority hypothesis testing are 1.5 for GMTs and 10% for seroconversion rates based on Food and Drug Administration (FDA) guidelines for licensure of seasonal influenza vaccine (11).

The non-inferiority objective will be achieved only if it is demonstrated for 4 strains and for both GMTs and seroconversion rates. Analyses will be performed for both the Full Analysis Set (FAS) and the Per-protocol Analysis Set (PPAS), but the conclusion will be made from PPAS results.

A sensitivity analysis will be performed with adjustment on the pre-vaccination HAI titers.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Immunogenicity

12.1.2.1.1 Hypotheses

Superiority of QIV-HD to TIV-HD1 or TIV-HD2

The superiority analyses will be demonstrated in all subjects. For each B strain, the immunogenicity of QIV-HD will be compared to that of TIV-HD group which does not contain the corresponding B strain.

A superiority approach will be used to compare post-vaccination GMTs and seroconversion rates between groups using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses:

- $$H_0^s : \frac{GMT_{QIV-HD}^s}{GMT_{TIV-HD}^s} \leq 1.5$$
  $$\Leftrightarrow log_{10}(GMT_{QIV-HD}^s) - log_{10}(GMT_{TIV-HD}^s) \leq log_{10}(1.5)$$

  $$H_A^s : \frac{GMT_{QIV-HD}^s}{GMT_{TIV-HD}^s} > 1.5$$
  $$\Leftrightarrow log_{10}(GMT_{QIV-HD}^s) - log_{10}(GMT_{TIV-HD}^s) > log_{10}(1.5)$$

- $$H_0^s : \pi_{QIV-HD}^s - \pi_{TIV-HD}^s \leq 0.1$$

  $$H_A^s : \pi_{QIV-HD}^s - \pi_{TIV-HD}^s > 0.1$$

with:

- s: strain in {B1 and B2}
- If s = B1, TIV-HD represents the TIV-HD2 group
- If s = B2, TIV-HD represents the TIV-HD1 group
- π: The seroconversion rate

Immunogenicity by HAI Method

No hypotheses will be tested.

Immunogenicity by SN Method

No hypotheses will be tested.

12.1.2.1.2 Statistical Methods

Assuming that $\log_{10}$ transformation of the data follows a normal distribution, the $\log_{10}$ (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMs.

Superiority of QIV-HD to TIV-HD1 or TIV-HD2

The statistical methodology will be based on the use of the 2-sided 95% CI of the ratio of post-vaccination GMTs and difference in seroconversion rates between the QIV-HD group and TIV-HD group. The 95% CIs will be calculated using normal approximation of log-transformed titers for GMTs and using the Newcombe-Wilson score method without continuity correction for seroconversion rates. For each strain, the 2-sided 95% CI should lie above 1.5 for GMTs and above 10% for seroconversion rates.

The superiority objective will be achieved if the superiority is demonstrated for both B strains and for both GMTs and seroconversion rates. Analyses will be performed for both FAS and PPAS but the conclusion will be made from FAS results.

Immunogenicity by HAI Method

The percentages of subjects achieving seroprotection and the corresponding 95% CIs (Clopper-Pearson method) (12) will be performed for pre-vaccination (V01) and post-vaccination immunogenicity (V02). The geometric mean titer ratios (GMTRs) will be calculated for post-vaccination immunogenicity (V02) over the baseline immunogenicity (V01) with the corresponding 95% CIs (assuming normal approximation of log-transformed values). Reverse cumulative distribution curves (RCDCs) against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (V02). Additional parameters may be displayed as appropriate.

Immunogenicity by SN Method

Immunogenicity in terms of GMTs, seroconversion, and percent of subjects with GMTs ≥ 1/40 [dil] will be summarized along with their 95% CIs for post-vaccination immunogenicity (V02). The normal approximation of log-transformed titers will be applied to calculate the 95% CIs for GMTs. The 95% CIs will be calculated using Clopper-Pearson method for percentages. The GMTRs will be calculated for post-vaccination immunogenicity (V02) over the baseline immunogenicity (V01) with the corresponding 95% CIs (assuming normal approximation of log-transformed values). RCDCs against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (V02). Additional parameters may be displayed as appropriate.

12.1.2.2 Safety

12.1.2.2.1 Hypotheses

No hypotheses will be tested.

12.1.2.2.2 Statistical Methods

Safety 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) (12).

- 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, intensity (Grade 1, Grade 2, or Grade 3), number of days of occurrence, action taken, and whether the reaction led to early termination from the trial. When more than 1 intensity level is reported within a time period, the highest intensity will be used
- Solicited systemic reactions (fever, headache, malaise, myalgia, and shivering) occurring within 7 days after the day of injection (D0 to D7) according to presence, time to onset, intensity (Grade 1, Grade2, or Grade 3), number of days of occurrence, action taken, and whether the reaction led to early termination from the trial. When more than 1 intensity level is reported within a time period, the highest intensity will be used
- Unsolicited AEs occurring within 28 days after injection by system organ class (SOC) and PT, relationship, intensity, time to onset, and duration
- All SAEs that occur throughout the trial by SOC and PT, seriousness criteria, time to onset, outcome, relationship, and whether the SAE led to early termination throughout the trial
- All AESIs reported throughout the trial by SOC and PT and relationship

12.2 Analysis Sets

Four main analysis sets will be used: the PPAS, the FAS, the Expanded Immunogenicity Subset, and the Safety Analysis Set (SafAS).

12.2.1 Full Analysis Sets

The FAS is defined as the subset of randomized subjects who received at least 1 dose of a trial vaccine and had a post-vaccination blood sample HAI result for at least 1 strain. Subjects will be analyzed according to the vaccine group to which they were randomized.

For the assessment of the immune response by virus SN method, the analysis will be performed on the subjects from the FAS randomized into the Expanded Immunogenicity Subset with at least one post-vaccination SN assay result for at least 1 strain.

12.2.2 Safety Analysis Set

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

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

12.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample (V02) in the proper time window (i.e., 28 to 35 days after vaccination) or a post-dose serology sample (V02) was not drawn
- Subject received a protocol-prohibited therapy / medication / vaccine

In addition to the criteria listed above, subjects will also be excluded from the PPAS if their post-vaccination serology sample did not produce a valid HAI test result (i.e., HAI results for all antigens are missing).

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

12.2.4 Populations Used in Analyses

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

The safety analyses will be performed on the SafAS.

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

The secondary SN immunogenicity analyses will be performed on the Expanded Immunogenicity Subset.

[a] for which safety data are scheduled to be collected

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

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

12.3.2 Immunogenicity

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

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

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

No test or search for outliers will be performed.

No replacement will be done for missing values. Based on the previous TIV-HD and QIV-SD trials in this population, the amount of missing immunogenicity data is expected to be ≤ 5% in this trial. Usually in vaccine trials, it seems generally reasonable to assume missing immunogenicity data are missing completely at random (MCAR) (13). Indeed, it is highly unexpected that the dropout (or any other reason for missing data) could be linked to the immune response of the subject. Therefore, confirming the results of the PPAS for the primary analysis with the FAS would be satisfactory in terms of sensitivity analysis.

12.4 Interim / Preliminary Analysis

The statistical analyses will be performed in 2 steps:

- First step will be the analysis of main HAI immunogenicity and safety results obtained on data collected within approximately 28 days following vaccination (from D0 to Visit 2). The study blind will be broken at that time.
- Second step will be assessing the remaining objectives of the study.

No statistical adjustment for the interim analysis is necessary because there are no repeat analyses of the same hypotheses.

12.5 Determination of Sample Size and Power Calculation

A total of 2616 adults aged 65 years and older will be enrolled. A sample size of 2616 is determined based on an overall power of 90% for demonstrating non-inferiority for both the HAI GMTs and seroconversion rates comparing QIV-HD vs TIV-HD1 and / or TIV-HD2 for all 4

virus strains. The non-inferiority margins are defined as 1.5 for GMTs and 10% for seroconversion rates.

Assumptions for the above calculations are:

- The expected seroconversion rates for the 4 strains: 45% for A1 strain, 70% for A2 strain, and 40% for both B strains.
- Assumed standard deviations for HAI GMTs are 0.63 for both A strains and 0.55 for both B strains.
- An 8% attrition rate which provides approximately 2407 evaluable adults for immunogenicity analysis.

Based on current sample size, there is 55.4% power to detect the superiority of each B strain comparing QIV-HD groups versus either the TIV-HD1 or TIV-HD2 group in the secondary objective. It is based on an assumption of expected GMT ratio of 1.8 with a standard deviation of 0.55, seroconversion rate of 8% in the group without the B strain and 22% increase in the group with the B strain, and a 5% attrition rate in FAS.

A subset of 300 subjects with 100 subjects from each group will be randomly selected for SN testing.

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Trial / Good Clinical Practice

The conduct of this trial 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 trial source documents is to document the existence of subjects and to substantiate the integrity of the trial 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 trial, regardless of the outcome.

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

13.3 Confidentiality of Data and Access to Subject Records

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

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

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the trial (i.e., before the inclusion of the first subject at the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the trial protocol and the detailed trial 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 trial has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the trial, 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 trial procedures such as the product management and sample-handling procedures.

After the start of the trial, 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:

[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.

- Evaluate the quality of the trial progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the trial, 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 trial 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 trial documents during these inspections and audits.

13.4.3 Archiving

The Investigator must keep all trial documents after the completion or discontinuation of the trial, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, trial documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any trial documents upon less than 90 days advance written notification to the Sponsor. In addition, trial documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the trial documents.

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

13.6 Stipends for Participation

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

13.7 Publication Policy

Data derived from this trial are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the trial must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the trial, any participating center may publish or otherwise use its own data provided that any publication of data from the trial gives recognition to the trial 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 trial 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 trial are not to be considered confidential.

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

14 References List

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15 Signature Pages

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