Efficacy, Immunogenicity, and Safety of High-Dose Quadrivalent Influenza Vaccine Compared with Standard-Dose Quadrivalent Influenza Vaccine in Children 6 Months through 35 Months of Age

Phase III, randomized, modified double-blind, active-controlled, multi-center study in children 6 months through 35 months of age in Northern and Southern Hemisphere countries

Clinical Study Protocol Amendment 2

Health Authority File Number(s):	BB-IND #: 017556 EudraCT #: 2019-004721-24 MX CTA #: MX 203301410A0141/2021
WHO Universal Trial Number (UTN):	U1111-1243-5993
Study Code:	QHD00014
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	Quadrivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (QIV-HD)
Form / Route:	Suspension for injection in pre-filled syringe / Intramuscular (IM)
Indication For This Study:	Active immunization for prevention of influenza in children 6 months through 35 months of age
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted] MD Division of Pediatric Infectious Diseases, Emory University School of Medicine, Atlanta, GA, USA Tel: [redacted] Fax: [redacted] Email: [redacted] This is a multi-center study with multiple investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document.

Sponsor's Responsible Medical Officer:	[redacted] MD Global Clinical Development Strategy Expert – Vaccines Global Clinical Sciences Department, Sanofi Pasteur Inc. Tel: [redacted] E-mail: [redacted]
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Version and Date of the Protocol:	Version 4.0 dated 01 October 2021

History of Protocol Versions

Version*	Date	Comments
1.0	16 January 2020	Version submitted to IEC/IRB
2.0	26 May 2020	Version not submitted to IEC/IRB. Changes required based on regulatory authority feedback; Amendment 1
3.0	27 May 2020	Administrative changes required immediately after CTL/RMO approval; Amendment 1, first version used in the study.
4.0	01 October 2021	Amendment 2; Administrative changes required due to the delay in study as a result of the COVID-19 pandemic.

*Versions in bold font have been approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and used in the study.

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	Quadrivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (QIV-HD)
Active Substances:	Influenza virus (inactivated, split) of the following strains: A/(H1N1), A/(H3N2), B (Victoria Lineage), and B (Yamagata Lineage)

Title of the Study:	Efficacy, Immunogenicity, and Safety of High-Dose Quadrivalent Influenza Vaccine Compared with Standard-Dose Quadrivalent Influenza Vaccine in Children 6 Months through 35 Months of Age
Development Phase:	Phase III
Coordinating Investigator:	[redacted] MD Division of Pediatric Infectious Diseases, Emory University School of Medicine, Atlanta, GA, USA
Study Sites:	This will be a multi-center study conducted at approximately 200 sites in approximately 9 countries in the Northern Hemisphere (NH) and approximately 6 countries in the Southern Hemisphere (SH). Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Note: The Sentinel Safety Cohort and associated study procedures were completed prior to Amendment 2 of this Protocol. The study is planned to start in September 2020 with the Sentinel Safety Cohort. Following the Sentinel Safety Cohort, the main efficacy cohort in the study is planned to be completed during 2 NH influenza seasons (2022-2023 [Season 1] and 2023-2024 [Season 3]) and 1 SH influenza season (2023 [Season 2]), unless the number of expected cases is insufficient for the primary endpoint requiring additional influenza seasons to be evaluated or a decision is made to stop the study earlier based on an interim analysis. Following the end of the Season 2 (2023 SH) influenza season, if the likelihood of achieving the expected[redacted] influenza cases at the end of Season 3 (2023-2024 NH influenza season) is low, and if at least[redacted] influenza cases meeting the primary endpoint have occurred, an interim analysis of the efficacy of high-dose quadrivalent influenza vaccine (QIV-HD) relative to a licensed standard-dose quadrivalent influenza vaccine (hereafter referred to as QIV-SD) for the primary efficacy endpoint is planned to be conducted by an independent statistician and reviewed by an independent data monitoring committee (IDMC) during Season 3. The IDMC may recommend stopping the study without adding any additional study seasons if the primary objective and first secondary objectives are demonstrated (ie, the stopping rule for superior efficacy is fulfilled), if there is a high probability to demonstrate these objectives at the end of the ongoing season, or for futility if the probability to demonstrate the primary objective at the end of the study is too low.
Study Design, Schedule of Study Procedures, and Methodology:	**General Study Design**

	QHD00014 is planned to be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in 13,320 (100 subjects will be in an open-label Sentinel Safety Cohort with no comparator vaccine while 13,220 will be randomized and double-blinded) children 6 months through 35 months of age to evaluate the relative efficacy, immunogenicity, and safety of QIV-HD administered by intramuscular (IM) route versus a QIV-SD vaccine. QHD00014 is planned to start during the 2020-2021 NH influenza season with the Sentinel Safety Cohort. The main efficacy cohort will be conducted during the 2022-2023 NH influenza season (Season 1), the 2023 SH influenza season (Season 2), and the 2023-2024 NH influenza season (Season 3). During each of these 3 study seasons, subjects will be randomized in a 1:1 ratio to receive either QIV-HD or QIV-SD prior to the start of the influenza season. Subjects will receive either 1 or 2 doses of study vaccine depending on whether they were previously vaccinated against influenza or previously unvaccinated against influenza, respectively. During the 2020-2021 NH influenza season, a sentinel cohort of 100 US subjects will be enrolled in an uncontrolled, open-label design without a comparator vaccine to evaluate the safety of QIV-HD prior to the enrollment of subjects in the main efficacy cohort. These Sentinel Safety Cohort subjects will not provide blood samples and will not be followed for influenza-like illness (ILI) surveillance. Enrollment in the main efficacy cohort will not begin until an IDMC reviews the safety of the Sentinel Safety Cohort. If the IDMC determines that there is no significant safety issue during their review of the Sentinel Safety Cohort data, then approximately [redacted] subjects will subsequently be enrolled in main efficacy cohort starting with Season 1 (ie, the 2022-2023 NH influenza season). The sample size in the subsequent seasons may be adjusted to maintain the likelihood of achieving the overall expected number of cases for the primary endpoint. The current estimated sample size for the efficacy cohort in Seasons 2 and 3 is [redacted] subjects [redacted] and an additional [redacted] subjects from Season 1's Immunogenicity Subset will be re-enrolled in Season 3 but will not be included in efficacy analysis for Season 3, for a total of 13,320 subjects in the entire study. Sentinel Safety Cohort subjects will be excluded from reenrollment in any subsequent seasons. During each influenza season, a subset of subjects (hereafter referred to as the Immunogenicity Subset) will be randomly selected using Interactive Response Technology (IRT) across participating sites to provide blood samples for immunogenicity testing: Total subjects with blood draws = approximately [redacted] subjects Season 1, NH = [redacted] subjects Season 2, SH = [redacted] of randomized subjects (approximately [redacted] subjects) Season 3, NH = [redacted] of randomized subjects (approximately [redacted] subjects) and [redacted] re-enrolled subjects who were part of Season 1* An Expanded safety analysis set (ESafAS) will also be selected for collection of reactogenicity and unsolicited adverse events as follows: Total subjects in ESafAS = [redacted] subjects Sentinel Safety Cohort (2020-2021 NH) = 100 subjects† Season 1, NH = [redacted] subjects (all subjects) † Season 2, SH = [redacted] of randomized subjects (approximately [redacted] subjects) Season 3, NH = [redacted] of randomized subjects (approximately [redacted] subjects) and [redacted] re-enrolled subjects from Season 1

	*A subset of approximately [redacted] subjects from Season 1 (2022-2023 NH) who are in the Immunogenicity Subset will be re-enrolled and re-randomized in Season 3 (hereafter referred as the Re-vaccination Cohort) and included in the ESafAS and the Immunogenicity Subset; these[redacted] subjects will not be followed for ILI surveillance during their participation in Season 3. †Note: For the Sentinel Safety Cohort season and Season 1: all enrolled subjects will be included in the ESafAS. For Seasons 2 and 3: the Immunogenicity Subset and the ESafAS will include the same subjects. ***Vaccination*** For the Sentinel Safety Cohort, eligible subjects will receive QIV-HD as follows: • Subjects enrolled in the Sentinel Safety Cohort who were previously vaccinated against influenza will receive 1 dose of the QIV-HD on Day (D) 0, with no comparator vaccine. • Subjects enrolled in the Sentinel Safety Cohort who were not previously vaccinated against influenza will receive 2 doses of the QIV-HD with no comparator vaccine. Each dose will be administered 28 days apart (at D0 and D28). All other eligible subjects will be randomized to receive either QIV-HD or QIV-SD: • Subjects previously vaccinated against influenza will receive 1 dose of the QIV-HD or the comparator vaccine on D0. • Subjects who had not previously been vaccinated against influenza will receive 2 doses of the QIV-HD or the comparator vaccine. Each dose will be administered 28 days apart (at D0 and D28). Note: Previously unvaccinated subjects are defined as subjects who have not received at least 2 doses of seasonal influenza vaccine in a prior influenza season. These subjects will receive 2 doses of study vaccine at least 28 days apart after enrolling in the study. Subjects who have received only one dose of any influenza vaccine in the past or subjects whose vaccination history is unknown will also be considered as previously unvaccinated when enrolling and receive 2 doses of study vaccine at least 28 days apart. Previously vaccinated subjects are defined as subjects who have received at least 2 doses of seasonal influenza vaccine in prior influenza seasons. These subjects will receive only 1 dose of study vaccine after enrolling in the study. In the Sentinel Safety Cohort, subjects will receive 1 or 2 doses of QIV-HD according to their influenza vaccination history as defined above. An unblinded administrator at each site will administer the vaccine. ***Definitions:*** Protocol-defined influenza-like illness (ILI): occurrence of fever ≥ 38°C (100.4°F) concurrently with at least one of the following symptoms: cough, wheezing, difficulty breathing, nasal congestion, rhinorrhea, pharyngitis (sore throat), otitis, vomiting, diarrhea, chills (shivering), tiredness (fatigue), headache, or myalgia (muscle aches). Modified Centers for Disease Control and Prevention (CDC)-defined ILI: occurrence of fever (defined as temperature > 38°C [>100.4°F]) with cough, pharyngitis, or sore throat. Laboratory-confirmed influenza: a positive influenza result on either polymerase chain reaction (PCR) or viral culture. Culture-confirmed influenza: a positive influenza result on viral culture.

Genetic similarity: Genetic similarity is defined when a laboratory-confirmed isolate is deemed similar to one of the viral strains contained in the vaccine formulations according to sequencing of full HA gene segments proteins.

Antigenic similarity: Antigenic similarity is defined when a laboratory-confirmed isolate is deemed similar to one of the viral strains contained in the vaccine formulations according to Ferret Antigenicity testing (hemagglutination inhibition [HAI] against a panel of known standard ferret reference antisera).

Similarity to vaccine components: For prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine in subjects 6 months through 35 months of age, laboratory-confirmed isolate is deemed similar to one of the vaccine components based on antigenic similarity only. For all the other endpoints, similarity is based on antigenic similarity when available or based on genetic similarity otherwise.

Acute lower respiratory infection (ALRI): pneumonia, bronchiolitis, bronchitis, or croup (laryngotracheobronchitis) based on a clinical and/or x-ray diagnosis.

Surveillance for Influenza-like illness:

Following randomization and vaccination(s), all subjects' parents/guardians (except those subjects in the Sentinel Safety Cohort) will be instructed to contact the PI staff (passive surveillance) if they experience symptoms of a protocol-defined ILI during the annual surveillance periods, from the 1st vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects.

In addition, during a period from the 1st vaccination until 30 April for NH seasons subjects or 31 October for SH season subjects, subjects will be contacted (active surveillance) once a week.

Collection of nasopharyngeal (NP) swabs:

During the period from D0 after vaccination (after the first vaccination in subjects receiving two doses of study vaccine) until 30 April of the following year for NH subjects or until 31 October of the same year for SH subjects, the site will arrange for an NP swab to be taken if the subject experiences a new onset of fever concomitantly with one or more of the above-mentioned symptoms of protocol-defined ILI (that persists for or reoccurs after a period of at least 12 hours).

The NP swab will be obtained as soon as possible and no later than 7 days (between D0 and D6) from the onset of the ILI.

Reporting of events temporally associated with an ILI:

In addition to obtaining an NP swab, the site will collect detailed information about the ILI, as well as information on occurrence of ALRI, otitis media, healthcare utilization events (hospitalizations, emergency room visits, and non-routine office visits [including urgent care visits]) and medication use (eg, antibiotics, antivirals).

In the event that an NP swab cannot be collected, the research site will still obtain the above information. All subjects' parents/guardians reporting a suspected ILI will have a 30-day follow-up telephone call.

Laboratory testing for the confirmation of influenza and determination of similarity to vaccine components:

All NP specimens will be submitted for analysis by both culture and PCR, and a positive result on either test will be considered a laboratory-confirmed case of influenza.

	Positive cultures or positive PCR samples* will undergo additional testing (typing, subtyping, and strain identification, utilizing genetic sequencing) to determine if the virus detected is similar to any of those contained in the vaccine formulation for the respective season. *Positive PCR samples that have negative culture results, or were unable to be expanded in culture, will not undergo additional testing. ***Blood sampling*** A subset of randomly selected subjects (immunogenicity subset) will provide 2 blood samples (5 mL each): • Previously vaccinated subjects will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V02 (D28 [+7 days]) for HAI testing and potential seroneutralization (SN) and enzyme-linked lectin assay (ELLA) testing. • Previously unvaccinated subjects will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (28 days after V02 [+7 days]) for HAI testing and potential SN and ELLA testing. ***Collection of safety data*** All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB) for subjects in the Sentinel Safety Cohort and ESafAS and in the source documentation for all other subjects. For subjects enrolled in the Sentinel Safety Cohort and in Season 1 (2022-2023 NH), solicited reactions will be collected through day 7 after each vaccination, and unsolicited AEs will be collected through day 28 after each vaccination in all subjects. During Season 2 (2023 SH) and Season 3 (2023-2024 NH), solicited reactions and unsolicited AEs will only be collected for those in the ESafAS. Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected in all subjects throughout the study (D0 through approximately 6 to 7 months after vaccination in each season). AESIs will be captured as SAEs in this study. AESIs include Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis. Parents / guardians of subjects will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study. Staff will review the safety data with subjects' parents / guardians at each visit. The IRT system will be used to randomly assign subjects to a study product and subsets 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:	The safety of the investigational product will be continuously monitored by the Sponsor. An early safety data review (ESDR) will be performed, the goal of which is to allow for a cautious, step-wise approach to vaccine administration. An initial safety review for this study is planned when the first 100 subjects are vaccinated, and safety has been captured for all in a Sentinel Safety Cohort. All 100 subjects are to receive QIV-HD (in this open-label cohort, no comparator vaccine will be administered). After the Sentinel Safety Cohort vaccinations have been provided and there is safety data for D0-D7 post-vaccination (using the data collection methods described in the clinical study protocol), an IDMC will convene and review the safety data. Following a satisfactory safety review by the IDMC, enrollment of subjects may start in Season 1 (2022-2023 NH).

	The safety data collected will be entered into the case report book (CRB) and will be summarized and reviewed by the Sponsor and the IDMC. It is understood that this review is based on preliminary data that have not been subject to validation and database lock. (The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined ESDR will continue unchanged.) The following safety parameters will be assessed as part of the ESDR review of the Sentinel Safety Cohort in an unblinded manner by the IDMC. They will be collected during a period of 7 days after the vaccination: • Immediate reactions • Solicited injection site and systemic reactions • Unsolicited AEs • SAEs (including AESIs) The data will be examined for the following occurrences: • An SAE (including AESIs) considered as related to the vaccination by the Investigator and Sponsor • > 10% of subjects experiencing Grade 3 fever within 7 days after vaccination If any of the above criteria are met, a recommendation will be made by the IDMC as to whether enrollment in the study will be allowed to resume. At the completion of the collection of safety data at the end of Season 1 (2022-2023 NH season), the IDMC will be convened to review the safety data of subjects. Enrollment will not be paused during this IDMC review. Throughout the course of the study, additional internal safety management team (SMT) meetings will be convened to conduct blinded analyses of safety data. Case unblinding may be performed if necessary. The Sponsor may also convene the IDMC for ad hoc review of the safety data if needed. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs / IRBs, and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects and should assure appropriate therapy and follow-up.
Interruption of the Study	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs / IRBs, the IDMC, or the governing regulatory authorities in the countries where the study is taking place. The study may also be interrupted prior to accrual of all expected protocol-defined influenza cases upon recommendation of the IDMC after an interim unblinded analysis to evaluate if early efficacy or futility criteria are met. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs / IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects' parents/guardians and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	***Efficacy objective*** To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type.
Primary Endpoint:	***Efficacy***

	Occurrence of laboratory-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI.
Secondary Objectives:	***Confirmatory Efficacy Objectives*** • To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type using a more stringent threshold • To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine • To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 23 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type **Other Secondary Objectives are for descriptive assessment:** ***Efficacy Descriptive Objectives:*** To assess the relative clinical efficacy of QIV-HD compared to QIV-SD in subjects for the prevention of: • laboratory-confirmed influenza illness caused by any influenza A or B type according to previous influenza vaccination status in prior seasons • laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine according to previous vaccination status • laboratory-confirmed influenza illness associated with acute otitis media (AOM based on clinical diagnosis) caused by any influenza A or B type • laboratory-confirmed influenza illness associated with AOM based on clinical diagnosis caused by viral strains similar to those contained in the vaccine • laboratory-confirmed influenza illness associated with ALRI based on a clinical and/or x-ray diagnosis caused by any influenza A or B type • laboratory-confirmed influenza illness associated with ALRI based on a clinical and/or x-ray diagnosis caused by viral strains similar to those contained in the vaccine • PCR-confirmed influenza illness caused by any influenza A or B type • PCR-confirmed influenza illness caused by viral strains similar to those contained in the vaccine • culture-confirmed influenza illness caused by any influenza A or B type • culture-confirmed influenza illness caused viral strains similar to those contained in the vaccine • laboratory-confirmed influenza illness associated with hospitalization and caused by any influenza A or B type • laboratory-confirmed influenza illness associated with hospitalization and caused by viral strains similar to those contained in the vaccine ***Immunogenicity*** • To compare the HAI immune response of QIV-HD to QIV-SD in subjects 6 months through 35 months of age • To describe the HAI immune response induced by each vaccine against the 4 vaccine strains and according to the different strain formulations used in each of the study influenza seasons

	• To describe the SN immune response induced by QIV-HD or QIV-SD against the 4 QIV-HD vaccine strains in a randomized subset of subjects • To describe the anti-neuraminidase (NA) immune response induced by QIV-HD or QIV-SD in a randomized subset of subjects ***Re-vaccination Response*** To describe the immune response (HAI method) to vaccination in Season 3 (NH) among subjects re-enrolled from Season 1 (NH) to Season 3 (NH), according to the vaccines received in both Season 1 (NH) and Season 3 (NH) ***Safety*** • To describe the safety profile (injection site reactions and systemic events) of each vaccine during the 28 days following each vaccination for the ESafAS (all subjects from Sentinel Safety Cohort, all subjects from Season 1, and a subset of subjects from Seasons 2 and 3) • To describe all SAEs (including AESIs) up to at least 180 days after the last vaccination in all subjects
Secondary Endpoints:	***Confirmatory Efficacy Endpoints*** The following endpoints will be used for efficacy comparisons: • Occurrence of laboratory-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI. • Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive for viral strains similar to those contained in the vaccine • Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive in subjects 6 through 23 months of age for any influenza A or B type ***Descriptive Efficacy Endpoints*** **In addition, the following endpoints will also be considered for the descriptive assessment of relative efficacy:** Occurrence of an ILI starting ≥ 14 days after vaccination: • laboratory-confirmed as positive for any influenza A or B type, in subjects according to their previous vaccination status • laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, in subjects according to their previous vaccination status • laboratory-confirmed as positive for any influenza A or B type, and associated with AOM based on clinical diagnosis occurrence • laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, and associated with AOM based on clinical diagnosis occurrence • laboratory-confirmed as positive for any influenza A or B type, and associated with ALRI based on a clinical and/or x-ray diagnosis occurrence • laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, and associated with ALRI based on a clinical and/or x-ray diagnosis occurrence • PCR-confirmed as positive for any influenza A or B types • PCR-confirmed as positive for viral strains similar to those contained in the vaccine • culture-confirmed as positive for any influenza A or B types • culture-confirmed as positive for viral strains similar to those contained in the vaccine

	• laboratory-confirmed as positive for any influenza A or B type and associated with hospitalization • laboratory-confirmed as positive for viral strains similar to those contained in the vaccine and associated with hospitalization ***Immunogenicity*** The following immunogenicity endpoints will be used for comparison in Immunogenicity Subset of Season 1: • Individual HAI titer on D0 and 28 days after the last vaccination • Seroconversion for subjects with a pre-vaccination titer < 10 (1/dil): post-injection titer ≥ 40 (1/dil) on 28 days after the last vaccination or significant increase for subjects with a pre-vaccination titer ≥ 10 (1/dil): ≥ 4-fold increase from pre- to post-injection titer on 28 days after the last vaccination In addition, the 2 above and the following endpoints will be considered in the Immunogenicity Subset for the descriptive assessment of immunogenicity: • Detectable HAI titer, ie, with a titer ≥ 10 (1/dilution [dil]) at D0 and 28 days after the last vaccination. • Individual titer ratio: 28 days after the last vaccination /D0. • Subjects with titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination. ***Immunogenicity by SN method*** Immunogenicity will be evaluated using the SN assay in a subset of subjects. For each vaccine strain, antibody titers will be expressed as SN titers. The following immunogenicity endpoints will be described: • Individual SN antibody (Ab) titer on D0 and 28 days after the last vaccination • Individual SN Ab titer ratio (fold increase in post-vaccination titer relative to D0) at 28 days after the last vaccination • Subjects with SN Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at 28 days after the last vaccination • Fold-increase in SN Ab titer [post/pre] ≥ 2 and ≥ 4 at 28 days after the last vaccination • Detectable SN Ab titer (SN Ab titer ≥ 10 [1/dil]) at D0 and 28 days after the last vaccination ***Immunogenicity by ELLA method*** For a subset of subjects, anti-N1 and anti-N2 titers will be measured for the 2 influenza A strains using ELLA and will be assessed based on the subject's individual anti-NA titer. The following immunogenicity endpoints will be described: • Individual anti-NA Ab titer on D0 and 28 days after the last vaccination • Individual anti-NA Ab titer ratio (fold-rise in anti-NA post-vaccination titer relative to D0) at 28 days after the last vaccination • Subjects with anti-NA Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at 28 days after the last vaccination • Fold-rise in anti-NA Ab titer [post/pre] ≥ 2 and ≥ 4 at 28 days after the last vaccination • Detectable anti-NA titer (anti-NA Ab titer ≥ 10 [1/dil]) at D0, and 28 days after the last vaccination ***Re-vaccination Response*** For the approximately [redacted] subjects who are re-enrolled in Season 3 (NH) and were part of the Immunogenicity Subset in Season 1 (NH), the HAI Ab titers against the 4 vaccine strains used in Season 3 (NH) will be measured at D0 and D28 in Season 3 (NH). The following endpoints will be described.

	• HAI individual titer on D0, and 28 days after the last vaccination • Individual HAI titer ratio: D28 days after the last vaccination /D0 • Detectable HAI titer, ie, with a titer ≥ 10 (1/dilution [dil]) at D0 and 28 days after the last vaccination • Subjects with titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination • Seroconversion for subjects with a pre-vaccination titer < 10 (1/dil): post-injection titer ≥ 40 (1/dil) on 28 days after the last vaccination or significant increase for subjects with a pre-vaccination titer ≥ 10 (1/dil): ≥ 4-fold increase from pre- to post-injection titer on 28 days after the last vaccination. ***Safety / Reactogenicity*** Reactogenicity will be described for the ESafAS: • Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccination • Occurrence of solicited (pre-listed in the subject's diary card and CRB) injection site reactions and systemic reactions occurring up to 7 days after vaccination • Occurrence of unsolicited AEs up to 28 days after vaccination SAEs/AESIs will be described in all subjects: • Occurrence of SAEs (including AESIs) throughout the study • Occurrence of AESIs throughout the study
Observational Objectives:	***Efficacy*** The following objectives will be assessed for laboratory-confirmed influenza illness due to any influenza A or B type, and due to viral strains similar to those contained in the vaccine. To assess the relative clinical efficacy of QIV-HD compared to QIV-SD in subjects 6 months through 35 months of age for the prevention of: • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination caused by each circulating influenza virus A subtype and B lineage • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination by age subgroup • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination by season • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination in previously unvaccinated subjects after 1st injection • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination in previously unvaccinated subjects between 1st and 2nd injections • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination and over the first 3 months after vaccination • laboratory-confirmed influenza illness starting ≥ 14 days after vaccination according to other ILI definitions (modified CDC-defined ILI) ***Influenza-associated Events/Health Care Utilization*** • To describe in each vaccine group the occurrence of AOM (based on clinical and/or x-ray diagnosis), within 30 days after the onset of a laboratory-confirmed ILI • To describe in each vaccine group the occurrence of AOM (based on clinical and/or x-ray diagnosis), within 30 days after the onset of any ILI

	• To describe in each vaccine group the occurrence of ALRI (based on clinical and/or x-ray diagnosis), within 30 days after the onset of a laboratory-confirmed ILI • To describe in each vaccine group the occurrence of ALRI (based on clinical and/or x-ray diagnosis), within 30 days after the onset of any ILI • To describe in each vaccine group the occurrence, duration, and intensity of ILI symptoms occurring within 30 days after the onset of a laboratory-confirmed ILI • To describe in each vaccine group the occurrence, duration, and intensity of ILI symptoms occurring within 30 days after the onset of ILI • To describe in each vaccine group the use of antibiotics and antivirals that are associated with cases of laboratory-confirmed ILI, within 30 days after the onset of the ILI • To describe in each vaccine group the use of antibiotics and antivirals that are associated with any ILI, within 30 days after the onset of the ILI • To describe in each vaccine group hospitalizations that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI • To describe in each vaccine group hospitalizations that are associated with any ILI, within 30 days after onset of the ILI • To describe in each vaccine group emergency room visits that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI • To describe in each vaccine group emergency room visits that are associated with any ILI, within 30 days after onset of the ILI • To describe in each vaccine group non-routine medical office visits (including urgent care visits) that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI • To describe in each vaccine group non-routine medical office visits (including urgent care visits) that are associated with any ILI, within 30 days after onset of the ILI • To describe in each vaccine group medication use that is associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI • To describe in each vaccine group medication use that is associated with any ILI, within 30 days after onset of the ILI • To describe in each vaccine group absenteeism (Parent(s) / guardian's absenteeism due to child sick days) that is associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI • To describe in each vaccine group absenteeism (Parent(s) / guardian's absenteeism due to child sick days) that is associated with any ILI, within 30 days after onset of the ILI ***Correlates of Protection Objective*** To assess the association of HAI titers to the 4 vaccine strains with the occurrence of laboratory-confirmed ILI of any influenza A or B type, or of viral strains similar to those contained in the vaccine. ***Antibody persistence*** To describe the persistence of immune response 1 year after vaccination among subjects from Season 1 (NH) who are re-enrolled for Season 3 (NH) according to the vaccine received in Season 1 (NH)

Observational Endpoints:	***Efficacy*** • Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive for each circulating influenza A subtype and B lineage: A/H1N1, A/H3N2, B/Victoria and B/Yamagata • Occurrence of an ILI starting ≥ 14 days after first vaccination, laboratory-confirmed as positive in each age subgroup of subjects • Occurrence of an ILI starting ≥ 14 days after first vaccination, laboratory-confirmed as positive in each season • Occurrence of an ILI starting ≥ 14 days after first vaccination, laboratory-confirmed as positive in subjects previously unvaccinated • Occurrence of an ILI starting ≥ 14 days after first vaccination and before second injection, laboratory-confirmed as positive in subjects previously unvaccinated • Occurrence of an ILI starting within 14-90 days after first vaccination, laboratory-confirmed as positive • Occurrence of a modified CDC-defined ILI starting ≥ 14 days after first vaccination, and laboratory-confirmed as positive • For subjects enrolled in both Season 1 (NH) and Season 3 (NH), occurrence of an ILI starting ≥ 14 days after first vaccination in Season 3 (NH), laboratory-confirmed as positive according to the vaccination pattern ***Influenza-associated Events/ Health care utilization*** The following events that are associated with ILI and occurring within 30 days after the ILI onset will be described for cases of laboratory-confirmed ILI caused by any viral type/subtype and for any ILI, respectively: • Occurrence of AOM based on clinical diagnosis • Occurrence of ALRI (eg, pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis, and croup) based on clinical and/or x-ray diagnosis • Occurrence, duration, and intensity of ILI symptoms • Occurrence of medication use (eg, antibiotics, antivirals) • Occurrence of hospitalizations • Occurrence of emergency room visits • Occurrence of non-routine medical office visits (including urgent care visits) • Occurrence of absenteeism ***Immunogenicity for correlate of protection*** • HAI titer for each vaccine strain 28 days after the last vaccination, together with occurrence of an ILI starting ≥ 14 days after vaccination, confirmed as positive for any influenza A or B type • HAI titer for each vaccine strain 28 days after the last vaccination, together with occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed for viral strains similar to those contained in the vaccine ***Antibody persistence*** For the approximately [redacted] subjects who are re-enrolled in Season 3 (NH) and were part of the Immunogenicity Subset in Season 1 (NH), the HAI Ab titers against the 4 vaccine strains used in Season 1 (NH) will be measured at D0 before starting vaccination in Season 3 (NH). The following endpoints will be described.

	• HAI individual titer on D0 and 28 days after the last vaccination of Season 1 (NH) and on D0 of Season 3 (NH) • Detectable HAI titer, ie, with a titer ≥ 10 (1/dilution [dil]) at D0 and 28 days after the last vaccination of Season 1 (NH) and on D0 of Season 3 (NH) • Subjects with titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination of Season 1 (NH) and on D0 of Season 3 (NH)

Planned Sample Size:

A total of approximately 13,320 subjects will be enrolled: 100 subjects will be enrolled in the open-label Sentinel Safety Cohort during the 2020-2021 NH influenza season and 13,220 subjects in the main cohort will be enrolled over 3 influenza seasons with a randomization ratio of 1:1 for QIV-HD to QIV-SD. [redacted] Season 1 subjects will also be re-vaccinated in Season 3.

Vaccine	Number of Subjects		
QIV-HD for open-label, Sentinel Safety Cohort	**100**		
Vaccine	**Season 1 (NH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 2 (SH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 3 (NH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	Season 3 (NH) Re-vaccination Cohort†		
QIV-HD	[redacted]		
QIV-SD			
Total			
Overall Total	**13,320 subjects with [redacted] tested for immunogenicity*, [redacted] for expanded safety, and 100 safety cohort subjects**		

Abbreviations: NH, Northern Hemisphere; QIV-HD, high-dose quadrivalent influenza vaccine; QIV-SD, standard-dose quadrivalent influenza vaccine; SH, Southern Hemisphere
* Number of subjects who provide blood samples in Season 1 (NH) is greater than in Season 2 (SH) or Season 3 (NH) because unlike the Season 2 and 3 sera, which will be used for the descriptive immunogenicity results and correlate of protection exploratory endpoint only, Season 1 (NH) sera will also be used to demonstrate immunogenicity superiority.
†Approximately [redacted] subjects from the Immunogenicity Subset of Season 1 (NH) will re-enroll in Season 3 (NH) to be evaluated for antibody persistence and re-vaccination immunogenicity endpoints. These subjects will not be part of the approximately [redacted] subjects in Season 3 who are being followed for ILI surveillance and efficacy.

	Samples sizes for evaluation based on assessment method are as follows: **Assessment Method** / **Number of Subjects** hemagglutination inhibition (HAI) / approximately [redacted] subjects (all subjects in the Immunogenicity Subset) seroneutralization (SN) / approximately [redacted] subjects in Season 1's Immunogenicity Subset enzyme-linked lectin assay (ELLA) / Approximately [redacted] subjects in Season 1's Immunogenicity Subset
	However, due to the unpredictable epidemiology of influenza, the sample size and/or the duration of the study may be adjusted based on the blinded number of influenza cases in order to maintain the likelihood of achieving the expected number of influenza cases for the primary endpoint. Following the end of the Season 2 (2023 SH) influenza season, if the likelihood of achieving the expected [redacted] cases at the end of the Season 3 is too low, and if at least [redacted] influenza cases meeting the primary endpoint have occurred, an interim analysis is planned to be conducted by an independent statistician and reviewed by an IDMC during Season 3. The study may stop after the third season if the primary objective and first secondary objective is demonstrated, if there is a high probability to demonstrate these objectives at the end of the ongoing season, or for futility if the probability to demonstrate the primary objective at the end of the study is too low.
Duration of Participation in the Study:	The duration of each subject's participation in the respective study year will be 6 to 7 months, depending on the time of enrollment and previous vaccination status.
Investigational Product:	Quadrivalent Influenza Vaccine (split virion, inactivated) High-Dose (QIV-HD), manufactured by Sanofi Pasteur.
Form:	Suspension for injection in pre-filled syringe
Composition:	Each 0.7 mL dose of QIV-HD will contain: *Strains are based on WHO recommendations for the considered season.* ***Active Substances:*** • A/(H1N1)-like strain 60 µg HA • A/(H3N2)-like strain 60 µg HA • B/(Victoria lineage)-like strain 60 µg HA • B/(Yamagata lineage)-like strain 60 µg HA ***Excipients:*** Buffered saline solution qs to appropriate volume Octylphenol Ethoxylate (Triton X-100) not more than 350 µg Preservative is not used in the manufacture of QIV-HD.
Route:	IM injection into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate
Batch Numbers:	To be determined
Control Product:	**Fluarix® Quadrivalent** (or other commercial names)**,** Influenza vaccine (split virion, inactivated) (QIV-SD) (GlaxoSmithKline Biologicals)
Form:	Suspension for injection, in pre-filled syringe
Composition:	Each 0.5 mL dose of QIV-SD will contain: *Strains are based on WHO recommendations for the considered season.* ***Active Substances:*** • A/(H1N1)-like strain 15 µg HA

	• A/(H3N2)-like strain 15 µg HA • B/(Victoria lineage)-like strain 15 µg HA • B/(Yamagata lineage)-like strain 15 µg HA ***Excipients:*** Buffered saline solution qs to appropriate volume Octylphenol-10 (Triton X-100) ≤ 0.115 mg α-Tocopheryl hydrogen succinate ≤ 0.135 mg Polysorbate 80 (Tween 80) ≤ 0.550 mg Fluarix® Quadrivalent vaccine does not contain a preservative.
Route:	IM injection into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate
Batch Numbers:	Commercial batches
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Aged 6 to 35 months on the day of the first study visit* 2) Informed consent form has been signed and dated by the parent(s) or guardian(s) and by an independent witness, if required by local regulations. 3) Subject and parent / guardian are able to attend all scheduled visits and to comply with all study procedures. 4) Covered by health insurance if required by local regulations 5) For Season 3 Re-vaccination Cohort: eligible subjects must have been enrolled in the Season 1 (2022-2023 NH season) immunogenicity subset and must have completed all study procedures (ie, blood draws and vaccinations) in Season 1. *Note: "6 to 35 months" means from the 6th month after birth to the day before the 36th month after birth.
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Participation at the time of study enrollment (or in the 4 weeks preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure. 2) For all subjects: Receipt of any vaccine in the 30 days preceding the first study vaccination. For subjects in immunogenicity subset: Planned receipt of any vaccine before Visit 2 for subjects receiving 1 dose of influenza vaccine or Visit 3 for subjects receiving 2 doses of influenza vaccine. 3) Previous vaccination against influenza in the preceding 6 months prior to study vaccination with either the study vaccine or another influenza vaccine 4) Receipt of immune globulins, blood or blood-derived products in the 3 months preceding the study vaccination. 5) Known or suspected congenital or acquired immunodeficiency (eg HIV); 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 study or to a vaccine containing any of the same substances. Exception: subjects with an egg allergy are allowed to enroll in the study.

	7) Thrombocytopenia, bleeding disorder, or receipt of anticoagulants that based on Investigator's judgment contraindicate intramuscular vaccination. 8) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion. 9) 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 study until the condition has resolved or the febrile event has subsided. Note: Subjects who test positive for COVID-19 infection or have been in close contact with individuals who have tested positive for COVID-19 within 14 days preceding the first study vaccination will also be excluded from participating in the study until they test negative for COVID-19. 10) Identified as natural or adopted child of the Investigator or employee with direct involvement in the proposed study. 11) Personal or family history of GBS. 12) Any condition that in the opinion of the Investigator would pose a health risk to the subject if enrolled or could interfere with the evaluation of the vaccine. 13) Personal history of clinically significant development delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder. 14) For Season 3 (2023-2024 NH) main cohort: subjects who were enrolled in a previous study season are excluded from Season 3, with the exception of the Re-vaccination Cohort.
Statistical Methods:	Following the end of the Season 2 (2023 SH), an interim analysis may be conducted by an independent statistician and reviewed by an IDMC during Season 3 in an attempt to stop the study at the end of the Season 3 and avoid study extension in case the planned [redacted] cases cannot be achieved in 3 seasons. Therefore, the interim analysis will only be conducted if the likelihood of achieving the expected [redacted] cases at the end of Season 3 is low (avoiding to conduct the interim analysis if the expected [redacted] cases will be achieved) and if at least [redacted] evaluable influenza cases are collected (to ensure enough power to assess the objectives). At the interim analysis, the primary objective and first secondary objective will be assessed and the predictive power to demonstrate these objectives at the end of the ongoing season and at the end of the study will be calculated. The IDMC may recommend stopping the study at the end of Season 3 if the primary objective and first secondary objective are demonstrated, if there is a high probability to demonstrate these objectives at the end of Season 3, or for futility if the probability to demonstrate the primary objective at the end of the study is too low. In addition, at the time of the interim analysis, other efficacy and safety objectives may be assessed on the available data for information. The full analysis of all study objectives will be performed at the end of the study. In case the study is to be stopped prematurely following the results of an interim analysis, the full statistical report may be delivered in more than one step if deemed necessary. ***Primary Objective Analyses*** <u>Efficacy</u> The vaccine efficacy of the 2 groups will be compared in a step-wise manner: A non-inferiority testing approach will be used first, using a non-inferiority margin of -10%. If non-inferiority is demonstrated, a superiority test will be used using a margin of 5%. Both tests will use a one-sided Type I error at 2.5%, and there is no need for multiplicity adjustment due to the step-wise approach. The rVE of QIV-HD to QIV-SD will be estimated for primary endpoint as follows:

	rVE= (1- (C_{HD} / N_{HD}) / (C_{SD} / N_{SD})) × 100% where: • C_{HD} and C_{SD} are the numbers of influenza cases meeting the considered primary endpoint definition in the QIV-HD and QIV-SD groups, respectively. • For analysis in per-protocol analysis set, the first episode among those occurring more than 14 days after the last vaccination will be considered. For analysis in full analysis set, the first episode among those occurring more than 14 days after the first vaccination will be considered. • If subject experiences multiple occurrences of the same endpoint, only the first episode will be considered • N_{HD} and N_{SD} are the numbers of subjects in the QIV-HD and QIV-SD groups, respectively. CIs for vaccine efficacy will be calculated by an exact method assuming a Binomial distribution of the number of cases in the vaccine group conditional on the total number of cases in both groups. The vaccine efficacy of QIV-HD will be considered as non-inferior to QIV-SD if the lower bound of the rVE is > -10%, and superior to QIV-SD if the lower bound of the CI for the rVE is > 5%. The Per-Protocol Analysis Set for Efficacy will be used as the primary analysis set for the non-inferiority test and the Full Analysis Set for Efficacy will be used as the primary analysis set for the superiority test. If the interim analysis is conducted, an alpha spending method quoted by Lan and Demets (power family, phi=2) will be used to maintain an overall Type I error (the 'alpha') of 0.025 one-sided, considering that[redacted] of information time is reached at the time. Consequently, a one-sided nominal alpha of[redacted] and[redacted] will be used at interim and final analysis, respectively. This corresponds to[redacted] and [redacted] two-sided CIs to be used at interim and final analysis, respectively. Should the interim analysis results fulfill the stopping rules, the study will be stopped at the end of Season 3. In the final analysis, the rVE will be estimated using a two-sided 95% CI if the stopping rule for superior efficacy is fulfilled at the interim analysis or a [redacted] CI will be used if otherwise. ***Secondary Objectives Analyses*** If the primary objective is demonstrated, the secondary confirmatory objectives will be tested. A hierarchical testing combined with graphical approach will be used to adjust the multiplicity of the 4 secondary confirmatory objectives, which prevents any inflation of the overall one-sided Type I error beyond 2.5%. <u>Efficacy</u> For the first secondary objective, a superiority test will be performed using a more stringent margin of [redacted] with the same nominal alpha levels being used in the interim analysis (ie, one-sided[redacted]) and in the final analysis (ie, one-sided[redacted] if the stopping rule for superior efficacy is not fulfilled at the interim analysis or one-sided 0.025 if otherwise) for the primary objective. At the time of the final analysis, if superiority is demonstrated, a graphical approach will be applied to control alpha within the 2 efficacy objectives. If one of them is claimed for efficacy using a two-sided 97.5% CI, then the other one will be tested using a two-sided 95% CI to assess the superiority. Estimation of relative efficacy for efficacy objectives will be the same as those described for the primary objective above except that QIV-HD will be considered as superior to QIV-SD if the lower bound of the CI for the corresponding rVE is > 0%.

Immunogenicity

If all of the above efficacy objectives are demonstrated, a superiority testing approach will be used to compare post-vaccination geometric mean titers (GMTs) and seroconversion rates between QIV-HD and QIV-SD groups for each strain using a one-sided test with Type I error rate of 0.025 following the individual hypotheses:

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

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

where

s: strain

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

Immunogenicity endpoints will be summarized for each vaccine strain with 95% CIs. The 95% CIs for the GMTs and GMT ratios (GMTRs) will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of GMTs will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the two-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Reverse cumulative distribution curves against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (D28 or D56 as appropriate).

Safety

Safety results will be described for each vaccine group. The main parameters will be described with 95% CI.

Observational Objectives Analyses

Estimation of efficacy for the observational objectives will be as described for the primary objective above; for each estimate of efficacy, a 95% CI will be calculated.

Descriptive analysis and statistical models will be used to [redacted]. As this analysis is exploratory, [redacted] These methods will be detailed in the statistical analysis plan (SAP).

SN and anti-NA immunogenicity results will be described for each vaccine group. The main parameters will be described with 95% CI.

Calculation of Sample Size

For efficacy assessments:

The sample size needed for the assessment of the primary objective of the study is expected to be approximately [redacted] subjects and may be adjusted based on the

	blinded number of cases in order to maintain the likelihood of achieving approximately [redacted] evaluable influenza cases meeting the primary endpoint. These required number of evaluable influenza cases would provide at least [redacted] power at final analysis to conclude on the primary objective under the following assumptions: • The true rVE of QIV-HD to QIV-SD is [redacted] • An overall one-sided Type I error rate 0.025 [redacted] spent at interim and final analysis, respectively) • The lower bound of the CI of rVE should be > 5% • An allocation ratio of QIV-HD to QIV-SD of 1:1 • An overall influenza attack rate of [redacted] for the occurrence of an influenza case in the QIV-SD group • [redacted] of enrolled subjects evaluable for the primary endpoint Based on the same assumptions and using a [redacted] threshold, the power for the first secondary objective at final analysis is expected at [redacted] approximately. For the assessment of the two remaining secondary confirmatory efficacy objectives, the assumptions will be similar to those for primary objective except • The lower bound of the CI for the corresponding rVE will be superior to 0%. • the true rVE of QIV-HD to QIV-SD is [redacted] for each subset (ie, subjects 6 through 35 months of age against similar strains and subjects 6 through 23 months against any strains) • [redacted] evaluable influenza cases ([redacted] of total cases) from each subset For each objective, a [redacted] power will be achieved with a two-sided 97.5% CI and an [redacted] power will be achieved with a two-sided 95% CI. <u>For the immunogenicity assessments:</u> Approximately [redacted] subjects will be assessed for HAI immunogenicity in Season 1. Based on Phase II immunogenicity results and assuming [redacted] of non-evaluable subjects, this provides approximately [redacted] probability to obtain 95% CIs of ratios of GMTs and differences in seroconversion rates excluding equality for a given season (formulation).

Table of Study Procedures 1 - Previously vaccinated subjects in the Sentinel Safety Cohort

Phase III Study, 2 Visits, 2 Telephone Calls, 1 Vaccination, approximately 180 Days' Duration per Subject

Visit/Contact	**V01**	**Telephone Call 01**	**V02**	**TC02**
Study timelines (days)	D0	D8	D28	180 days after V01
Time windows (days)		+2	+7	+14
Informed consent form signed and dated	X			
Inclusion / exclusion criteria	X			
Physical examination*	X		X	
Collection of demographic data	X			
Medical history†	X			
History of seasonal influenza vaccination	X			
Collection of concomitant medications	At any time during the study period			
IRT Contact allocation of subject number and unique dose number‡	X			
Vaccination	X			
Immediate surveillance (30 min)	X			
DC provided§	X			
DC reviewed and collected			X	
Reporting of solicited injection site and systemic reactions (for 7 days after vaccination)	X			
Collection of unsolicited adverse events (for 28 days after vaccination)	X			
MA provided**			X	
Study active phase termination record			X	
Follow-up telephone call		X††		X‡‡
Reporting of SAEs (including AESIs)§§	To be reported at any time during the study			

Abbreviations: AESI, adverse event of special interest; D, day; DC, diary card; MA, memory aid; SAE, serious adverse event; TC, telephone call; V, visit.

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

† With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection.

§ Subject's parents / guardians will use the diary card to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D0 to D7 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02

** Subject's parents / guardians will use this MA to collect information on medications, SAEs, and AESIs from V02 to the end of the 6-month safety follow-up period.

†† During this telephone call, staff will record relevant information concerning the subject's health status, will find out whether the subject experienced any SAEs and AESIs not yet reported, and will remind the subjects' parent / guardian to bring the completed diary card to the next visit.

‡‡ During this telephone call, staff will review the MA to record medications and identify the occurrence of any SAEs and AESIs that have not yet been reported.

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

Note: *Study procedures for the Sentinel Safety Cohort were completed prior to Amendment 2 of this protocol.*

Table of Study Procedures 2 - Previously unvaccinated subjects in the Sentinel Safety Cohort

Phase III Study, 3 Visits, 3 Telephone Calls, 2 Vaccinations, approximately 208 Days' Duration per Subject

Visit/Contact	**V01**	**Telephone Call 01**	**V02**	**TC02**	**V03**	**TC03**
Study timelines (days)	D0	D8	D28	8 days after V02	28 days after V02	180 days after V02
Time windows (days)		+2	+7	+2	+7	+14
Informed consent form signed and dated	X					
Inclusion / exclusion criteria	X					
Physical examination*	X		X		X	
Collection of demographic data	X					
Medical history†	X					
History of seasonal influenza vaccination	X					
Collection of concomitant medications	At any time during the study period					
IRT Contact -allocation of subject number and unique dose number‡	X					
Allocation of unique dose number			X			
Temporary and definitive contraindications			X			
Vaccination	X		X			
Immediate surveillance (30 min)	X		X			
DC provided§	DC1		DC2			
DC reviewed and collected			DC1		DC2	
Recording of solicited injection site and systemic reactions (for 7 days after vaccination)	X		X			
Collection of unsolicited adverse events (for 28 days after vaccination)	X			X		
MA provided**					X	
Study active phase termination record					X	
Follow-up telephone call		X††		X††		X‡‡
Reporting of serious adverse events (SAEs) (including AESIs) §§	To be reported at any time during the study					

Abbreviations: AESI, adverse event of special interest; BL, blood sampling; D, day; DC, diary card; SAE, serious adverse event; TC, telephone call; V, visit.

* Targeted physical examination based on medical history will be performed at V01. Targeted physical examination may also be performed at V02 and V03, if necessary.

† With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection

§ Subject's parents / guardians will use the diary cards to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs after each vaccination (from V01 to TC01 and from V02 to TC02) and will continue to record information about unsolicited AEs, SAEs, and AESIs from TC01 to V02 and D36 to V03.

**Subject's parents / guardians will use this MA to collect information on medications, SAEs, and AESIs from V03 to the end of the 6-month safety follow-up period.

†† During this telephone call, staff will record relevant information concerning the subject's health status, will find out whether the subject experienced any SAEs and AESIs not yet reported, and will remind the subjects' parent / guardian to bring the completed diary card to the next visit.

‡‡ During this telephone call, staff will review the MA to record medications and identify the occurrence of any SAEs and AESIs that have not yet been reported.

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

Note: *Study procedures for the Sentinel Safety Cohort were completed prior to Amendment 2 of this protocol.*

Table of Study Procedures 3 (previously influenza vaccinated subjects 6 months through 35 months of age)

Phase III Study, 1 Visit, 1 Telephone Call, 1 Vaccination, approximately 6 Months Duration per Subject per Study Year

Visit/Contact	**V01**	**Follow-up Telephone Call**
Study timelines (days)	D0	D180 + 14 after V01 or end of influenza season if later than D180
Time windows (days)		+14
Informed consent form signed and dated	X	
Inclusion / exclusion criteria	X	
Physical examination*	X	
Collection of demographic data	X	
Medical history†	X	
History of seasonal influenza vaccination	X	
Collection of concomitant medications	At any time during the study period	
Contact IRT system for randomization, subject number, and unique dose number allocation ‡	X	
Vaccination	X	
Immediate surveillance (30 min)	X	
Provision of Memory Aid§	X	
Review of Memory Aid		X
Study active phase termination record		X
Reporting of SAEs (including AESIs) **	To be reported at any time during the study	
Collection of ILI symptoms through passive and active surveillance	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post-vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April of the following year, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October of the same year, subjects' parents/guardians will be contacted once a week.	
Collection of nasopharyngeal swabs for laboratory confirmation of influenza††	From D0 post-vaccination 1 until 30 April of the following year for NH subjects or until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or the following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset).	

Collection of ALRI, AOM, absenteeism, and health care information ‡‡	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7 days) following the start of ILI regardless of whether or not an NP swab is obtained.

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; TC, telephone call; V, visit.

* Targeted physical examination will be performed at V01.

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection

§Subject's parents / guardians will use this MA to collect information on medications, SAEs, AESIs, and ILI from V01 through approximately 6 to 7 months after vaccination in each season.

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

††Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination 1 and later (start date after D0).

‡‡Occurrences of any of the following in association with any protocol-defined ILI on or after D0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table of Study Procedures 4 (previously influenza unvaccinated subjects 6 months through 35 months of age)

Phase III Study, 2 Visits, 1 Telephone Call, 2 Vaccinations, approximately 7 months' Duration per Subject per Study Year

Visit/Contact	**V01**	**V02**	**Follow-up Telephone Call**
Study timelines (days)	D0	D28	D208 (180+14 days after V02) or the end of influenza season if later than D208
Time windows (days)		+7	+14
Informed consent form signed and dated	X		
Inclusion / exclusion criteria	X		
Physical examination*	X	X	
Collection of demographic data	X		
Medical history†	X		
History of seasonal influenza vaccination	X		
Collection of concomitant medications	At any time during the study period		
Contact IRT system for randomization, subject number, and unique dose number allocation‡	X		
Temporary and definitive contraindications		X	
IRT Contact for allocation of unique dose number		X	
Vaccination	X	X	
Immediate surveillance (30 min)	X	X	
Provision of Memory Aid§	X		
Review of Memory Aid		X	X
Study active phase termination record			X
Reporting of SAEs (including AESIs)**	To be reported at any time during the study		
Collection of ILI symptoms through passive and active surveillance	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post-vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October, subjects' parents/guardians will be contacted once a week.		

Collection of nasopharyngeal swabs for laboratory confirmation of influenza††	From D0 post-vaccination 1 until 30 April of the following year for NH subjects and until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset).
Collection of ALRI, AOM, absenteeism, and health care information‡‡	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7 d) following the start of ILI regardless of whether or not an NP swab is obtained.

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; TC, telephone call; V, visit.

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

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ IRT will also be used to randomly select subjects to participate in the immunogenicity subset

§ Subject's parents / guardians will use this MA to collect information on medications, ILI, SAEs and AESIs from V01 through approximately 6 to 7 months after vaccination in each season.

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

†† Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination 1 and later (start date after D0).

‡‡ Occurrences of any of the following in association with any protocol-defined ILI on or after Day 0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table of Study Procedures 5 (previously influenza vaccinated subjects in the Expanded safety analysis set [ESafAS] with or without inclusion in the Immunogenicity Subset)

Phase III Study, 2 Visits, 1 Telephone Calls, 1 Vaccination, 2 blood samples, approximately 7 months' Duration per Subject per Study Year

Visit/Contact	**V01**	**V02**	**Follow-up Telephone Call**
Study timelines (days)	D0	D28	D180 (180 +14 after V01) or the end of influenza season if later than D180
Time windows (days)		+7	+14
Informed consent form signed and dated	X		
Inclusion / exclusion criteria	X		
Physical examination*	X	X	
Collection of demographic data	X		
Medical history†	X		
History of seasonal influenza vaccination	X		
Collection of concomitant medications	At any time during the study period		
Contact IRT system for randomization, subject number, and unique dose number allocation‡	X		
Blood sampling (BL) for immunogenicity subset only, 5 mL	BL0001§	BL0002	
Vaccination	X		
Immediate surveillance (30 min)	X		
DC provided**	X		
DC reviewed & collected		X	
Reporting of solicited injection site and systemic reactions (for 7 days after vaccination)	X		
Collection of unsolicited adverse events (for 28 days after vaccination)	X		
Provision of Memory Aid††		X	
Review of Memory Aid			X
Study active phase termination record			X
Reporting of serious adverse events (SAEs) (including AESIs) ‡‡	To be reported at any time during the study		

Collection of ILI symptoms through passive and active surveillance§§	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post-vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October, subjects' parents/guardians will be contacted once a week. *Excluding the Season 3 Re-vaccination Cohort.*
Collection of nasopharyngeal swabs for laboratory confirmation of influenza***	From D0 post-vaccination until 30 April of the following year for NH subjects and until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset). *Excluding the Season 3 Re-vaccination Cohort.*
Collection of ALRI, AOM, absenteeism, and health care information†††	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7 d) following the start of ILI regardless of whether or not an NP swab is obtained. *Excluding the Season 3 Re-vaccination Cohort.*

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; BL, blood sampling; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; V, visit.

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

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection. IRT will also be used to randomly select subjects to participate in the immunogenicity subset

§ Blood sampling to occur prior to vaccination.

** Subjects / parents / guardians will use the diary cards to record information about solicited reactions, unsolicited AEs, SAEs, AESIs, ILI symptoms after each vaccination (from D0 to D7) and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02.

††Subjects / parents / guardians will use this MA to collect information on SAEs, AESIs, and ILI from V02 to the end of the 6-month safety follow-up period.

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

§§ The subset of approximately [redacted] subjects from Season 1 (2022-2023 NH) who are in the Immunogenicity Subset and who will be re-enrolled and re-randomized in Season 3 will not participate in collection of ILI symptoms through passive and active surveillance in Season 3 (NH).

***Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination and later (start date after D0).

†††Occurrences of any of the following in association with any protocol-defined ILI on or after Day 0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table of Study Procedures 6 (previously influenza unvaccinated subjects the Expanded safety analysis set [ESafAS] with or without inclusion in the Immunogenicity Subset)

Phase III Study, 3 Visits, 1 Telephone Call, 2 Vaccinations, 2 blood samples, approximately 7 months' Duration per Subject per Study Year

Visit/Contact	**V01**	**V02**	**V03**	**Follow-up Telephone Call**
Study timelines (days)	D0	D28	28 days after V02	D208 (180 +14 days after V02) or at the end of influenza season if later than D208
Time windows (days)		+7	+7	+14
Informed consent form signed and dated	X			
Inclusion / exclusion criteria	X			
Physical examination*	X	X		
Collection of demographic data	X			
Medical history†	X			
History of seasonal influenza vaccination	X			
Collection of concomitant medications	At any time during the study period			
Contact IRT system for randomization, subject number, and unique dose number allocation‡	X			
IRT Contact for allocation of unique dose number		X		
Temporary and definitive contraindications		X		
Blood sampling (BL) for immunogenicity subset only, 5 mL	BL0001§		BL0002	
Vaccination	X	X		
Immediate surveillance (30 min)	X	X		
DC provided**	DC1	DC2		
DC reviewed & collected		DC1	DC2	
Reporting of solicited injection site and systemic reactions (for 7 days after vaccination)	X	X		
Collection of unsolicited adverse events (for 28 days after vaccination)	X			
Provision of Memory Aid††			X	
Review of Memory Aid				X
Study active phase termination record				X

Reporting of serious adverse events (SAEs) (including AESIs) ‡‡	To be reported at any time during the study
Collection of ILI symptoms through passive and active surveillance§§	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post-vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October, subjects' parents/guardians will be contacted once a week. *Excluding the Season 3 Re-vaccination Cohort.*
Collection of nasopharyngeal swabs for laboratory confirmation of influenza***	From D0 post-vaccination until 30 April of the following year for NH subjects and until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset). *Excluding the Season 3 Re-vaccination Cohort.*
Collection of ALRI, AOM, absenteeism, and health care information†††	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7 d) following the start of ILI regardless of whether or not an NP swab is obtained. *Excluding the Season 3 Re-vaccination Cohort.*

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; BL, blood sampling; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; V, visit.

* Targeted physical examination will be performed at V01. Targeted physical examination may also be performed at V02 and V03, as necessary.

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ IRT will also be used to randomly select subjects to participate in the immunogenicity subset

§ Blood sampling to occur prior to vaccination.

** Subjects / parents / guardians will use the diary cards to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs after each vaccination (from D0 to D7) and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02 and D36 to V03.

††Subjects / parents / guardians will use this MA to collect information on SAEs, AESIs, and ILI from V03 to the end of the 6-month safety follow-up period.

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

§§ The subset of approximately [redacted] subjects from Season 1 (2022-2023 NH) who are in the Immunogenicity Subset and who will be re-enrolled and re-randomized in Season 3 will not participate in collection of ILI symptoms through passive and active surveillance in Season 3 (NH).

***Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination 1 and later (start date after D0).

†††Occurrences of any of the following in association with any protocol-defined ILI on or after Day 0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table of Study Procedures 7

Follow-up of ILI

Days After protocol-defined ILI Onset	**D0*- D6**	**D0 – D6**	**D30** (+ 7 d) †
Contact type	Telephone Call	Visit	Telephone Call
Verify information on respiratory illnesses, and schedule appointment for an NP swab within 7 days of illness start date	X		
Remind subject to complete Memory Aid or Diary Card	X		
Collection of NP swab		X	
Collection of ALRI, AOM, absenteeism, and health care information	X	X	X
Collection of information on protocol-defined ILI symptoms ‡	X	X	X

* Day 0 (protocol-defined ILI Start Date) refers to the first day of fever. The end of an ILI episode is considered as the last day of fever ≥ 38°C. An interval of 2 days will have to have passed after the end of an ILI episode to be consider a new ILI episode.

† The 7-day window allows provision to complete the telephone call. The data collected are inclusive from Day 0 through Day 30 of protocol-defined ILI; information > 30 days from protocol-defined ILI onset does not need to be collected.

‡ During collection of information on protocol-defined ILI symptoms, the presence, or not, of concurrent ILI symptoms (ie, cough, wheezing, difficulty breathing, nasal congestion, rhinorrhea, sore throat, pharyngitis, otitis, vomiting, diarrhea, chills [shivering], tiredness [fatigue], headache, or myalgia [muscle aches])

Note: *The subset of approximately [redacted] subjects from Season 1 (2022-2023 NH) who are in the Immunogenicity Subset and who will be re-enrolled and re-randomized in Season 3 will not participate in collection of ILI symptoms through passive and active surveillance in Season 3 (NH).*

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALRI	acute lower respiratory infection
AOM	acute otitis media
AR	adverse reaction
CBER	Center for Biologics Evaluation and research
CDC	Centers for Disease Control and Prevention
CDM	Clinical Data Management
COVID-19	Coronavirus Disease 2019
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
EDC	electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELLA	enzyme-linked lectin assay
EMA	European Medicines Agency
ESafAS	Expanded safety analysis set
ESDR	Early safety data review
FASE	full analysis set for efficacy
FASI	full analysis set for immunogenicity
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré Syndrome
GCDSE-V	Global Clinical Development Strategy Expert – Vaccines
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	Geometric mean titer
GPV	Global Pharmacovigilance
GSK	Glaxo Smith Kline
HAI	Hemagglutination inhibition
IAS	immunogenicity analysis set
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILI	Influenza-like illness
IME	important medical event
IND	investigational new drug (application)

IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
MA	Memory aid
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NH	Northern Hemisphere
NP	Nasopharyngeal
PCR	Polymerase chain reaction
PPASE	per-protocol analysis set for efficacy
PPASI	per-protocol analysis set for immunogenicity
QIV	Quadrivalent influenza vaccine
R&D GO SML	Research and Development Global Operations Sample Management and Logistics
RBC	Red blood cell
RMO	Responsible Medical Officer
SAE	serious adverse event
SafAS	safety analysis set
SAP	Statistical Analysis Plan
SD	Standard-dose
SH	Southern Hemisphere
SMT	Safety management team
SN	seroneutralization
TIV	Trivalent influenza vaccine
TMF	trial master file
ULOQ	upper limit of quantitation
UTM	universal transport medium
WHO	World Health Organization

1 Introduction

1.1 Background

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. The virus is transmitted easily from person to person via droplets and small particles produced when infected people cough or sneeze. Members of high-risk groups, such as infants and younger children as well as children with underlying medical conditions, are at increased risk of influenza and its complications. Complications in the pediatric population include secondary bacterial pneumonia, acute otitis media, bronchitis, febrile seizures, Reye's syndrome, myositis, neurologic conditions, and exacerbations of underlying conditions (1) (2) (3). One study assessing the impact of influenza infection on young children, their family, and the health care system found that 28.6% of children with influenza had a secondary complication (pneumonia/chest infection, febrile convulsion, otitis media, croup), 40.9% were prescribed antibiotics, 65.4% of children missed school/day care, and 53.4% of parents missed work (4).

In adults, influenza is typically characterized by the rapid onset of fever, myalgia, sore throat, and non-productive cough, and can also cause severe malaise lasting for several days. The clinical manifestations in children, especially in young children less than 5 years of age, are less characteristic and may be more diverse than the clinical symptoms seen in adults (2). Besides symptoms of non-productive cough, nasal congestion, rhinitis, and sore throat, gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain can occur for 10–30% of children with influenza (5) (6).

The burden of influenza disease has been estimated in several modeling studies. In a 2018 study, Iuliano et al. estimated the number of global annual influenza-associated respiratory deaths using country-specific influenza-associated excess respiratory mortality estimates from 1999–2015 and reported that 9,243 to 105,690 influenza-associated respiratory deaths occur in children younger than 5 years each year (7). Matias et al. investigated the average seasonal burden of influenza-attributable hospitalizations in the US from 1997 to 2009 and found that children 0-4 and 5-17 years of age were estimated to have an annual mean rate of 128 and 20, respectively, per 100,000 population (8). About half of the cases in children were due to influenza A infections and the other half due to influenza B infections.

Vaccination currently represents the most effective medical intervention against influenza and its severe complications. Thus, the World Health Organization (WHO) recommends that people who are most at risk for severe seasonal influenza, including children less than 5 years of age (9) (10), should receive an annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (11) (12). The effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age and immune competence of the vaccine recipient. Infants and young children remain at increased risk for influenza because of their maturing immune system and lack of prior exposure and thus lack of immunity. Furthermore, during 4 recent influenza seasons in the United States of America (US 2015-2016, 2016-2017, 2017-2018, 2018-2019 seasons), vaccine effectiveness in children 6 months to 8 years of age was 51%, 57%, 68%, and 48%, respectively (13). Thus, there is further

room for improvement in increasing the vaccine efficacy against influenza in the pediatric population.

Standard-dose (SD) influenza vaccines contain 15 µg hemagglutinin (HA) of each of the 4 virus strains recommended by the WHO for use in that hemisphere's upcoming influenza season, for a total of 60 µg of HA antigen per dose. The immune response to an SD influenza vaccine is lower in adults 65 years of age and older than in younger healthy adults (14). Thus, Fluzone® High-Dose influenza vaccine (high-dose trivalent influenza vaccine [TIV-HD]), containing 60 µg HA of each of 3 virus strains (4 times more antigen than standard-dose trivalent influenza vaccine [TIV-SD], for a total of 180 µg of HA antigen per dose) was developed by Sanofi Pasteur.

1.2 Background of the Investigational Product

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

A Phase III immunogenicity bridging study (QHD00013) was conducted in adults 65 years of age and older during the 2017-2018 influenza season and demonstrated the non-inferiority of the hemagglutination inhibition (HAI) antibody responses between QIV-HD and TIV-HD (15). Furthermore, QHD00013 demonstrated that the addition of a 2nd B strain to TIV-HD did not interfere with the immune response to the other vaccine components or adversely affect the safety profile of the vaccine; in order to demonstrate the added value of the 2nd B strain in QIV-HD, superiority of antibody responses to each B strain in QIV-HD compared with the TIV-HD that does not contain the corresponding B strain was also demonstrated. Based on the comparability of responses to the TIV and QIV formulations, QIV-HD is expected to be more efficacious than SD influenza vaccines in preventing influenza disease in adults 60 years of age and older.

In November 2019, QIV-HD was licensed in the US for adults 65 years of age and older. QIV-HD has since been approved in more than 30 countries. Recently QIV-HD has been approved outside the US in adults aged 60 years and older.

Recognizing a similar need to improve influenza vaccine performance in infants and young children, the impact of increasing the antigen dose on immune responses has recently been evaluated with SD vaccines. Several studies have examined the safety and immunogenicity of the pediatric half-dose (0.25 mL) versus full-dose (0.5 mL) standard dose influenza vaccine (16) (17) (18), and an increase in immunogenicity has been observed, while maintaining safety and tolerability. Thus, QIV-HD, which contains 4 times as much HA per strain per dose as compared to the full-dose (0.5 mL) standard dose influenza vaccine, may demonstrate a further increase in immunogenicity which could lead to better protection against influenza and its complications.

In order to assess the safety and immunogenicity of QIV-HD compared with QIV-SD, a Phase II study in children 6 months through 17 years of age (QHD04) was conducted in the US and Canada during the 2018-2019 influenza season. Three different dose formulations (30 µg, 45 µg,

and 60 µg of HA/strain/dose) of QIV-HD were evaluated in this dose exploration study to determine the appropriate QIV-HD dose in children for Phase III studies. Two comparator vaccines were used in the study: a QIV-SD vaccine (GSK's Fluarix® Quadrivalent) at US sites and an adjuvanted trivalent influenza vaccine (Seqirus' Fluad®) at Canadian sites. The QHD04 study results showed that of the 3 dose formulations of QIV-HD studied, when compared to QIV-SD, the 60 µg HA/strain/dose QIV-HD formulation generated higher immune responses as assessed by HAI geometric mean titer (GMT), seroconversion rates, and seroneutralization (SN) GMT. In all 4 age groups assessed, the highest GMT ratios were seen in children 6 through 35 months of age who received the QIV-HD 60 µg dose formulation versus children who received QIV-SD. No safety issues were observed with QIV-HD administered in children 6 months through 17 years of age. Slightly higher injection site reactogenicity was seen in the QIV-HD group compared with QIV-SD group, but systemic reactogenicity was similar between groups. Similar injection site and systemic reactogenicity profiles were seen between the QIV-HD and adjuvanted TIV groups. Reactogenicity was also similar between all 3 QIV-HD dose formulations (30 µg, 45 µg, and 60 µg of HA/strain/dose) evaluated. In children who received 2 doses of QIV-HD 28 days apart, no trend towards increased reactogenicity was seen between the 1st and 2nd dose administered.

Despite the limitations of the sample size, the safety profile of QIV-HD and the higher immune responses support a pediatric dose selection of 60 µg HA/strain/dose, the same dose indicated for adults 60 years of age and older, as the most appropriate dose to evaluate in a Phase III efficacy study in order to provide the highest probability of success in demonstrating superior protection against influenza when compared with a licensed standard dose influenza vaccine.

Thus, the goal of this Phase III study is to demonstrate the safety, superior efficacy, and superior immunogenicity of QIV-HD compared with a QIV-SD (Glaxo Smith Kline's [GSK's] Fluarix® Quadrivalent or other tradenames) in children 6 through 35 months of age.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects enrolled in Study QHD00014 will receive an influenza vaccine which will be either the investigational QIV-HD, or the licensed comparator vaccine, QIV-SD. Therefore, they will be vaccinated against the influenza viruses recommended by the WHO for the 2020-2021 Northern Hemisphere (NH) season if they were in the sentinel cohort, or if in the main cohort, they will be vaccinated with the 2022-2023 or 2023-2024 NH influenza seasons or 2023 Southern Hemisphere (SH) influenza season depending on which country they are enrolled in. These children may be protected against those strains and may be less likely to catch influenza or develop complications during the respective influenza seasons.

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 (ie, 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 (eg, fainting). If pressure is not applied long enough to the venipuncture site, bruising due to bleeding beneath the skin may occur. Infection at the site of needle insertion could theoretically occur but is exceedingly rare when the standard sterile technique is utilized.

Possible Reactions to Vaccination

The most frequent side effect of influenza vaccination is pain or tenderness at the injection site that usually resolves within 3 days. Injection site reactions are generally mild.

Systemic findings such as crying, irritability, or fever (young children); malaise or myalgia (older children); and other systemic symptoms can occur following vaccination and most often affect persons who have had no prior exposure to the vaccine antigens (eg, young children) (19).

These reactions usually begin 6 to 12 hours after vaccination and usually resolve within 3 days.

The following additional adverse events have been spontaneously reported during the postmarketing use of TIV-HD in adults, and may occur in people receiving QIV-HD

Blood and Lymphatic System Disorders: Thrombocytopenia, lymphadenopathy

Immune System Disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)

Eye Disorders: Ocular hyperemia

Nervous System Disorders: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), paresthesia

Vascular Disorders: Vasculitis, vasodilatation

Gastrointestinal Disorders: Vomiting

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, wheezing, throat tightness, oropharyngeal pain, and rhinorrhea

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome

General Disorders and Administration Site Conditions: Asthenia, chest pain

Prior to any vaccination, all known precautions should be taken to prevent hypersensitivity reactions. This includes a review of the patient's prior vaccination history with respect to possible hypersensitivity to the vaccine or similar vaccines.
Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions (eg, anaphylaxis).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Cases of demyelinating disorders (eg, incident multiple sclerosis in adults, acute disseminated encephalomyelitis, transverse myelitis), have been reported following influenza vaccines,

although the National Academy of Medicine (formerly, Institute of Medicine) concluded that the evidence is inadequate to accept or reject a causal relationship (20).

In a study of the 2010–2011 influenza season, the CDC found that there was a risk of fever-associated seizure (convulsion) occurring on the day of influenza vaccination and for 1 day after vaccination in children 6 months through 4 years of age. The risk was higher among children who received concomitant inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine and peaked at approximately age 16 months. The magnitude of the increased risk was less than 1 episode per 1000 immunized children. A similar risk was found during the 2011–2012 season (in which the formulation of the influenza vaccine used was the same as that used during the 2010–2011 season); however, an increased risk for febrile seizures following influenza vaccination was not observed during the 2012–2013 influenza season. No increased risk was found for children older than 4 years of age. After taking into consideration the benefits and risks of vaccination, no policy change was recommended for use of inactivated influenza vaccine or 13-valent pneumococcal conjugate vaccine (21).

The potential risks listed here are not exhaustive; refer to the US package insert (Fluarix® Quadrivalent) or investigator brochure of the marketed vaccines for additional information regarding potential risks (22) (23).

1.4 Rationale for the Study

While influenza affects all age groups, infants and young children remain at increased risk for influenza because of their maturing immune system, lack of prior exposure to influenza virus, and thus limited immunity against influenza viruses. Although standard dose influenza vaccines are effective, there is still room for further improvement in the currently licensed influenza vaccines' ability to protect children from influenza and its complications. Therefore, following the successful approach taken for adults 60 years of age and older, Sanofi Pasteur is evaluating whether an increased antigen dose as contained in the QIV-HD vaccine can provide increased efficacy against influenza over the existing standard dose influenza vaccines.

In the absence of a proven quantitative correlate of protection in the pediatric population for influenza vaccines, an efficacy study is recognized as the gold standard to demonstrate vaccine benefit (24). Based on the results of the Phase II QHD04 study, the Phase III QHD00014 study is designed to evaluate the relative efficacy (for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type), the superior immunogenicity, and the safety of QIV-HD 60 µg HA/strain/dose formulation versus a QIV-SD (Fluarix® Quadrivalent vaccine) in approximately 13,320 children 6 through 35 months of age.

2 Study Objectives

2.1 Primary Objective

Efficacy

To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type.

The endpoint for the primary objective is presented in Section 9.2

2.2 Secondary Objectives

Confirmatory Objectives

- To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type using a more stringent threshold
- To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine
- To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 23 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type

Other Secondary Objectives are for descriptive assessment

Efficacy

To assess the relative clinical efficacy of QIV-HD compared to QIV-SD in subjects for the prevention of:

- laboratory-confirmed influenza illness caused by any influenza A or B type according to previous influenza vaccination status in prior seasons
- laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine according to previous vaccination status
- laboratory-confirmed influenza illness associated with acute otitis media (AOM based on clinical diagnosis) caused by any influenza A or B type
- laboratory-confirmed influenza illness associated with AOM based on clinical diagnosis caused by viral strains similar to those contained in the vaccine
- laboratory-confirmed influenza illness associated with ALRI based on a clinical and/or x-ray diagnosis caused by any influenza A or B type
- laboratory-confirmed influenza illness associated with ALRI based on a clinical and/or x-ray diagnosis caused by viral strains similar to those contained in the vaccine
- PCR-confirmed influenza illness caused by any influenza A or B type

- PCR-confirmed influenza illness caused by viral strains similar to those contained in the vaccine
- culture-confirmed influenza illness caused by any influenza A or B type
- culture-confirmed influenza illness caused viral strains similar to those contained in the vaccine
- laboratory-confirmed influenza illness associated with hospitalization and caused by any influenza A or B type
- laboratory-confirmed influenza illness associated with hospitalization and caused by viral strains similar to those contained in the vaccine

Immunogenicity

- To compare the HAI immune response of QIV-HD to QIV-SD in subjects 6 months through 35 months of age
- To describe the HAI immune response induced by each vaccine against the 4 vaccine strains and according to the different strain formulations used in each of the study influenza seasons
- To describe the SN immune response induced by QIV-HD or QIV-SD against the 4 QIV-HD vaccine strains in a randomized subset of subjects
- To describe the anti-neuraminidase (NA) immune response induced by QIV-HD or QIV-SD in a randomized subset of subjects

Re-vaccination Response

To describe the immune response (HAI method) to vaccination in Season 3 (NH) among subjects re-enrolled from Season 1 (NH) to Season 3 (NH), according to the vaccines received in both Season 1 (NH) and Season 3 (NH)

Safety

- To describe the safety profile (injection site reactions and systemic events) of each vaccine during the 28 days following each vaccination for the ESafAS (all subjects from Sentinel Safety Cohort, all subjects from Season 1, and a subset of subjects from Seasons 2 and 3)
- To describe all SAEs (including AESIs) up to at least 180 days after the last vaccination in all subjects

The endpoints for the secondary objectives are presented in Section 9.3

2.3 Observational Objectives

Efficacy

The following objectives will be assessed for laboratory-confirmed influenza illness due to any influenza A or B type, and due to viral strains similar to those contained in the vaccine. To assess the relative clinical efficacy of QIV-HD compared to QIV-SD in subjects 6 months through 35 months of age for the prevention of:

- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination caused by each circulating influenza virus A subtype and B lineage

- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination by age subgroup
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination by season
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination in previously unvaccinated subjects after 1st injection
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination in previously unvaccinated subjects between 1st and 2nd injections
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination and over the first 3 months after vaccination
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination according to other ILI definitions (modified CDC-defined ILI)

Influenza-associated Events/Health care utilization

- To describe in each vaccine group the occurrence of AOM (based on clinical and/or x-ray diagnosis), within 30 days after the onset of a laboratory-confirmed ILI
- To describe in each vaccine group the occurrence of AOM (based on clinical and/or x-ray diagnosis), within 30 days after the onset of any ILI
- To describe in each vaccine group the occurrence of ALRI (based on clinical and/or x-ray diagnosis), within 30 days after the onset of a laboratory-confirmed ILI
- To describe in each vaccine group the occurrence of ALRI (based on clinical and/or x-ray diagnosis), within 30 days after the onset of any ILI
- To describe in each vaccine group the occurrence, duration, and intensity of ILI symptoms occurring within 30 days after the onset of a laboratory-confirmed ILI
- To describe in each vaccine group the occurrence, duration, and intensity of ILI symptoms occurring within 30 days after the onset of ILI
- To describe in each vaccine group the use of antibiotics and antivirals that are associated with cases of laboratory-confirmed ILI, within 30 days after the onset of the ILI
- To describe in each vaccine group the use of antibiotics and antivirals that are associated with any ILI, within 30 days after the onset of the ILI
- To describe in each vaccine group hospitalizations that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group hospitalizations that are associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group emergency room visits that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group emergency room visits that are associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group non-routine medical office visits (including urgent care visits) that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI

- To describe in each vaccine group non-routine medical office visits (including urgent care visits) that are associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group medication use that is associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group medication use that is associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group absenteeism (Parent(s) / guardian's absenteeism due to child sick days) that is associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group absenteeism (Parent(s) / guardian's absenteeism due to child sick days) that is associated with any ILI, within 30 days after onset of the ILI

Correlates of Protection Objective

To assess the association of HAI titers to the 4 vaccine strains with the occurrence of laboratory-confirmed ILI of any influenza A or B type, or of viral strains similar to those contained in the vaccine.

Antibody persistence

To describe the persistence of immune response 1 year after vaccination among subjects from Season 1 (NH) who are re-enrolled for Season 3 (NH) according to the vaccine received in Season 1 (NH).

The endpoints for the observational objectives are presented in Section 9.4.

3 Investigators and Study Organization

This study will be conducted in approximately 200 centers in approximately 9 countries in the Northern Hemisphere and approximately 6 countries in the Southern Hemisphere. There will be 1 global Coordinating Investigator and Coordinating Investigators in countries where required. Details of the study centers, the Investigators at each center, and the Coordinating Investigators are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal safety management team (SMT) will perform blinded analyses of safety data throughout the study at pre-specified time points as described in the SMT Charter. Ad hoc analysis can be performed by the SMT at any time during the conduct of the study if necessary.

An Independent Data Monitoring Committee (IDMC), composed of members independent from the Sponsor, Coordinating Investigator, and Investigators, will be established to review early safety data, influenza cases, and efficacy. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the IDMC Charter.

The Sponsor's Responsible Medical Officer (the RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted] MD, Global Clinical Development Strategy Expert – Vaccines (GCDSE-V).

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational sites and before the inclusion of the first subject, this protocol, informed consent forms (ICFs), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

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

The Investigator or Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the study that are related to the product administered or not related to the product will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

Note: The Sentinel Safety Cohort and associated study procedures were completed prior to Amendment 2 of this Protocol.

5.1.1 Study Design

QHD00014 is planned to be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in 13,320 (100 subjects will be in an open-label Sentinel Safety Cohort with no comparator vaccine while 13,220 will be randomized and double-blinded) children 6 months through 35 months of age to evaluate the relative efficacy, immunogenicity, and safety of QIV-HD administered by intramuscular (IM) route versus a QIV-SD vaccine.

QHD00014 is planned to be conducted during the 2020-2021 NH influenza season (Sentinel Safety Cohort), the 2022-2023 NH influenza season (Season 1), the 2023 SH influenza season (Season 2), and the 2023-2024 NH influenza season (Season 3). During Seasons 1 through 3, subjects will be randomized in a 1:1 ratio to receive either QIV-HD or QIV-SD prior to the start of the influenza season. Subjects will receive either 1 or 2 doses of study vaccine depending on whether they were previously vaccinated against influenza or previously unvaccinated against influenza, respectively.

During the 2020-2021 NH influenza season, a Sentinel Safety Cohort of 100 US subjects will be enrolled in an uncontrolled, open-label design without a comparator vaccine to evaluate the safety of QIV-HD prior to the enrollment of additional subjects. These subjects will not provide blood

samples and will not be followed for ILI surveillance. Following the enrollment of the Sentinel Safety Cohort and prior to the start of Season 1 (2022-2023 NH), an IDMC will review the safety of this sentinel cohort. If the IDMC determines there is no significant safety issue during their review of the Sentinel Safety Cohort's data, approximately[redacted] subjects will subsequently be allowed to be enrolled in Season 1.

The sample size in the subsequent seasons may be adjusted to maintain the likelihood of achieving the overall expected number of cases for the primary endpoint. The current estimated sample size for the efficacy cohort in Seasons 2 and 3 is[redacted]subjects ([redacted] in the SH and[redacted] in the NH) and an additional[redacted] subjects from Season 1's Immunogenicity Subset will be re-enrolled in Season 3 but will not be included in efficacy analysis for Season 3, for a total of 13,320 subjects in the entire study. Sentinel Safety Cohort subjects will be excluded from reenrollment in any subsequent seasons.

During each influenza season, a subset of subjects (hereafter referred to as the Immunogenicity Subset) will be randomly selected using Interactive Response Technology (IRT) across participating sites to provide blood samples for immunogenicity testing:

Total subjects with blood draws = approximately[redacted] subjects

- Season 1, NH = [redacted] subjects
- Season 2, SH =[redacted] of randomized subjects (approximately[redacted]subjects)
- Season 3, NH =[redacted] of randomized subjects (approximately[redacted] subjects) and[redacted] re-enrolled subjects who were part of Season 1*

An Expanded safety analysis set (ESafAS) will also be selected for collection of reactogenicity and unsolicited adverse events as follows:

Total subjects in ESafAS =[redacted] subjects

- Sentinel Safety Cohort (2020-2021 NH) = 100 subjects†
- Season 1, NH =[redacted] subjects (all subjects)†
- Season 2, SH =[redacted] of randomized subjects (approximately[redacted] subjects)
- Season 3, NH =[redacted] of randomized subjects (approximately[redacted] subjects) and[redacted] re-enrolled subjects from Season 1

*A subset of approximately[redacted] subjects from Season 1 (2022-2023 NH) who are in the Immunogenicity Subset will be re-enrolled and re-randomized in Season 3 (hereafter referred as the Re-vaccination Cohort) and included in the ESafAS and the Immunogenicity Subset; these [redacted] subjects will not be followed for ILI surveillance during their participation in Season 3.

†Note: For the Sentinel Safety Cohort season and Season 1: all enrolled subjects will be included in the ESafAS.

For Seasons 2 and 3: the Immunogenicity Subset and the ESafAS will include the same subjects.

5.1.2 Justification of the Study Design

Justification for the age range and correlate of protection evaluation

Health authorities such as the US Food and Drug Administration and European Medicines Agency (EMA) have accepted non-inferior immunogenicity studies in support of licensure of new influenza vaccine. Non-inferior immunogenicity is demonstrated by comparing the new SD influenza vaccine to a licensed SD influenza vaccine, for which there are existing efficacy data, through HAI titers and seroconversion rates against the strains contained in the vaccines. However, demonstrating superior immunogenicity for QIV-HD is not sufficient evidence for demonstrating superior efficacy, therefore a relative efficacy study needs to be conducted to demonstrate superior efficacy.

Table 5.1 shows that in the Phase II QHD04 study, children 6 through 35 months of age vaccinated with QIV-HD 60 µg HA/strain/dose had the highest HAI GMT ratios (post-vaccination GMTs of QIV-HD/QIV-SD) compared to the other 2 dose formulations evaluated (30 and 45 µg HA/strain/dose). Results of the seroneutralization assay also showed that the QIV-HD 60µg HA/strain/dose formulation generated the highest geometric mean fold rises than the other 2 QIV-HD dose formulations evaluated. Thus, the QIV-HD dose formulation of 60 µg HA/strain/dose was chosen to be evaluated in the Phase III QIV-HD studies in children.

Table 5.1: QHD04 study: HAI GMT ratios (QIV-HD/QIV-SD)

Strain	Children 6 months through 35 months of age					
	QIV-HD 30µg		QIV-HD 45µg		QIV-HD 60µg	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)	GMT ratio	(95% CI)
A/H1N1	2.13	(0.83 ; 5.47)	1.75	(0.69 ; 4.38)	4.24	(2.05 ; 8.76)
A/H3N2	0.93	(0.40 ; 2.15)	1.49	(0.61 ; 3.60)	3.14	(1.53 ; 6.44)
B/Victoria	1.23	(0.58 ; 2.62)	1.38	(0.64 ; 2.98)	2.04	(1.10 ; 3.77)
B/Yamagata	1.10	(0.55 ; 2.22)	1.18	(0.55 ; 2.54)	1.92	(1.08 ; 3.41)

QHD04 also showed that children 6 through 35 months of age vaccinated with QIV-HD 60 µg HA/strain/dose had the highest GMT ratios (post-vaccination GMTs of QIV-HD/QIV-SD) compared to the other 3 age ranges evaluated (3 through 4 years, 5 through 8 years, and 9 through 17 years of age). Thus, the relative efficacy study QHD00014 will be conducted in children 6 through 35 months of age as this age range is the most likely age group to be able to demonstrate superior relative efficacy against a QIV-SD. These children are also the most vulnerable children to influenza and its complications given their immature immune system and naïve exposure to influenza.

Justification for the number of influenza seasons evaluated

QHD00014 is planned to be conducted during the 2020-2021 NH influenza season (Sentinel Safety Cohort), the 2022-2023 NH influenza season, the 2023 SH influenza season, and the 2023-2024 NH influenza season. Evaluating the relative efficacy over multiple seasons will allow for the assessment of the vaccine efficacy across different influenza seasons, different recommended strains each season, and potentially matched or mismatched influenza strains.

Justification for the choice of comparator control vaccine

The QHD00014 study design is a relative efficacy study which will demonstrate the superior efficacy of QIV-HD compared to a licensed standard dose influenza vaccine. Thus, all children participating in the study will receive an influenza vaccine as per the WHO recommendation that children less than 5 years should receive an annual vaccination against influenza because influenza vaccines have been shown to be effective in reducing influenza-associated morbidity and mortality.

GSK's QIV-SD (Fluarix® Quadrivalent vaccine, or other tradenames) will be the comparator in the QHD00014 study. Fluarix Quadrivalent vaccine was chosen because it is licensed in children 6 months of age and older in more countries around the world compared with other standard dose influenza vaccines. This will allow for a single comparator QIV-SD to be used in all countries proposed for the study.

Justification for modified-double blind during the entire study

Since the QIV-HD dose volume of 0.7 mL is different than the QIV-SD comparator dose volume of 0.5 mL and the QIV-SD comparator will appear different, the QHD00014 study will be a modified double-blind study in which a designated unblinded administrator at each study site will know which vaccine has been administered. The Investigator/Sub-Investigator/staff involved in the safety assessment and influenza surveillance will be blinded in order to decrease the risk of potential bias in safety and efficacy assessment.

Since the study will be conducted over multiple NH influenza seasons, a cohort of [redacted] subjects who participated in Season 1 (2022-2023 NH) and were part of the Immunogenicity Subset may participate in Season 3 (2023-2024 NH), and the blind will be maintained throughout all seasons of the subject's participation. Subjects in the Sentinel Safety Cohort (2020-2021 NH) will not be re-enrolled in later seasons.

The Sentinel Safety Cohort of 100 subjects at the start of the study will not be blinded as all subjects in the Sentinel Safety Cohort will receive QIV-HD.

Justification of vaccination schedule

In order to maintain consistent vaccination schedule rules across all countries and sites for the classification of children considered previously influenza vaccinated and previously influenza unvaccinated, all global study sites will follow the US Advisory Committee on Immunization Practices recommendations for influenza vaccine (25).

- Previously unvaccinated subjects are defined as subjects who have not received at least 2 doses of seasonal influenza vaccine in prior influenza seasons. These subjects will receive 2 doses of study vaccine at least 28 days apart after enrolling in the study. Subjects who have received only one dose of any influenza vaccine in the past or subjects whose vaccination

history is unknown will also be considered as previously unvaccinated subjects when enrolling and receive 2 doses of study vaccine at least 28 days apart.

- Previously vaccinated subjects are defined as subjects who have received at least 2 doses of seasonal influenza vaccine in prior influenza seasons. These subjects will receive only 1 dose of study vaccine after enrolling in the study.

5.1.3 Study Plan

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

The study will span several influenza seasons in different countries and recruitment will encompass subjects who may receive 1 or 2 vaccinations and may provide blood draws defined according to the pursued objectives.

Vaccination

For the Sentinel Safety Cohort, eligible subjects will receive QIV-HD as follows:

- Subjects enrolled in the Sentinel Safety Cohort who were previously vaccinated against influenza will receive 1 dose of the QIV-HD on Day (D) 0, with no comparator vaccine.
- Subjects enrolled in the Sentinel Safety Cohort who were not previously been vaccinated against influenza will receive 2 doses of the QIV-HD with no comparator vaccine. Each dose will be administered 28 days apart (at D0 and D28).

For all other eligible subjects will be randomized to receive either QIV-HD or QIV-SD:

- Subjects previously vaccinated against influenza will receive 1 dose of the QIV-HD or the comparator vaccine on D0.
- Subjects who had not previously been vaccinated against influenza will receive 2 doses of the QIV-HD or the comparator vaccine. Each dose will be administered 28 days apart (at D0 and D28).

An unblinded administrator at each site will administer the vaccine.

Surveillance for Influenza-like illness (not applicable for Sentinel Safety Cohort or Re-vaccination Cohort):

Passive Surveillance: Following randomization and vaccinations, all subjects' parents/guardians (except those in the Sentinel Safety Cohort and the Re-vaccination Cohort) will be instructed to contact the site if the subject experiences symptoms of a protocol-defined ILI during the annual surveillance periods, from the 1st vaccination until 30 April of the following year for subjects in the NH or until 31 October of the same year for subjects in the SH.

Active Surveillance: During a period from the first vaccination until approximately 30 April for NH seasons or 31 October for SH seasons, subjects' parents and/or guardians will be contacted by telephone once a week.

Collection of nasopharyngeal (NP) swabs

During the period from D0 after vaccination (after the first vaccination in subjects receiving two doses of study vaccine) until 30 April of the following year for NH subjects or until 31 October of the same year for SH subjects, the site will arrange for an NP swab to be taken if the subject

experiences a new onset of fever concomitantly with one or more of the above-mentioned symptoms of protocol-defined ILI (that persists for or reoccurs after a period of at least 12 hours).

The NP swab will be obtained as soon as possible and no later than 7 days (between D0 and D6) from the onset of the ILI.

Reporting of events temporally associated with an ILI

In addition to obtaining an NP swab, the site will collect detailed information about the ILI, as well as information on occurrence of ALRI, otitis media, healthcare utilization events (hospitalizations, emergency room visits, and non-routine office visits [including urgent care visits]) and medication use (eg, antibiotics, antivirals).

In the event that an NP swab cannot be collected, the research site will still obtain the above information. All subjects' parents/guardians reporting a suspected ILI will have a 30-day follow-up telephone call.

Laboratory testing for the confirmation of influenza and determination of similarity to vaccine components

All NP specimens will be submitted for analysis by both culture and PCR, and a positive result on either test will be considered a laboratory-confirmed case of influenza.

Positive cultures or positive PCR samples will undergo additional testing (typing, subtyping, and strain identification, utilizing genetic sequencing) to determine if the virus detected is similar to any of those contained in the vaccine formulation for the respective season.

Note: Positive PCR samples that have negative culture results, or were unable to be expanded in culture, will not undergo additional testing.

Blood sampling

A subset of randomly selected subjects (Immunogenicity Subset) will provide 2 blood samples (5 mL each):

- Previously vaccinated subjects will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V02 (D28 [+7 days]) for HAI testing and potential seroneutralization (SN) and enzyme-linked lectin assay (ELLA) testing.
- Previously unvaccinated subjects will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (28 days after V02 [+7 days]) for HAI testing and potential SN and ELLA testing.

Note: the Re-vaccination Cohort will automatically be part of the Immunogenicity Subset

Collection of safety data

All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB) for subjects in the sentinel cohort and ESafAS and in the source documentation for all other subjects.

For subjects in the Sentinel Safety Cohort and Season 1 (NH), solicited reactions will be collected through day 7 after each vaccination, and unsolicited AEs will be collected through day 28 after each vaccination in all subjects. During study Seasons 2 (2023 SH) and 3 (2023-2024 NH),

solicited reactions and unsolicited AEs will only be collected for those in the ESafAS. Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected in all subjects throughout the study (D0 through approximately 6 to 7 months after vaccination in each season). AESIs will be captured as SAEs in this study. AESIs include GBS, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

Parents / guardians of subjects will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study.

Staff will review the safety data with subjects' parents / guardians at each visit. The IRT system will be used to randomly assign subjects to a study product and subsets and to assign subject numbers in each of the groups.

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

COVID-19 Risk Assessment

The QHD00014 study may be conducted during the ongoing outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the human population considered as pandemic by the WHO on 11 March 2020.

QIV-HD is an inactivated influenza vaccine and is not expected to cause immune suppression. Therefore, the risk that a subject in this study will contract Coronavirus Disease 2019 (COVID-19) solely due to the administration of the study vaccine will be similar to the risk that a person not participating in this study will contract COVID-19.

However, the risk of exposure to infected people cannot be completely excluded as the subjects in QHD00014 may be exposed to people and surfaces commuting to the study and in waiting rooms and exam rooms at the study sites.

COVID-19 Risk Mitigation

- Reevaluate the start of the study at a site or in a region as the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are evaluated by the study team.
- The number of on-site study visits has been decreased for the Sentinel Safety Cohort to reduce risk.
- Continued risk assessment by the Investigator and the Sponsor prior to each study visit and throughout each season of the study.

5.1.4 Visit Procedures

The visit procedures are described per group and correspond to the Table of Study Procedures. Note that all Visit 1 procedures are common until the randomization.

5.1.4.1 Visit Procedures for subjects in the Sentinel Safety Cohort only

Note: Visit procedures for the Sentinel Safety Cohort detailed in Section 5.1.4.1 were completed prior to Amendment 2 of this protocol.

Subjects in the Sentinel Safety Cohort will receive open-label QIV-HD, these visit procedures correspond to Tables of Study Procedures 1 and 2.

5.1.4.1.1 Visit Procedures for previously influenza vaccinated subjects in the Sentinel Safety Cohort

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

The Investigator or delegate will:

1) Give the subject's parent / guardian information about the study.
2) Obtain informed consent and answer any questions to ensure that the subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to allow their child to participate.
3) Date and sign the ICF after it has been signed and dated by the subject's parent / guardian. Retain the original and give a signed copy to the subject's parent / guardian.
4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through targeted physical examination per standard site-specific immunization practices (including recording temperature in source documents) and medical interview of the subject's parent / guardian. If the subject is not eligible, only the specific form entitled "Recruitment log" will state the subject identification, no CRB will be completed.
5) Collect relevant demographic information (eg, date of birth, sex, ethnicity, and race).
6) Obtain verbal information on medical history (including information on breastfeeding and gestational age) and collect information on any medications (see Section 6.6).
7) Obtain information on seasonal influenza vaccination history to determine if the subject is previously influenza vaccinated or previously influenza unvaccinated
8) Call the IRT for assignment of the 12-digit subject number and allocation of a dose number (see Section 6.4).
9) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate
10) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.
11) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
12) Give the subject's parent / guardian the Diary Card (DC) to record any injection site reactions and systemic AEs (including SAEs), and medications together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs.
13) Give the subject's parent / guardian a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement, and instructions on how to use them.

14) Remind the subject's parent / guardian to promptly notify the site in case of an SAE/AESI that may occur at any time during the study.

15) Schedule Telephone Call 1 (to occur 8 days after Visit 1).

16) Complete the relevant CRB forms for this visit.

Telephone Call 1 (Day 8+2): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day.

The Investigator or delegate will:

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's parent / guardian to do the following:
   - Complete the remaining pages of the DC and bring the completed diary to V02
   - Remind the subject's parent / guardian to promptly notify the site in case of an SAE/AESI that may occur at any time during the study.

3) Schedule Visit 2 (to occur 28 days after Visit 1) if not already done.

Visit 2 (Day 28+7): Collection of Safety Information

The Investigator or delegate will:

1) Review and collect the DC information with the subject's parent / guardian and clarify with the subject's parent / guardian, if required, any AEs, or SAEs that occurred since V01. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Collect information on any medications taken (see Section 6.6).

3) If deemed necessary, perform and document a targeted physical examination per standard site-specific immunization practices and record temperature in the source documents.

4) Provide the subjects' parent / guardian with a memory aid (MA) and review the directions for its use.

5) Remind the subject's parent / guardian to promptly notify the site in case of an SAE/AESI that may occur at any time during the study.

6) Schedule the 6-month safety follow-up phone call

7) Record all applicable information obtained into the CRB

8) Complete the active phase termination record of the CRB.

Telephone call 2 (180 [+14] days after Visit 1): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day.

The Investigator or delegate will:

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) Collect information on any medications taken during the study period
3) Record all applicable information obtained into the CRB

5.1.4.1.2 Visit Procedures for previously influenza unvaccinated subjects in the Sentinel Safety Cohort

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

The Investigator or delegate will:

1) Give the subject's parent / guardian information about the study.
2) Obtain informed consent and answer any questions to ensure that the subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to allow their child to participate.
3) Date and sign the ICF after it has been signed and dated by the subject's parent / guardian. Retain the original and give a signed copy to the subject's parent / guardian.
4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through targeted physical examination per standard site-specific immunization practices (including recording temperature in source documents) and medical interview of the subject's parent / guardian. If the subject is not eligible, only the specific form entitled "Recruitment log" will state the subject identification, no CRB will be completed.
5) Collect relevant demographic information (eg, date of birth, sex, ethnicity, and race).
6) Obtain verbal information on medical (including information on breastfeeding and gestational age) history and collect information on any medications (see Section 6.6).
7) Obtain information on seasonal influenza vaccination history to determine if the subject is previously influenza vaccinated or previously influenza unvaccinated
8) Call the IRT for assignment of the 12-digit subject number, , and allocation of a dose number (see Section 6.4).
9) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate.
10) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.
11) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
12) Give the subject's parent / guardian the Diary Card (DC1) to record any injection site reactions and systemic AEs (including SAEs), and medications, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs.
13) Give the subject's parent / guardian a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement, and instructions on how to use them.

14) Remind the subject's parent / guardian to promptly notify the site in case of an SAE/AESI that may occur at any time during the study.

15) Schedule Telephone Call 1 to occur 8 Days after Visit 1.

16) Complete the relevant CRB forms for this visit.

Telephone Call 1 (Day 8+2): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day.

The Investigator or delegate will:

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's parent / guardian to do the following:
   - Complete the remaining pages of the DC1 and bring the completed diary to V02
   - Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI that may occur at any time during the study.

3) Schedule Visit 2 (to occur 28 days after Visit 1) if not already done.

Visit 2 (Day 28+7): Dose Allocation, Vaccination, and Collection of Safety Information

The Investigator or delegate will:

1) Review and collect the DC1 information with the subject's parent / guardian and clarify with the subject's parent / guardian, if required, any AEs, or SAEs that occurred since V01. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Collect information on any medications taken during the study period.

3) If deemed necessary, perform and document a targeted physical examination per standard site-specific immunization practices and record temperature in the source documents.

4) Review temporary and definitive contraindications to vaccination.

5) Contact IRT for allocation of unique dose number.

6) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate

7) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

8) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.

9) Provide the subjects' parent / guardian with DC2.

10) Schedule Telephone Call 2 (to occur 8 days after Visit 2).

11) Complete relevant CRB forms for this visit.

Telephone Call 2 (Day 8 + 2 after Visit V02)***: Collection of Safety Information***

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next 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's parent / guardian to do the following:
   - Complete the remaining pages of the DC2 and bring the completed diary to V03
   - Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI that may occur at any time during the study.
3) Schedule Visit 3 (to occur 28 days after Visit 2) if not already done.

Visit 3 (Day 28 + 7 after Visit V02): Collection of Safety Information

1) Review and collect the DC2 information with the subject's parent / guardian and clarify with the subject's parent / guardian, if required, any AEs, or SAEs that occurred since V01. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Collect information on any medications taken (see Section 6.6).
3) If deemed necessary, perform and document a targeted physical examination per standard site-specific immunization practices and record temperature in the source documents.
4) Provide the subjects' parent / guardian with a memory aid (MA) and review the directions for its use.
5) Remind the subject's parent / guardian to promptly notify the site in case of an SAE/AESI symptoms that may occur at any time during the study.
6) Schedule the 6-month safety follow-up phone call
7) Record all applicable information obtained into the CRB
8) Complete the active phase termination record of the CRB.

Telephone call 3 (180 [+14] days after Visit 2): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day.

The Investigator or delegate will:

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) Collect information on any medications taken during the study period
3) Record all applicable information obtained into the CRB

5.1.4.2 Visit Procedures for previously influenza vaccinated subjects

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

The Investigator or delegate will:

1) Give the subject's parent / guardian information about the study.

2) Obtain informed consent and answer any questions to ensure that the subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to allow their child to participate.
3) Date and sign the ICF after it has been signed and dated by the subject's parent / guardian. Retain the original and give a signed copy to the subject's parent / guardian.
4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through targeted physical examination per standard site-specific immunization practices (including recording temperature in source documents) and medical interview of the subject's parent / guardian. If the subject is not eligible, only the specific form entitled "Recruitment log" will state the subject identification, no CRB will be completed.
5) Collect relevant demographic information (eg, date of birth, sex, ethnicity, and race).
6) Obtain verbal information on medical history (including information on breastfeeding and gestational age) and collect information on any medications (see Section 6.6).
7) Obtain information on seasonal influenza vaccination history to determine if the subject is previously influenza vaccinated or previously influenza unvaccinated
8) Call the IRT for assignment of the 12-digit subject number, randomization, and allocation of a dose number (see Section 6.4).

The unblinded qualified study staff member will:

1) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate.
2) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

The Investigator or delegate will:

1) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
2) Give the subject or subject's parent / guardian the Memory Aid to record ILI information, medications, and SAEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of SAEs.
3) Give the subject or subject's parent / guardian a thermometer for temperature measurement, and instructions on how to use them.
4) Schedule the 6-month follow-up telephone call to be conducted approximately 180 days after V01.
5) Remind the subject or subject's parent / guardian to promptly notify the site in case of ILI symptoms or an SAE/AESI that may occur at any time during the study.
6) Complete the relevant CRB forms for this visit.

Telephone call (180 [+14] days after Visit 1 or end of influenza season if later than D180): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day. Also, the telephone call must not be before the end of the influenza surveillance period for that season (ie. 30 April for NH and 31 October for SH subjects).

The Investigator or delegate will:

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE/AESI occurred, follow the instructions in Section 10 for reporting it.
2) Collect information on any medications taken during the study period
3) Complete active phase termination record.

5.1.4.3 Visit Procedures for previously influenza unvaccinated subjects

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

The Investigator or delegate will:

1) Give the subject's parent / guardian information about the study.
2) Obtain informed consent and answer any questions to ensure that the subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to allow their child to participate.
3) Date and sign the ICF after it has been signed and dated by the subject's parent / guardian. Retain the original and give a signed copy to the subject's parent / guardian.
4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through targeted physical examination per standard site-specific immunization practices (including recording temperature in source documents) and medical interview of the subject's parent / guardian. If the subject is not eligible, only the specific form entitled "Recruitment log" will state the subject identification, no CRB will be completed.
5) Collect relevant demographic information (eg, date of birth, sex, ethnicity, and race).
6) Obtain verbal information on medical history (including information on breastfeeding and gestational age) and collect information on any medications (see Section 6.6).
7) Obtain information on seasonal influenza vaccination history to determine if the subject is previously influenza vaccinated or previously influenza unvaccinated.
8) Call the IRT for assignment of the 12-digit subject number, randomization, and allocation of a dose number (see Section 6.4).

The unblinded qualified study staff member will:

1) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate.
2) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

The Investigator or delegate will:

1) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
2) Give the subject or subject's parent / guardian the Memory Aid to record any ILI information, medications, and SAEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of SAEs.
3) Give the subject or subject's parent / guardian a thermometer for temperature measurement, and instructions on how to use them.
4) Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI or ILI symptoms that may occur at any time during the study.
5) Schedule Visit 2 to occur 28 Days after Visit 1.
6) Complete the relevant CRB forms for this visit.

Visit 2 (Day 28+7): Dose Allocation and Vaccination

The Investigator or delegate will:

1) Collect information on any medications taken during the study period.
2) If deemed necessary, perform and document a targeted physical examination per standard site-specific immunization practices and record temperature in the source documents.
3) Review temporary and definitive contraindications to vaccination.
4) Contact IRT for allocation of unique dose number.

The unblinded qualified study staff member will:

1) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate.
2) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

The Investigator or delegate will:

1) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
2) Schedule the 6-month follow-up telephone call to be conducted approximately 180 days after V02.
3) Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI or ILI symptoms that may occur at any time during the study.
4) Complete relevant CRB forms for this visit.

Telephone call (180 [+14] days after Visit 2 or end of influenza season if later than D180): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day. Also, the telephone call must not be before the end of the influenza surveillance period for that season (ie. 30 April for NH and 31 October for SH subjects).

The Investigator or delegate will:

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE has occurred, follow the instructions in Section 10 for reporting it.
2) Collect information on any medications taken during the study period
3) Complete active phase termination record.

5.1.4.4 Visit Procedures for previously influenza vaccinated subjects who have been randomized into the Expanded safety analysis set (ESafAS) with or without Immunogenicity Subset

Visit 1 (Day 0): Inclusion, Randomization, Vaccination, and Blood Sample (for Immunogenicity Subset)

The Investigator or delegate will:

1) Give the subject's parent / guardian information about the study.
2) Obtain informed consent and answer any questions to ensure that the subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to allow their child to participate.
3) Date and sign the ICF after it has been signed and dated by the subject's parent / guardian. Retain the original and give a signed copy to the subject's parent / guardian.
4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through targeted physical examination per standard site-specific immunization practices (including recording temperature in source documents) and medical interview of the subject's parent / guardian. If the subject is not eligible, only the specific form entitled "Recruitment log" will state the subject identification, no CRB will be completed.
5) Collect relevant demographic information (eg, date of birth, sex, ethnicity, and race).
6) Obtain verbal information on medical history (including information on breastfeeding and gestational age) and collect information on any medications (see Section 6.6).
7) Obtain information on seasonal influenza vaccination history to determine if the subject is previously influenza vaccinated or previously influenza unvaccinated
8) Call the IRT for assignment of the 12-digit subject number, randomization, and allocation of a dose number (see Section 6.4).
9) If the subject is randomized into the Immunogenicity Subset: perform the following step prior to vaccination
    a. Draw approximately 5 mL of blood sample (The blood sampling should be performed before vaccination). Process the blood sample as specified in the "Management of

Samples" section (see Section 7).
N**ote:** If 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.
Note: If the subject's parent / guardian 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.

The unblinded qualified study staff member will:

1) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate (the vaccine must be administered on the side opposite to that of the blood sampling, if applicable).
2) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

The Investigator or delegate will:

1) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
2) Give the subject or subject's parent / guardian the Diary Card (DC) to record any injection site reactions and systemic AEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs.
3) Give the subject's parent / guardian the diary card to record ILI information, medications, and SAEs/AESIs, together with instructions for its completion.
4) Give the subject or subject's parent / guardian a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement, and instructions on how to use them.
5) Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI or ILI symptoms that may occur at any time during the study.
6) Schedule Visit 2 (to occur 28 days after Visit 1).
7) Complete the relevant CRB forms for this visit.

Visit 2 (Day 28+7): Blood Sample (for Immunogenicity Subset) and Collection of Safety Information

The Investigator or delegate will:

1) Collect information on any medications taken (see Section 6.6).
2) If deemed necessary, perform and document a targeted physical examination per standard site-specific immunization practices and record temperature in the source documents.
3) Review and collect completed DC.
4) If the subject is part of the Immunogenicity Subset: perform the following step prior to vaccination

a. Draw approximately 5 mL of blood sample. Process the blood sample as specified in the "Management of Samples" section (see Section 7).
N**ote:** If 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.

5) Give the subject's parent / guardian the memory aid to record ILI information (except for subjects from Re-vaccination Cohort), medications, and SAEs/AESIs, together with instructions for its completion.

6) Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI or ILI symptoms that may occur at any time during the study.

7) Schedule 6-month follow-up telephone call to be conducted approximately 180 days after V01.

8) Complete the relevant CRB forms for this visit.

Telephone call (180 [+14] days after Visit 1 or end of influenza season if later than D180): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day. Also, the telephone call must not be before the end of the influenza surveillance period for that season (ie. 30 April for NH and 31 October for SH subjects).

The Investigator or delegate will:

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) Collect information on any medications taken during the study period

3) Complete active phase termination record.

5.1.4.5 Visit Procedures for previously influenza unvaccinated subjects who have been randomized into the Expanded safety analysis set (ESafAS) with or without Immunogenicity Subset

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

The Investigator or delegate will:

1) Give the subject's parent / guardian information about the study.

2) Obtain informed consent and answer any questions to ensure that the subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to allow their child to participate.

3) Date and sign the ICF after it has been signed and dated by the subject's parent / guardian. Retain the original and give a signed copy to the subject's parent / guardian.

4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through targeted physical examination per standard site-specific immunization practices (including recording temperature in source documents) and medical interview of the subject's

parent / guardian. If the subject is not eligible, only the specific form entitled "Recruitment log" will state the subject identification, no CRB will be completed.

5) Collect relevant demographic information (eg, date of birth, sex, ethnicity, and race).
6) Obtain verbal information on medical history (including information on breastfeeding and gestational age) and collect information on any medications (see Section 6.6).
7) Obtain information on seasonal influenza vaccination history to determine if the subject is previously influenza vaccinated or previously influenza unvaccinated
8) Call the IRT for assignment of the 12-digit subject number, randomization, and allocation of a dose number (see Section 6.4).
9) If the subject has been randomized into the Immunogenicity Subset: draw approximately 5 mL of blood sample (The blood sampling should be performed before vaccination). Process the blood sample as specified in the "Management of Samples" section (see Section 7).
   N**ote:** If 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.
   Note: If the subject's parent / guardian 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.

The unblinded qualified study staff member will:

1) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate (the vaccine must be administered on the side opposite to that of the blood sampling).
2) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

The Investigator or delegate will:

1) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
2) Give the subject or subject's parent / guardian the Diary Card (DC1) 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.
3) Give the subject's parent / guardian the diary card to record ILI information (except for subjects in the Re-vaccination Cohort), medications, and SAEs/AESIs, together with instructions for its completion.
4) Give the subject or subject's parent / guardian a ruler to measure the size of any injection site reaction, a thermometer for temperature measurement, and instructions on how to use them.
5) Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI or ILI symptoms that may occur at any time during the study.
6) Schedule Visit 2 (to occur 28 days after Visit 1).
7) Complete the relevant CRB forms for this visit.

Visit 2 (Day 28+7): Dose Allocation, Vaccination and Collection of Safety Information

The Investigator or delegate will:

1) Collect information on any medications taken during the study period.
2) Review and collect completed DC1
3) If deemed necessary, perform and document a targeted physical examination per standard site-specific immunization practices and record temperature in the source documents.
4) Review temporary and definitive contraindications to vaccination.
5) Contact IRT for allocation of unique dose number.

The unblinded qualified study staff member will:

1) Administer the appropriate vaccine intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle of the upper arm, as appropriate
2) Record the injection site / side / route / dose number and affix the detachable corresponding label in the source documents.

The Investigator or delegate will:

1) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any SAE in the source documents.
2) Provide the subjects' parent / guardian with DC2.
3) Schedule Visit 3 (to occur 28 days after Visit 2).
4) Complete relevant CRB forms for this visit.

Visit 3 (Day 28 + 7 after Visit V02): Post-Vaccination Blood Sample (for Immunogenicity Subset) and Collection of Safety Information

The Investigator or delegate will:

1) Collect information on medication taken during the study.
2) Review and collect DC2.
3) If the subject is part of the Immunogenicity Subset:
    a. Draw approximately 5 mL of blood sample. Process the blood sample as specified in the "Management of Samples" section (see Section 7).
    N**ote:** If 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.
4) Give the subject's parent / guardian the memory aid to record ILI information (except for subjects in the Re-vaccination Cohort), medications, and SAEs/AESIs, together with instructions for its completion.
5) Remind the subject or subject's parent / guardian to promptly notify the site in case of an SAE/AESI or ILI symptoms that may occur at any time during the study.

6) Schedule 6-month follow-up telephone call to be conducted approximately 180 days after V02.

7) Complete the relevant CRB forms for this visit.

Telephone call (180 [+14] days after Visit 2 or end of influenza season if later than D180): Collection of Safety Information

Note: If the telephone call falls on a weekend or a holiday, the telephone call may be scheduled on the next business day. Also, the telephone call must not be before the end of the influenza surveillance period for that season (ie, 30 April for NH and 31 October for SH subjects).

The Investigator or delegate will:

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) Collect information on any medications taken during the study period

3) Complete active phase termination record.

5.1.5 Collection of ILI Symptoms through Passive and Active Surveillance

5.1.5.1 ILI Surveillance and Influenza Confirmation Process for all subjects (except Sentinel Safety Cohort subjects)

ILI surveillance (not applicable to subjects in the Re-vaccination Cohort)

From the first vaccination to the end of the influenza season, passive surveillance will be performed. Subjects' parent(s) / guardian(s) will be instructed to contact the site as soon as possible (within 24 hours) if their child experiences symptoms of an ILI.

In addition, from the first vaccination to the end of the influenza season (30 April for NH and 31 October for SH subjects); the Investigator or delegate will contact the subjects' parent(s) / guardian(s) once a week. This contact may be done via telephone or via an optional electronic application. This will be described in the Operating Guidelines and will be in accordance with local regulations.

During these weekly contacts, the Investigator or delegate will:

1) Interview the subjects' parent(s) or guardian(s) in order to detect a possible ILI.

2) Arrange an ILI visit at the study site or at home visit if an ILI is suspected. The ILI visit has to be scheduled at the earliest opportunity for laboratory confirmation of influenza (within 7 days after the onset of the ILI considering that Day 0 is the day of fever onset).

3) Remind subject's parent(s) / guardian(s) to record information about ILI symptoms, associated events, medications, and healthcare utilization in the DC or MA given.

ILI Visit (within 7 days of ILI onset)

Only for subjects reporting qualifying symptoms of ILI during phone calls from first vaccination until 30 April (NH) or 31 October (SH) of the following year etc.

The Investigator or delegate will:

1) Collect and review information on ILI symptoms, associated events, medications, and healthcare utilization and will confirm clinically the ILI diagnosis.
2) Information on ILI symptoms, associated events, medications and healthcare utilization includes:
    - Information on occurrence, duration, and intensity of ILI symptoms after the onset of the ILI
    - Information on occurrence of AOM and ALRI after the onset of the ILI
    - Information on healthcare utilization events (inpatient hospitalization, outpatient visit, medications, parent(s) / guardian(s) absenteeism due to child sick days) after the onset of the ILI
    - Information on medications given to the subject
3) Perform the NP swab if ILI diagnosis is clinically confirmed
4) Schedule the ILI follow-up phone call 30 days after the ILI onset
5) Remind the parent(s) / guardian(s) that the ILI surveillance will continue (active and passive surveillance) and to record information about ILI symptoms, associated events, and healthcare utilization in the MA
6) Record all applicable information obtained into the CRF

ILI follow-up Phone call(s) – 30 + 7 days after ILI onset

For subjects who reported protocol-defined ILI symptoms.

The Investigator or delegate will:

1) Collect detailed information on ILI symptoms, medications, associated events, and healthcare utilization and their resolution
2) Remind the parent(s) / guardian(s) that the ILI surveillance will continue (active and passive surveillance) and to record information about ILI, associated events, and healthcare utilization in the MA
3) Record all applicable information obtained into the CRF

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

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

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

5.1.6 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject): September 2020 to July 2024

Planned end of study: October 2024

Planned date of final clinical study report: Jan 2025

5.1.7 Early Safety Data Review

The safety of the investigational product will be continuously monitored by the Sponsor. An ESDR will be performed, the goal of which is to allow for a cautious, step-wise approach to vaccine administration. An initial safety review for this study is planned when the first 100 subjects are enrolled in a Sentinel Safety Cohort. All 100 subjects will receive QIV-HD (in this open-label cohort, no comparator vaccine will be administered). After the Sentinel Safety Cohort has been vaccinated and has provided safety data for D0-D7 post-vaccination (using the data collection methods described in the clinical study protocol), an IDMC will convene and review the safety data. Following a satisfactory safety review by the IDMC, enrollment of subjects will commence in Season 1.

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

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

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

The data will be examined for the following occurrences:

- An SAE (including AESIs) considered as related to the vaccination by the Investigator and Sponsor
- > 10% of subjects experiencing Grade 3 fever within 7 days after vaccination

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

At the completion of the collection of safety data at the end of Season 1 (2022-2023 NH season), the IDMC will be convened to review the safety data of subjects. Enrollment will not be paused during this IDMC review.

Throughout the course of the study, additional internal SMT meetings will be convened to conduct blinded analyses of safety data. Case unblinding may be performed if necessary. The Sponsor may also convene the IDMC for ad hoc review of the safety data if needed.

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

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

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

5.2.2 Informed Consent Procedures

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

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

If the subject's parent or guardian 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's parent or his / her guardian.

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 parent's and / or guardian's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

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

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

Rationale for Including Subjects Unable to Give Consent:

See Section 1.4 for the rationale for conducting this study in pediatric population.

5.2.3 Screening Criteria

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

5.2.4 Inclusion Criteria

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

1) Aged 6 to 35 months on the day of the first study visit[a]
2) Informed consent form has been signed and dated by the parent(s) or guardian(s) and by an independent witness, if required by local regulations.
3) Subject and parent / guardian are able to attend all scheduled visits and to comply with all study procedures.
4) Covered by health insurance if required by local regulations
5) For Season 3 Re-vaccination Cohort: eligible subjects must have been enrolled in the Season 1 (2022-2023 NH season) Immunogenicity Subset and must have completed all study procedures (ie, blood draws and vaccinations) in Season 1.

5.2.5 Exclusion Criteria

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

1) Participation at the time of study enrollment (or in the 4 weeks preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.
2) For all subjects: Receipt of any vaccine in the 30 days preceding the first study vaccination. For subjects in Immunogenicity Subset: Planned receipt of any vaccine before Visit 2 for subjects receiving 1 dose of influenza vaccine or Visit 3 for subjects receiving 2 doses of influenza vaccine.
3) Previous vaccination against influenza in the preceding 6 months with either the study vaccine or another influenza vaccine
4) Receipt of immune globulins, blood or blood-derived products in the past 3 months.
5) Known or suspected congenital or acquired immunodeficiency (eg, HIV); 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).

[a] "6 to 35 months" means from the 6th month after birth to the day before the 36th month after birth.

6) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances[a]. Exception: subjects with an egg allergy are allowed to enroll in the study.
7) Thrombocytopenia, bleeding disorder, or receipt of anticoagulants that based on Investigator's judgment contraindicate intramuscular vaccination
8) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[b].
9) 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 study until the condition has resolved or the febrile event has subsided.

   Note: Subjects who test positive for COVID-19 infection or have been in close contact with individuals who have tested positive for COVID-19 within 14 days preceding the first study vaccination will also be excluded from participating in the study until they test negative for COVID-19.

10) Identified as natural or adopted child of the Investigator or employee with direct involvement in the proposed study.
11) Personal or family history of GBS.
12) Any condition that in the opinion of the Investigator would pose a health risk to the subject if enrolled or could interfere with the evaluation of the vaccine.
13) Personal history of clinically significant development delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.
14) For Season 3 (2023-2024 NH) main cohort: subjects who were enrolled in a previous study season are excluded from Season 3, with the exception of the Re-vaccination Cohort.

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

5.2.6 Medical History

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

[a] The components of the QIV-HD are listed in Section 6.1 and in the Investigator's Brochure, the components of QIV-SD are listed in Section 6.1 and the package insert

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

systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.
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 [eg, respiratory, cardiac, blood, endocrine, and kidney disorders] listed in the CRB and other significant chronic conditions, as judged by the Investigator)
2) Other conditions (eg, egg allergy, eczema, febrile seizure)

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

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

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

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

5.2.7 Contraindications for Subsequent Vaccinations

The contraindications apply only to previously influenza unvaccinated subjects who are going to receive 2 vaccine doses, 28 (+7) days apart.

5.2.7.1 Temporary Contraindications

Should a subject experience a condition listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the Table of Study Procedures.

- 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 study until the condition has resolved or the febrile event has subsided.

5.2.7.2 Definitive Contraindications

Should a subject experience 1 of the conditions listed below, the Investigator will discontinue vaccination:

1) An anaphylactic or other significant allergic reaction to the previous dose of the vaccine
2) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances
3) Receipt of immune globulins, blood or blood-derived products since the preceding injection
4) Known or suspected congenital or acquired immunodeficiency (eg, HIV); or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, since the preceding visit; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks since the preceding visit)

5) Thrombocytopenia, bleeding disorder or receipt of anticoagulants in the 3 weeks preceding vaccination, contraindicating intramuscular vaccination based on investigator's judgment
6) Chronic illness that, in the opinion of the Investigator, is might interfere with subject safety, study conduct or completion
7) An SAE related to the study vaccines following the previous study vaccination, based on investigator's judgment

Subjects with a definitive contraindication will continue to be followed up for the study-defined safety, efficacy, and immunogenicity assessments, as applicable.

In the event of a local or national immunization program with a pandemic influenza vaccine or other vaccine, subjects who receive pandemic influenza vaccine or other vaccine at any time during the study will not be withdrawn from the study.

5.2.8 Conditions for Withdrawal

Subject's parents / guardians will be informed that they have the right to withdraw their child from the study at any time.

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

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

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

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

5.2.10 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.3.3.2. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the Investigator and returned unsigned, and the subject's parent/guardian did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant non-compliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is not an SAE or AE. • The subject's parent/guardian signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject's Parent / Guardian	To be used: • When the subject's parent/guardian indicated unwillingness to continue in the study • When the subject's parent/guardian made the decision to discontinue their child's participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

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

For subjects where the reason for early termination was lost to follow-up or if the subject's parent / guardian 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's Parent / Guardian", the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the

appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

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

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.3.

5.4 Modification of the Study and Protocol

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

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

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

5.5 Interruption of the Study

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

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

The study may also be interrupted before the expected number of evaluable cases has been reached upon recommendation of the IDMC after interim analysis, if efficacy or futility criteria are met (See Section 12.4 for further details). In any case, the study will not stop before the 3 influenza seasons are completed.

6 Products Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

The investigational QIV-HD is a quadrivalent influenza vaccine (split virion, inactivated) (60 µg HA/strain) containing virus strains chosen by the WHO (and recommended by Vaccines and Related Biological Products Advisory Committee [VRBPAC] in the US and EMA in EU) for the respective 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 suspension for IM injection.

QIV-HD vaccine does not contain preservative and is prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.1.1 Composition

Each 0.7 mL dose of vaccine contains the following components:

Strains are based on WHO recommendations for the considered influenza season.

Active Substances:

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

Excipients:

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

Preservative is not used in the manufacture of QIV-HD. QIV-HD may contain traces of eggs, such as ovalbumin, formaldehyde which are used during the manufacturing process.

6.1.1.2 Preparation and Administration

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

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.2.1), 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 each vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

The vaccination schedule is per standard practice for receipt of annual influenza vaccination for previously influenza vaccinated and influenza unvaccinated subjects and subjects 6 through 35 months of age.

6.1.2 Identity of Control Product

The control product, Fluarix Quadrivalent (or other tradenames) is an influenza vaccine (split virion, inactivated), presented in a pre-filled syringe (QIV-SD) (GlaxoSmithKline Biologicals). The vaccine contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages). Each pre-filled syringe contains a total of 60 µg HA antigen per 0.5 mL dose provided in suspension for IM injection. QIV-SD is registered in all countries where the trial will be conducted.

6.1.2.1 Composition

Each 0.5 mL dose contains 15 µg of HA for each of the following strains:

Strains are based on WHO recommendations for the considered influenza season.

Active Substances:

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

Excipients:

Octylphenol-10 (Triton X-100)	≤ 0.115 mg
α-Tocopheryl hydrogen succinate	≤ 0.135 mg
Polysorbate 80 (Tween 80)	≤ 0.550 mg

QIV-SD does not contain a preservative. QIV-SD may contain traces of eggs (such as ovalbumin, chicken proteins), formaldehyde, gentamicin sulphate and sodium deoxycholate which are used during the manufacturing process

6.1.2.2 Preparation and Administration

QIV-SD will be prepared and administered according to manufacturer's package insert.

6.1.2.3 Dose Selection and Timing

The vaccination schedule is per standard practice for receipt of annual influenza vaccination for previously influenza vaccinated and influenza unvaccinated subjects and subjects 6 through 35 months of age.

6.2 Product Logistics

6.2.1 Labeling and Packaging

The investigational and control vaccines for this study will be provided by the Sponsor and will be labeled in accordance with national regulations.

The investigational QIV-HDs will be supplied in single dose syringes with investigational labeling and packaging. Each single dose will be identified by a unique medication number on the label and on the carton. The comparator vaccine, Fluarix Quadrivalent, will be supplied in single dose syringes with the manufacturer label on the syringes and an investigational label on the syringe and 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.

6.2.2 Product Shipment, Storage, and Accountability

6.2.2.1 Product Shipment

The Vaccine Trial Supply Operations Manager or designee will contact the Investigator or a designee to determine the dates and times of delivery of products.

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

6.2.2.2 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 study site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.2.2.3 Product Accountability

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

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

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

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

6.2.3 Replacement Doses

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

6.2.4 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 study period.

6.2.5 Recall of Products

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

6.3 Blinding and Code-breaking Procedures

Except for an open-label, unblinded Sentinel Safety Cohort for early safety data review, the study is designed as a modified double-blind study with the following measures to ensure the integrity of the data:

- The unblinded qualified study staff member, independent of the safety evaluation, ILI surveillance, and other study evaluations, will administer the vaccine
- The Investigators (or delegates) in charge of safety assessment and ILI surveillance, the study staff who collect the safety data and ILI surveillance, and the laboratory personnel who analyze the blood samples or NP samples will not know which product was administered
- The subject's parent / guardian will not know which product was administered. To maintain the blinding of the subject's parent / guardian, the vaccine syringe label will be covered with appropriate materials prior to administration.

- 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 the commercial vaccines syringes. The IRT system will be responsible for providing the subject identification and dose number to be received by the enrolled subject. The subject's parent / guardian, the Investigator, and study staff members who collect the safety data/ILI symptoms and laboratory personnel who analyze the blood samples or NP 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/efficacy data.

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

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

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

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

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.

An interim analysis may be conducted by an independent statistician and reviewed by an IDMC during Season 3 if the likelihood of achieving the expected [redacted] cases at the end of the Season 3 is low and if at least [redacted] evaluable influenza cases are collected. Unblinding is, therefore, necessary to the IDMC, but the information will not be communicated to either the Investigator or the Sponsor study team before the end of surveillance and database lock.

6.4 Randomization and Allocation Procedures

The Sentinel Safety Cohort enrolled during the 2020-2021 NH influenza season, is uncontrolled and open-label. On the day of enrollment, subjects who fulfilled all the inclusion criteria and none of the exclusion criteria and complete the informed consent process will receive QIV-HD at 60 µg

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

HA/strain/dose. For all other subjects, the study will be randomized and modified double-blinded. On the day of enrollment, subjects who fulfilled all the inclusion criteria and none of the exclusion criteria and complete the informed consent process will be randomly assigned to receive either QIV-HD at 60 µg HA/strain/dose or Fluarix Quadrivalent in a 1:1 ratio.

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the subjects number, dose assignment and subset assignment for non-sentinel subjects. Randomization of subjects into vaccine groups will be performed with the permuted block method with stratification by site, previous influenza vaccination history, and age subgroup (< 24 months and ≥ 24 months), via Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS). Subjects that participate in Season 1 that are subsequently enrolled in the Season 3 Re-vaccination Cohort will be assigned a new subject number. IRT will also be used to randomize subjects into the immunogenicity and ESafAS subsets as defined in the protocol.

The full detailed procedures for randomization are described in the Operating Guidelines and IRT specifications. 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 assigned in IRT will consist of a string of digits that will include information on the country, study site, and cohort/subset assignment. Details are provided in the Operating Guidelines.

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

6.5 Treatment Compliance

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

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

6.6 Concomitant Medications and Other Therapies

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

All medications and vaccines will be considered reportable medications and will be coded in this study.

Documentation in the CRB of all ongoing concomitant medication(s) will be collected.

Medications will be collected in the CRB from the day of vaccination to the end of the study period (ie, follow-up telephone call).

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

- Trade name or generic name
- Origin of prescription: prophylaxis[a] Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the "Action Taken" section of the AE collection tables.
- Start and stop dates
- Route of administration
- Dosage
- Dose schedule
- Reason for treatment

Homeopathic medication and topical treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded in this specific instance.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visits 1 and 2 for previously influenza vaccinated subjects and Visits 1 and 3 for previously influenza unvaccinated subjects that are randomized into the Immunogenicity Subset. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

7.1.1 Blood Samples

For subjects randomized into the Immunogenicity Subset, at Visit(s) 1 and 2 or 1 and 3 depending on influenza vaccination status described above, 5 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

[a] Prophylactic medication in this study is defined as a medication taken to prevent any AEs that may occur following the administration of the study vaccine(s) (vaccines listed in the trial product section of the protocol) during the solicited follow-up period.

7.1.2 Nasopharyngeal Samples

For assessment of influenza virus by cell culture and PCR, an NP swab sample will be collected from both nasal passages using the same swab applicator and placed in a tube of universal transport medium (UTM) provided by the Sponsor. Immediately prior to taking the sample, the person performing the procedure will verify the subject's identity and will confirm that the 8-digit subject number and any other required information are those of the subject. Each tube of UTM will be clearly labeled with a self-adhesive bar-coded label that will be applied to the tube immediately before collection of the NP swab.

7.2 Sample Preparation

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

7.2.1 Blood Samples

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours 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 study code, the subject's number and the sampling stage or visit number.

The subject's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and the parent's / guardian's consent for future use of his / her child's 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.

7.2.2 Nasopharyngeal Swabs

Detailed instructions for the preparation of NP samples are described in the Operating Guidelines provided to the site.

The subject's identification number and any other required information, the date of sampling, and the date and time of preparation will be clearly documented.

7.3 Sample Storage and Shipment

7.3.1 Blood Samples

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

during the entire study. If it rises above -10°C for any period of time, the Cold Chain Break Group 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 Monitoring Team. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to Global Clinical Immunology (GCI) under the oversight of Research and Development Global Operations Sample Management and Logistics (R&D GO SML) at Sanofi Pasteur. The address is provided in the Operating Guidelines.

7.3.2 Nasopharyngeal Samples

Detailed instructions for the storage of NP swabs at study site and shipment of NP swab samples to testing laboratory (a laboratory under the guidance of GCI, USA) are described in the Operating Guidelines provided to the site.

7.4 Future Use of Stored Biological Samples for Research

Any unused part of the serum samples and NP swab-derived products will be securely stored at the Sanofi Pasteur serology laboratory (GCI under the oversight of R&D GO SML), Swiftwater, Pennsylvania, USA) for up to 25 years after the end of the study (or more if required by local regulations). These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

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

8 Clinical Supplies

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

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

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

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

9 Endpoints and Assessment Methods

9.1 Definitions

Protocol-defined ILI: occurrence of fever ≥ 38°C (100.4°F) concurrently with at least one of the following symptoms: cough, wheezing, difficulty breathing, nasal congestion, rhinorrhea, pharyngitis (sore throat), otitis, vomiting, diarrhea, shivering (chills), fatigue (tiredness), headache, or myalgia (muscle aches).

Modified CDC-defined ILI: occurrence of fever (defined as temperature > 38°C [> 100.4°F]) with cough, pharyngitis, or sore throat

Laboratory-confirmed influenza: a positive influenza result on either polymerase chain reaction (PCR) or viral culture.

Culture-confirmed influenza: a positive influenza result on viral culture.

Genetic similarity: Genetic similarity is defined when a laboratory-confirmed isolate is deemed similar to one of the viral strains contained in the vaccine formulations according to sequencing of full HA gene segments proteins.

Antigenic similarity: Antigenic similarity is defined when a laboratory-confirmed isolate is deemed similar to one of the viral strains contained in the vaccine formulations according to Ferret Antigenicity testing (hemagglutination inhibition [HAI] against a panel of known standard ferret reference antisera).

Similarity to vaccine components: For prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine in subjects 6 months through 35 months of age, laboratory-confirmed isolate is deemed similar to one of the vaccine components based on antigenic similarity only. For all the other endpoints, similarity is based on antigenic similarity when available or based on genetic similarity otherwise.

ALRI: pneumonia, bronchiolitis, bronchitis, or laryngotracheobronchitis (croup) based on a clinical and/or x-ray diagnosis

9.2 Primary Endpoints and Assessment Methods

9.2.1 Efficacy

9.2.1.1 Efficacy Endpoints

The primary endpoint for the evaluation of efficacy is the occurrence of laboratory-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI.

9.2.1.2 Efficacy Assessment Methods

ILI Assessment

ILI assessment will be based on information captured in the CRF reflecting information reported by the subject's parent / guardian in the diary card or memory aid.

Table 9.1 present the terminology used for ILI symptoms: the terms used in the CRF after investigator's diagnosis and the corresponding ones used in the diary card / memory aid for the parent(s) / guardian to help them detecting an ILI.

Table 9.1: ILI symptoms: terminology

CRF term	Diary card / memory aid term
Fever	Temperature
Cough	Cough
Nasal congestion	Stuffy nose
Rhinorrhea	Runny nose
Otitis	Earache
Vomiting	Vomiting
Diarrhea	Diarrhea
Wheezing	Wheezing
Difficulty Breathing	Difficulty Breathing
Pharyngitis (sore throat)	Sore Throat
Shivering	Chills
Fatigue	Tiredness
Headache	Headache
Myalgia	Muscle Aches

Influenza Culture and Virus Isolation:

NP swab samples from subjects with ILI will be used to inoculate and infect influenza virus susceptible tissue culture cell lines. Influenza positive cultures will be confirmed by using

immunofluorescence techniques with influenza type–specific (eg, for influenza A and influenza B) antibodies.

Molecular Detection (PCR):

Clinical samples collected during the study period will undergo an extraction procedure to isolate the viral RNA from the NP swab prior to testing.

The initial molecular test will be a real-time Reverse Transcriptase mediated Polymerase Chain Reaction (RT-PCR) based assay to determine if either Influenza A and/or Influenza B virus are present in the clinical sample.

Note: All assays will be under the supervision of Sanofi Pasteur GCI, Swiftwater, PA.

9.2.2 Immunogenicity

There are no primary objectives for immunogenicity.

9.2.3 Safety

There are no primary objectives for safety.

9.3 Secondary Endpoints and Assessment Methods

9.3.1 Efficacy

9.3.1.1 Efficacy Endpoints

The following endpoints will be used for efficacy comparisons:

- Occurrence of laboratory-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI.
- Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive for viral strains similar to those contained in the vaccine
- Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive in subjects 6 through 23 months of age for any influenza A or B type

Descriptive Efficacy Endpoints

In addition, the following endpoints will also be considered for the descriptive assessment of relative efficacy:

Occurrence of an ILI starting ≥ 14 days after vaccination:

- laboratory-confirmed as positive for any influenza A or B type, in subjects according to their previous vaccination status
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, in subjects according to their previous vaccination status

- laboratory-confirmed as positive for any influenza A or B type, and associated with AOM based on clinical diagnosis occurrence
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, and associated with AOM based on clinical diagnosis occurrence
- laboratory-confirmed as positive for any influenza A or B type, and associated with ALRI based on a clinical and/or x-ray diagnosis occurrence
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, and associated with ALRI based on a clinical and/or x-ray diagnosis occurrence
- PCR-confirmed as positive for any influenza A or B types
- PCR-confirmed as positive for viral strains similar to those contained in the vaccine
- culture-confirmed as positive for any influenza A or B types
- culture-confirmed as positive for viral strains similar to those contained in the vaccine
- laboratory-confirmed as positive for any influenza A or B type and associated with hospitalization
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine and associated with hospitalization

9.3.1.2 Efficacy Assessment Methods

Influenza Culture (Virus Isolation) and Molecular Detection (PCR):

The assessment methods for the secondary efficacy objectives are the same as those listed for the primary efficacy assessment methods above in Section 9.2.1.2.

Sequencing Methodology:

For samples that exhibit as positive for influenza in viral culture and/or in the real-time RT-PCR detection assay, further testing by Sanger sequencing of the HA and NA full gene segments will be instituted to identify the specific subtype of the influenza strain.

Note: Positive PCR samples that have negative culture results, or were unable to be expanded in culture, will not undergo additional testing.

Ferret Antigenicity Testing:

Influenza virus culture-positive samples will be typed using the HAI assay method against a panel of known standard ferret reference antisera to different influenza virus strains. The reference ferret antisera are pretreated enzymatically to remove non-specific inhibitors and incubated with test virus antigen and/or reference virus antigen. Turkey Red Blood Cells (RBCs) are prepared for use in the assay by washing and then added to the virus/antisera mixture. Following incubation, the reading is done by observing hemagglutination or inhibition of hemagglutination in the wells. The endpoint titer of the antisera against a specific virus antigen is the highest serum dilution in which complete inhibition of hemagglutination occurs.

Antibodies directed against the viral HA prevent the binding of HA to its receptors, sialic acid containing glycoprotein present on the surface of RBCs, thereby preventing agglutination of RBCs by the virus. Antigenic variations in the hemagglutinin are reflected in differences in the ability of specific antisera to inhibit hemagglutination. The influenza virus antigen in the sample will be

considered to be antigenically similar to the vaccine strain (matching) if there is a ≤ 4-fold difference in the titer of the clinical isolate and the vaccine strain against a reference antiserum homologous to the vaccine.

9.3.2 Immunogenicity

9.3.2.1 Immunogenicity Endpoints

The following immunogenicity endpoints will be used for comparison in Immunogenicity Subset of Season 1:

- Individual HAI titer on D0 and 28 days after the last vaccination
- Seroconversion for subjects with a pre-vaccination titer < 10 (1/dil): post-injection titer ≥ 40 (1/dil) on 28 days after the last vaccination or significant increase for subjects with a pre-vaccination titer ≥ 10 (1/dil): ≥ 4-fold increase from pre- to post-injection titer on 28 days after the last vaccination

In addition, the 2 above and the following endpoints will be considered in the Immunogenicity Subset for the descriptive assessment of immunogenicity:

- Detectable HAI titer, ie, with a titer ≥ 10 (1/dilution [dil]) at D0 and 28 days after the last vaccination
- Individual titer ratio: 28 days after the last vaccination /D0
- Subjects with titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination

Immunogenicity by SN method

Immunogenicity will be evaluated using the SN assay in a subset of subjects from the Immunogenicity Subset. For each vaccine strain, antibody titers will be expressed as SN titers. The following immunogenicity endpoints will be described:

- Individual SN antibody (Ab) titer on D0 and 28 days after the last vaccination
- Individual SN Ab titer ratio (fold increase in post-vaccination titer relative to D0) at 28 days after the last vaccination
- Subjects with SN Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D0 and 28 days after the last vaccination
- Fold-increase in SN Ab titer [post/pre] ≥ 2 and ≥ 4 at 28 days after the last vaccination
- Detectable SN Ab titer (SN Ab titer ≥ 10 [1/dil]) at D0 and 28 days after the last vaccination

Immunogenicity by ELLA method

For a subset of subjects, anti-N1 and anti-N2 titers will be measured for the 2 influenza A strains using ELLA and will be assessed based on the subject's individual anti-NA titer. The following immunogenicity endpoints will be described:

- Individual anti-NA Ab titer on D0 and 28 days after the last vaccination
- Individual anti-NA Ab titer ratio (fold-rise in anti-NA post-vaccination titer relative to D0) at 28 days after the last vaccination
- Subjects with anti-NA Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D0 and 28 days after the last vaccination
- Fold-rise in anti-NA Ab titer [post/pre] ≥ 2 and ≥ 4 at 28 days after the last vaccination

- Detectable anti-NA titer (anti-NA Ab titer ≥ 10 [1/dil]) at D0, and 28 days after the last vaccination

Re-vaccination Response

For subjects enrolled in both Season 1 (NH) and Season 3 (NH), HAI Ab titers against the 4 vaccine strains used in Season 3 (NH) will be measured at D0 and D28 in Season 3 (NH). The following endpoints will be described.

- HAI individual titer on D0, and 28 days after the last vaccination
- Individual HAI titer ratio: D28 days after the last vaccination /D0
- Detectable HAI titer, ie, with a titer ≥ 10 (1/dilution [dil]) at D0 and 28 days after the last vaccination
- Subjects with titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination
- Seroconversion for subjects with a pre-vaccination titer < 10 (1/dil): post-injection titer ≥ 40 (1/dil) on 28 days after the last vaccination or significant increase for subjects with a pre-vaccination titer ≥ 10 (1/dil): ≥ 4-fold increase from pre- to post-injection titer on 28 days after the last vaccination.

9.3.2.2 Immunogenicity Assessment Methods

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

Anti-Influenza Virus Ab Titration by Inhibition of Hemagglutination

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 an RBC suspension. Following this, the mixtures are centrifuged and the supernatants containing the treated sera are collected for testing. Ten twofold 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 an 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 can either be tested in singleton (ie, one assay run) or in 2 independent assay runs (duplicate) which will include 2 independent samplings of the original serum and 2 independent preparations of influenza virus antigen. The decision to test the study samples, either in singleton or duplicate HAI, will be taken by the study team prior to the execution of clinical testing by the laboratory. 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 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).

Influenza Virus Neutralization Test (also called serum neutralization (SN) assay in this protocol)

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

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

Influenza Virus Antibody Titration by Enzyme-linked Lectin Assay

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

9.3.3 Safety

9.3.3.1 Safety Endpoints

Reactogenicity will be described for the ESafAS:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccination
- Occurrence of solicited (pre-listed in the subject's diary card and CRB) injection site reactions and systemic reactions occurring up to 7 days after vaccination
- Occurrence of unsolicited AEs up to 28 days after vaccination

SAEs/AESIs will be described in all subjects:

- Occurrence of SAEs (including AESIs) throughout the study
- Occurrence of AESIs throughout the study

9.3.3.2 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

- Results in death

- Is life-threatening[a]

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

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

Adverse Reaction:

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

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

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

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

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

Unsolicited AE / AR:

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

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

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

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

Injection Site Reaction:

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

Systemic AE

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

Adverse Event of Special Interest (AESI):

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

9.3.3.3 Safety Assessment Methods

At Visit 1, the Investigator or a clinical delegate will perform a clinical or medically-driven physical examination.

At subsequent visits for subjects that are randomized to be included in the immunogenicity or Expanded safety analysis sets, the Investigator or delegate may perform a clinical or medically-driven physical examination as necessary and will ask the subjects' parent / guardian 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.

9.3.3.3.1 Immediate Post-vaccination Observation Period

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

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected) for subjects in the expanded safety analysis set.
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination for subjects in the expanded safety analysis set.

- For all subjects SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

9.3.3.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 7 After Each Vaccination)

After each vaccination for subjects randomized into the Expanded safety analysis set, subjects' parent(s) / guardian(s) will be provided with a diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (ie, Day 0 through Day 7) until resolution:

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

  The action(s) taken by the subjects' parent or guardian 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
  - Discontinuation of study vaccination

Table 9.2 and Table 9.3 present, respectively, the injection site reactions and systemic reactions that are pre-listed in the diary cards and CRB, together with the intensity scales.

Table 9.2: Solicited injection site reactions for children 6 through 35 months of age: terminology, definitions, and intensity scales

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

CRB term (MedDRA LLT)	Injection site tenderness	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3 **(CRB)**: Cries when injected limb is mobilized, or the movement of the injected limb is reduced Grade 3 **(diary card)**: Cries when injected limb is moved or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

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

Table 9.3: Solicited systemic reactions for children 6 through 35 months of age: terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
MedDRA PT	Pyrexia	Vomiting	Crying	Somnolence	Decreased appetite	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	Grade 2: 2–5 episodes per 24 hours	Grade 2: 1–3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 2: Missed 1 or 2 feeds / meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

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

Important notes for the accurate assessment of temperature:

Subjects' parent(s) / guardian(s) are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card / memory aid, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is rectal for subjects enrolled in this study, however axillary is also acceptable if subjects' parent(s) / guardian(s) are unable to obtain the preferred route of measurement. Pre-vaccination temperature is also systematically collected by the Investigator on the source document. Tympanic thermometers must not be used.

9.3.3.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects' parent(s) / guardian(s) of subjects randomized into the Expanded safety analysis set will be instructed to record any other medical events that may occur during the 28-day period after each vaccination to be taken as per the study design. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from Day 0 until the 6-month follow-up phone call or end of influenza season surveillance. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the “Serious” box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the “Guideline for definition and collection of cases of febrile convulsion”, and this event will be considered an SAE. See Section 10 for further details on SAE reporting.

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

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

  For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.2 and Table 9.3).

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

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

- Grade 1
  CRF: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living
  Diary card: No interference with usual activities.
- Grade 2
  CRF: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant
  Diary card: Some interference with usual activities.
- Grade 3
  CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention
  Diary card: Significant; prevents usual activities.

- 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 9.3.3.3.5.

- Action taken for each AE (eg, medication)

  The action(s) taken by the subjects' parent or guardian 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
  - Discontinuation of study vaccination

- 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

9.3.3.3.4 Adverse Events of Special Interest

AESIs will be captured as SAEs and will be collected throughout the study. These include new onset of GBS, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis (26) (27) (28).

9.3.3.3.5 Assessment of Causality

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

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

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

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

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

9.4 Observational Endpoints and Assessment Methods

9.4.1 Efficacy

9.4.1.1 Efficacy Endpoints

- Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive for each circulating influenza A subtype and B lineage: A/H1N1, A/H3N2, B/Victoria and B/Yamagata
- Occurrence of an ILI starting ≥ 14 days after first vaccination, laboratory-confirmed as positive in each age subgroup of subjects
- Occurrence of an ILI starting ≥ 14 days after first vaccination, laboratory-confirmed as positive in each season
- Occurrence of an ILI starting ≥ 14 days after first vaccination, laboratory-confirmed as positive in subjects previously unvaccinated
- Occurrence of an ILI starting ≥ 14 days after first vaccination and before second injection, laboratory-confirmed as positive in subjects previously unvaccinated
- Occurrence of an ILI starting within 14-90 days after first vaccination, laboratory-confirmed as positive

- Occurrence of a modified CDC-defined ILI starting ≥ 14 days after first vaccination, and laboratory-confirmed as positive
- For subjects enrolled in both Season 1 (NH) and Season 3 (NH), occurrence of an ILI starting ≥ 14 days after first vaccination in Season 3 (NH), laboratory-confirmed as positive according to the vaccination pattern

Influenza-associated Events/ Health care utilization

The following events that are associated with ILI and occurring within 30 days after the ILI onset will be described for cases of laboratory-confirmed ILI caused by any viral type/subtype and for any ILI, respectively:

- Occurrence of AOM based on clinical diagnosis
- Occurrence of ALRI (eg, pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis, and croup) based on clinical and/or x-ray diagnosis
- Occurrence, duration, and intensity of ILI symptoms
- Occurrence of medication use (eg, antibiotics, antivirals)
- Occurrence of hospitalizations
- Occurrence of emergency room visits
- Occurrence of non-routine medical office visits (including urgent care visits)
- Occurrence of absenteeism

9.4.1.2 Efficacy Assessment Methods

9.4.2 Immunogenicity

9.4.2.1 Immunogenicity Endpoints

Immunogenicity for correlate of protection

- HAI titer for each vaccine strain 28 days after the last vaccination, together with occurrence of an ILI starting ≥ 14 days after vaccination, confirmed as positive for any influenza A or B type
- HAI titer for each vaccine strain 28 days after the last vaccination, together with occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed for viral strains similar to those contained in the vaccine

Antibody persistence

For subjects enrolled in both Season 1 (NH) and Season 3 (NH) and who are randomized to the Immunogenicity Subset, the HAI Ab titers against the 4 vaccine strains used in Season 1 (NH) will be measured at D0 before starting vaccination in Season 3 (NH). The following endpoints will be described.

- HAI individual titer on D0 and 28 days after the last vaccination of Season 1 (NH) and on D0 of Season 3 (NH)
- Detectable HAI titer, ie, with a titer ≥ 10 (1/dilution [dil]) at D0 and 28 days after the last vaccination of Season 1 (NH) and on D0 of Season 3 (NH)
- Subjects with titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination of Season 1 (NH) and on D0 of Season 3 (NH)

9.4.2.2 Immunogenicity Assessment Methods

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

A description of the anti-influenza antibody titration by inhibition of hemagglutination is found in Section 9.3.2.2.

9.4.3 Safety

There are no observational safety objectives.

10 Reporting of Serious Adverse Events

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

10.1 Initial Reporting by the Investigator

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

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

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

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

- By fax, to the following number: +1 570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address:

  Global PharmacoVigilance, Sanofi Pasteur
  Discovery Drive
  Swiftwater, PA 18370

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

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

10.2 Follow-up Reporting by the Investigator

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

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

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

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

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.3.3.3.5.

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

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

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

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

The Sponsor's RMO ([redacted] MD, GCDSE-V) will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the study protocol according to local regulations.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study subjects in the ESafAS for the recording of daily safety, ILI symptoms and associated events, and healthcare utilization described in Section 9.3.3.3. These diary cards will include pre-listed terms and intensity scales (see Table 9.2 and Table 9.3) as well as areas for free text to capture additional safety information or other relevant details. Subject's parent(s) / guardian(s) in the ESafAS 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' parent(s) / guardian(s) on how to correctly use these tools.

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

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

At specified intervals, the Investigator or an authorized designee will interview the subjects' parent(s) / guardian(s) to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for

this study under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

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

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

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

11.2 Data Management

Management of SAE Data

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

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

Management of Clinical and Laboratory Data

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

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

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

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

11.3 Data Review

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

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above (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.

Following the end of the Season 2, an interim analysis may be conducted by an independent statistician and reviewed by an IDMC during Season 3 in an attempt to stop the study at the end of Season 3 and avoid study extension in case the planned[redacted] cases cannot be achieved in 3 seasons. So the interim analysis will only be conducted if the likelihood of achieving the expected [redacted] cases at the end of Season 3 is low (avoiding to conduct the interim analysis if the expected [redacted] cases will be achieved) and if at least[redacted] evaluable influenza cases are collected (to ensure enough power to assess the objectives). At the interim analysis, the primary objective and first secondary objective will be assessed and the predictive power to demonstrate these objectives at the end of the ongoing season and at the end of the study will be calculated. The IDMC may recommend stopping the study at the end of Season 3 if the primary objective and first secondary objective are demonstrated (ie, the stopping rule for superior efficacy), if there is a high probability to demonstrate these objectives at the end of Season 3, or for futility if the probability to demonstrate the primary objective at the end of the study is too low. In addition, at the time of the interim analysis, other efficacy and safety objectives may be assessed on the available data for information.

The full analysis of all study objectives will be performed at the end of the study. In case the study is to be stopped prematurely following the results of an interim analysis, the full statistical report may be delivered in more than one step if deemed necessary.

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Hypotheses

12.1.1.2 Statistical Methods

Efficacy

The vaccine efficacy of the 2 groups will be compared in a step-wise manner:

A non-inferiority testing approach will be used first, using a non-inferiority margin of -10%. If non-inferiority is demonstrated, a superiority test will be used using a margin of 5%. Both tests will use a one-sided Type I error at 2.5%, and there is no need for multiplicity adjustment due to the step-wise approach.

The rVE of QIV-HD to QIV-SD will be estimated for primary endpoint as follows:

rVE= (1- (CHD / NHD) / (CSD / NSD)) × 100%

where:

- CHD and CSD are the numbers of influenza cases meeting the considered primary endpoint definition in the QIV-HD and QIV-SD groups, respectively.
- For analysis in per-protocol analysis set, the first episode among those occurring more than 14 days after the last vaccination will be considered. For analysis in full analysis set, the first episode among those occurring more than 14 days after the first vaccination will be considered.
- If subject experiences multiple occurrences of the same endpoint, only the first episode will be considered
- NHD and NSD are the numbers of subjects in the QIV-HD and QIV-SD groups, respectively.

CIs for vaccine efficacy will be calculated by an exact method assuming a Binomial distribution of the number of cases in the QIV-HD group conditional on the total number of cases in both groups.

The vaccine efficacy of QIV-HD will be considered as non-inferior to QIV-SD if the lower bound of the rVE is > -10%, and superior to QIV-SD if the lower bound of the CI for the rVE is > 5%. The Per-Protocol Analysis Set for Efficacy (PPASE) will be used as the primary analysis set for the non-inferiority test and the Full Analysis Set for Efficacy (FASE) will be used as the primary analysis set for the superiority test.

If the interim analysis is conducted, an alpha spending method quoted by Lan and Demets (power family, phi=2) will be used to maintain an overall Type I error (the 'alpha') of 0.025 one-sided, considering that[redacted] of information time is reached at the time. Consequently, a one-sided nominal alpha of [redacted] and [redacted] will be used at interim and final analysis, respectively. This corresponds to [redacted] and [redacted] two-sided CIs to be used at interim and final analysis, respectively.

Should the interim analysis results fulfill the stopping rules as defined in Section 12.4, the study will be stopped at the end of Season 3 and the rVE will be estimated in the final analysis using a two-sided 95% CI if the superior efficacy stopping rule is fulfilled at the interim analysis or [redacted] CI if otherwise.

A sensitivity analysis of the primary objective excluding all siblings participating in the study will also be provided to eliminate potential bias due to within-siblings flu contamination.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses

12.1.2.1.1 Statistical Methods

If the primary objective is demonstrated, the secondary confirmatory objectives will be tested. A hierarchical testing combined with graphical approach will be used to adjust the multiplicity of the 4 secondary confirmatory objectives, which prevents any inflation of the overall one-sided Type I error beyond 2.5%.

Efficacy

For the first secondary objective, a superiority test will be used using a more stringent margin of [redacted] with the same nominal alpha levels being used in the interim analysis (ie, one-sided[redacted]) and in the final analysis (ie, one-sided[redacted] if the stopping rule for superior efficacy is not fulfilled at the interim analysis or one-sided[redacted] if otherwise) for the primary objective.

At the time of the final analysis, if superiority is demonstrated, a graphical approach will be applied to control alpha within the 2 efficacy objectives. If one of them is claimed for efficacy using a two-sided 97.5% CI, then the other one will be tested using a two-sided 95% CI to assess superiority.

Estimation of rVE for efficacy objectives will be the same as those described for the primary objective above in Section 12.1.1.2 except that QIV-HD will be considered as superior to QIV-SD if the lower bound of the CI for the corresponding rVE is > 0%. The FASE will be used as the mains analysis set.

A complementary analysis of comparing Kaplan-Meier curves between QIV-HD and QIV-SD groups for the above secondary efficacy objectives will be performed.

For the prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine in subjects 6 months through 35 months of age, a secondary analysis using similarity based on genetic sequencing and an exploratory analysis using similarity based on antigenic similarity when available or genetic similarity otherwise will be performed.

A sensitivity analysis considering the first episode occurring from the first dose will be performed for the primary endpoint on the PPASE and FASE.

Estimation of efficacy for other secondary objectives will be as described for the primary objective above; for each estimate of efficacy, a 95% CI will be calculated.

Immunogenicity

If all of the above confirmatory efficacy objectives are demonstrated, a superiority testing approach will be used to compare post-vaccination GMTs and seroconversion rates between QIV-HD and QIV-SD groups for each strain using a one-sided test with Type I error rate of 0.025 following the individual hypotheses:

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

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

where s: strain

If superiority is demonstrated for post-vaccination GMTs and seroconversion rates for the 4 strains, the immunogenicity of QIV-HD will be considered as superior to QIV-SD. The Full analysis set for immunogenicity (FASI) will be used as the main analysis set.

Immunogenicity endpoints will be summarized for each vaccine strain with 95% CIs. The 95% CIs for the GMTs and GMT ratios (GMTRs) will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of GMTs will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the two-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Reverse cumulative distribution curves against each strain will be performed for baseline (V01) and post-vaccination immunogenicity (D28 or D56 as appropriate).

Safety

Safety results will be described for each vaccine group. The main parameters will be described with 95% CI.

12.1.3 Statistical Methods for Observational Objective(s)

Estimation of efficacy for the observational objectives will be as described for the primary objective; for each estimate of efficacy, a 95% CI will be calculated.

Descriptive analysis and statistical models will be used to investigate [redacted] As this analysis is exploratory, several statistical approaches such as [redacted]. These methods will be detailed in the SAP.

12.2 Analysis Sets

Seven main analysis sets will be used: the FASE, the PPASE, the full analysis set for Immunogenicity (FASI), the per-protocol analysis set for Immunogenicity (PPASI), the Immunogenicity Analysis Set (IAS), the safety analysis set (SafAS), and the expanded safety analysis set (ESafAS).

12.2.1 Full Analysis Set for Efficacy

The FASE will be used for the analysis of all efficacy objectives and is defined as the subset of randomized subjects who received at least 1 dose of the study vaccine. Subjects will be analyzed as randomized.

12.2.2 Safety Analysis Set

The SafAS will be used for SAEs/AESIs analyses and is defined as those subjects who have received at least one dose of the study vaccine(s). In particular, sentinel subjects and the Re-vaccination Cohort will be included in SafAS.

12.2.3 Expanded Safety Analysis Set

The ESafAS will be used for the analysis of solicited and unsolicited AEs and is defined as the sentinel subjects, subjects in the main cohort randomized in ESafAS and the Re-vaccination Cohort in Season 3 who received at least 1 dose of the study vaccine.
All subjects will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the 1st dose.

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

12.2.4 Per-Protocol Analysis Set for Efficacy

The PPASE is a subset of the FASE and will be used for primary and secondary efficacy objectives. The subjects presenting with at least one of the following conditions will be excluded from the PPASE:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule according to their previous vaccination history
- 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
- For previously unvaccinated subjects, subject did not receive 2nd injection in the proper time window (28 days to 38 days after first injection)
- Subject received non-study influenza vaccine

- Subject did not have at least one contact point more than 14 days after vaccination and before the end of the surveillance period

For note, any cases between dose 1 and dose 2 for subjects receiving two doses will not be considered in the PPASE analysis.

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

In the event of a local or national immunization program with a pandemic influenza vaccine or other vaccine, subjects who receive 1 or more doses of pandemic influenza vaccine or other vaccine at any time during the study will not be withdrawn from the study.

Subjects will be analyzed as treated.

12.2.5 Full Analysis Set for Immunogenicity

The FASI will be used as the main analysis set for secondary superior immunogenicity objective and is defined as the subjects randomized in Immunogenicity Subset in Season 1 who received at least 1 dose of the study vaccine and had one post-vaccination blood sample. Subjects will be analyzed as randomized.

12.2.6 Per-Protocol Analysis Set for Immunogenicity

The PPASI is a subset of the FASI and will be used for secondary superior immunogenicity objective as a sensitivity analysis. The subjects presenting with at least one of the following conditions will be excluded from the PPASI:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule according to their previous vaccination history
- 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
- For previously unvaccinated subjects, subject did not receive 2nd injection in the proper time window (28 days to 38 days after first injection)
- Subject did not provide post-dose serology samples in the proper time window or a post-dose serology sample was not drawn
- Subject received concomitant treatment that may affect the immunogenicity[a] or a non-study influenza vaccine, prior to the post-vaccination blood sample

[a] other vaccines, blood products, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors

In the event of a local or national immunization program with a pandemic influenza vaccine or other vaccine, subjects who receive 1 or more doses of pandemic influenza vaccine or other vaccine at any time during the study will not be withdrawn from the study.

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

Subjects will be analyzed as treated.

12.2.7 Immunogenicity Analysis Set

The IAS will be used for all descriptive immunogenicity objectives and is defined as the subjects in the main cohort randomized in Immunogenicity Subset and the subjects in the Re-vaccination Cohort in Season 3 who received at least 1 dose of the study vaccine and had one post-vaccination blood sample. Subjects will be analyzed as treated.

For analysis of immunogenicity by NT and ELLA methods, the subset of IAS with available results on the considered serological method will be used.

For correlate of protection assessment, subjects part of both IAS and FASE will be considered.

12.2.8 Populations Used in Analyses

In addition to the ones above, all randomized subjects with data in the CRB will be taken into account in the description of the population (eg, the disposition, the demographic, or baseline characteristics).

12.3 Handling of Missing Data and Outliers

12.3.1 Efficacy

For primary objective, a time-to-event analysis will be conducted to address the possible imbalance in the drop-out rates between vaccine groups. Further details will be described in SAP.

12.3.2 Immunogenicity

For HAI and ELLA tests, in order to appropriately manage replicate values for analysis purposes, the individual geometric mean of all values will be computed for each blood sample after managing extreme values as described. The computed value is then considered the titer for that particular blood sample.

- If a titer is < LLOQ, then the computed value, LLOQ/2, will be used.
- If a titer is ≥ LLOQ and < upper limit of quantitation (ULOQ) , 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.

For the secondary confirmatory immunogenicity objective, if the degree of missing immunogenicity data in FASI is unexpectedly high (more than[redacted]) on HAI data for at least one strain, a sensitivity analysis with multiple imputation methods will be performed.

12.3.3 Safety

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

12.4 Interim / Preliminary Analysis

Due to the unpredictable epidemiology of influenza, the sample size and/or the duration of the study may be adjusted based on the blinded number of influenza cases in order to maintain the likelihood of achieving the expected number of influenza cases for the primary endpoint.

In any case, the study will not stop before the 3 influenza seasons are completed. However, following the end of the second influenza season, if the likelihood of achieving the expected[redacted] cases at the end of the Season 3 is too low, and if at least[redacted] influenza cases meeting the primary endpoint have occurred, an interim analysis is planned to be conducted by an independent statistician and reviewed by an IDMC during Season 3. The study may stop if the primary objective and first secondary objectives are demonstrated, if there is a high probability to demonstrate these objectives at the end of the ongoing season, or for futility if the probability to demonstrate the primary objective at the end of the study is too low.

The stopping rules are:

[redacted]

Detailed statistical methods for the calculation of predicted total number of evaluable cases and the predictive power will be provided in the SAP.

12.5 Determination of Sample Size and Power Calculation

A total of approximately 13,320 subjects will be enrolled: 100 subjects will be enrolled in the 2020-2021 NH influenza season in the open-label Sentinel Safety Cohort and 13,220 subjects in the main cohort will be enrolled over 3 subsequent influenza seasons with a randomization ratio of 1:1 for QIV-HD to QIV-SD.

Table 12.1: Planned sample size by vaccine and influenza season

Vaccine	Number of Subjects		
QIV-HD for open-label, Sentinel Safety Cohort	**100**		
Vaccine	**Season 1 (NH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis set**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 2 (SH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis set (ESafAS)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 3 (NH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis set (ESafAS)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	Season 3 (NH) Re-vaccination Cohort†		
QIV-HD	[redacted]		
QIV-SD			
Total			
Overall Total	**13,320 subjects with [redacted] tested for immunogenicity*, [redacted] for expanded safety, and 100 Sentinel Safety Cohort subjects**		

Abbreviations: NH, Northern Hemisphere; QIV-HD, high-dose quadrivalent influenza vaccine; QIV-SD, standard-dose quadrivalent influenza vaccine; SH, Southern Hemisphere

* Number of subjects who provide blood samples in Season 1 (NH) is greater than in Season 2 (SH) or Season 3 (NH) because unlike the Season 2 and 3 sera, which will be used for the descriptive immunogenicity results and [redacted] Season 1 (NH) sera will also be used to demonstrate immunogenicity superiority.

†Approximately [redacted] subjects from the Immunogenicity Subset of Season 1 (NH) will re-enroll in Season 3 (NH) to be evaluated for antibody persistence and re-vaccination immunogenicity endpoints. These subjects will not be part of the approximately [redacted] subjects in Season 3 who are being followed for ILI surveillance and efficacy.

Table 12.2: Samples sizes for evaluation based on assessment method

Assessment Method	Number of Subjects
hemagglutination inhibition (HAI)	approximately [redacted] subjects (all subjects in the Immunogenicity Subset)
seroneutralization (SN)	approximately [redacted] subjects in Season 1's Immunogenicity Subset
enzyme-linked lectin assay (ELLA)	Approximately [redacted] subjects in Season 1's Immunogenicity Subset

Calculation of Sample Size

For efficacy assessments:

The sample size needed for the assessment of the primary objective of the study is expected to be approximately [redacted] subjects and may be adjusted based on the blinded number of cases in order to maintain the likelihood of achieving approximately [redacted] evaluable influenza cases from the PPASE meeting the primary endpoint.

These required numbers of evaluable influenza cases would provide at least [redacted] power at final analysis to conclude on the primary objective under the following assumptions:

- The true rVE of QIV-HD to QIV-SD is [redacted]
- An overall one-sided Type I error rate 0.025 ([redacted] spent at interim and final analysis, respectively)
- The lower bound of the CI of rVE should be > 5%
- An allocation ratio of QIV-HD to QIV-SD of 1:1
- An overall influenza attack rate of [redacted] for the occurrence of an influenza case in the QIV-SD group
- [redacted] of enrolled subjects evaluable for the primary endpoint

Based on the same assumptions and using a [redacted] threshold, the power for the first secondary objective at final analysis is expected at [redacted] approximately.

For the assessment of the two other secondary confirmatory efficacy objectives, the assumptions will be similar to those for primary objective except

- The lower bound of the CI for the corresponding rVE will be superior to 0 %.
- The true rVE of QIV-HD to QIV-SD is [redacted] for each subset (ie, subjects 6 through 35 months of age against similar strains and subjects 6 through 24 months of age against any strains)
- [redacted] evaluable influenza cases ([redacted] of total cases) from each subset

For each objective, a [redacted] power will be achieved with a two-sided 97.5% CI and an [redacted] power will be achieved with a two-sided 95% CI.

For the immunogenicity assessments:

Approximately [redacted] subjects will be assessed for HAI immunogenicity in Season 1. Based on Phase II immunogenicity results and assuming [redacted] of non-evaluable subjects, this provides approximately [redacted] probability to obtain 95% CIs of ratios of GMTs and differences in seroconversion rates excluding equality for a given season (formulation).

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

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

13.2 Source Data and Source Documents

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

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

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

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

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

[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.

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

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

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

Subjects' race and ethnicity will be collected in this study because these data are required by regulatory agencies (30).

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

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

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

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

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

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

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

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

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

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

13.4.2 Audits and Inspections

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

13.4.3 Archiving

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

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

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

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

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

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

13.7 Publication Policy

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

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

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

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15 Signature Page

Signature Page for VV-CLIN-0563179 v4.0
flu-qiv-hd-qhd00014-protocol

Approve & eSign	[redacted] Clinical [redacted]