NCT03698279

Safety and Immunogenicity of Different Dosages of High-Dose Quadrivalent Influenza Vaccine in Children 6 Months to 17 Years of Age

Phase II, randomized, staged, modified double-blind, multi-center study in the United States and Canada to evaluate the safety and immunogenicity of 3 dosages of QIV-HD administered intramuscularly in children 6 months to 17 years of age.

Clinical Study Protocol Amendment 1

Health Authority File Number:	BB-IND #: 17556
WHO Universal Trial Number (UTN):	U1111-1189-3713
Study Code:	QHD04
Development Phase:	Phase II
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2018–2019 Strains (QIV-HD)
Form / Route:	Liquid / Intramuscular
Indication For This Study:	One dose or 2 doses for subjects 6 months to 17 years of age
Manufacturer:	Same as Sponsor
Coordinating Investigator	[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]
Global Safety Officer:	[redacted]

Clinical Trial Manager: [redacted]

Version and Date of the Protocol: Version 3.0 dated 25 February 2019

History of Protocol Versions

Version	Date	Comments
1.0	29 March 2018	Version submitted to the IEC/IRB
2.0	**24 July 2018**	**Version approved by the IEC/IRB and used in the study**

Table of Contents

List of Tables

List of Figures

Synopsis

Company:	Sanofi Pasteur Inc.
Investigational Product:	High-Dose Quadrivalent Influenza Vaccine, (Zonal Purified, Split Virus) 2018-2019 Strains (QIV-HD)
Active Substances:	A/(H1N1), A/(H3N2), B (Victoria Lineage), and B (Yamagata Lineage)

Title of the Study:	Safety and Immunogenicity of Different Dosages of High-Dose Quadrivalent Influenza Vaccine in Children 6 Months to 17 Years of Age
Development Phase:	Phase II
Coordinating Investigator:	[redacted]
Study Sites:	This will be a multi-center study conducted at 16 sites in the United States (US) and Canada. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	October 2018 to October 2019
Study Design, Schedule of Study Procedures, **and Methodology:**	QHD04 will be a Phase II, randomized, staged, modified double-blind, active-controlled, multi-center study to be conducted in 700 children 6 months to 17 years of age to evaluate the safety and immunogenicity of 3 dosages of high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) route versus standard-dose quadrivalent influenza vaccine (QIV-SD) or adjuvanted trivalent influenza vaccine (TIV). The study will be divided into 13 groups and will enroll in 4 stages. The study will use a stepwise age de-escalation and dose ascension design for children 6 months to < 5 years of age. Children 5 to 8 years of age will also undergo a dose ascension design and begin enrollment in Stage 1. Children 9 to 17 years of age will be enrolled in Stage 1 and randomized to receive all 3 dose formulations (ie, 30 µg, 45 µg, and 60 µg hemagglutinin [HA]/strain/dose). An early safety data review (ESDR) will be conducted after Visit (V) 02 (at Day [D] 8 post-vaccination) of Stages 1, 2, and 3 for children 6 months to < 5 years of age and Stages 1 and 2 for children 5 to 8 years of age. The ESDR for children 6 months to < 5 years of age will be independent of the ESDR for children 5 to 8 years of age. Enrollment of subjects in the next stage will be initiated if the safety review results are satisfactory. The details of the safety reviews are described in the ESDR section. The study groups and stages are described in Table S1 and the study flow chart is summarized in Figure S1, Figure S2, and Figure S3.

Table S1: Description of study design

Stage (Country)	Age Group (Vaccination Status*)	Study Group	N	Vaccine	Vaccine Dosage (µg HA/strain/dose)†
1 (US)	9 to 17 years (previously vaccinated and unvaccinated)	12	30	QIV-HD	30
			30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
	9 to 17 years (previously vaccinated and unvaccinated)	13	30	QIV-HD	60
			30	unadjuvanted QIV-SD	15
	5 to 8 years (previously vaccinated and unvaccinated)	9	30	QIV-HD	30
			10	unadjuvanted QIV-SD	15
	36 months to < 5 years (previously vaccinated and unvaccinated)	1	30	QIV-HD	30
			10	unadjuvanted QIV-SD	15
2 (US)	5 to 8 years (previously vaccinated and unvaccinated)	10	30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
	36 months to < 5 years (previously vaccinated and unvaccinated)	2	30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
	6 to < 36 months (previously vaccinated and unvaccinated)	3	30	QIV-HD	30
			10	unadjuvanted QIV-SD	15
3 (US)	5 to 8 years (previously vaccinated and unvaccinated)	11	30	QIV-HD	60
			30	unadjuvanted QIV-SD	15
	36 months to < 5 years (previously vaccinated and unvaccinated)	4	45	QIV-HD	60
			45	unadjuvanted QIV-SD	15
	6 to < 36 months (previously vaccinated and unvaccinated)	5	30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
4 (US)	6 to < 36 months (previously unvaccinated)	6	30	QIV-HD	30, 45, or 60†
			30	unadjuvanted QIV-SD	15
	6 to < 36 months (previously vaccinated)	7	30	QIV-HD	30, 45, or 60†
			30	unadjuvanted QIV-SD	15
4 (Canada)	6 to < 24 months (previously unvaccinated)	8	30	QIV-HD	30, 45, or 60†
			30	adjuvanted TIV	7.5

Abbreviations: HA, hemagglutinin; QIV-SD, standard-dose quadrivalent influenza vaccine; TIV, trivalent influenza vaccine; µg, microgram.

* Vaccination status is determined by information provided by the parent / guardian.

† Dosage selection will be based on the ESDR of the prior Stages. The highest dosage with an acceptable safety review from prior Stages will determine the dose evaluated in Stage 4.

Figure S1: Study design flow chart for subjects 6 months to < 5 years of age

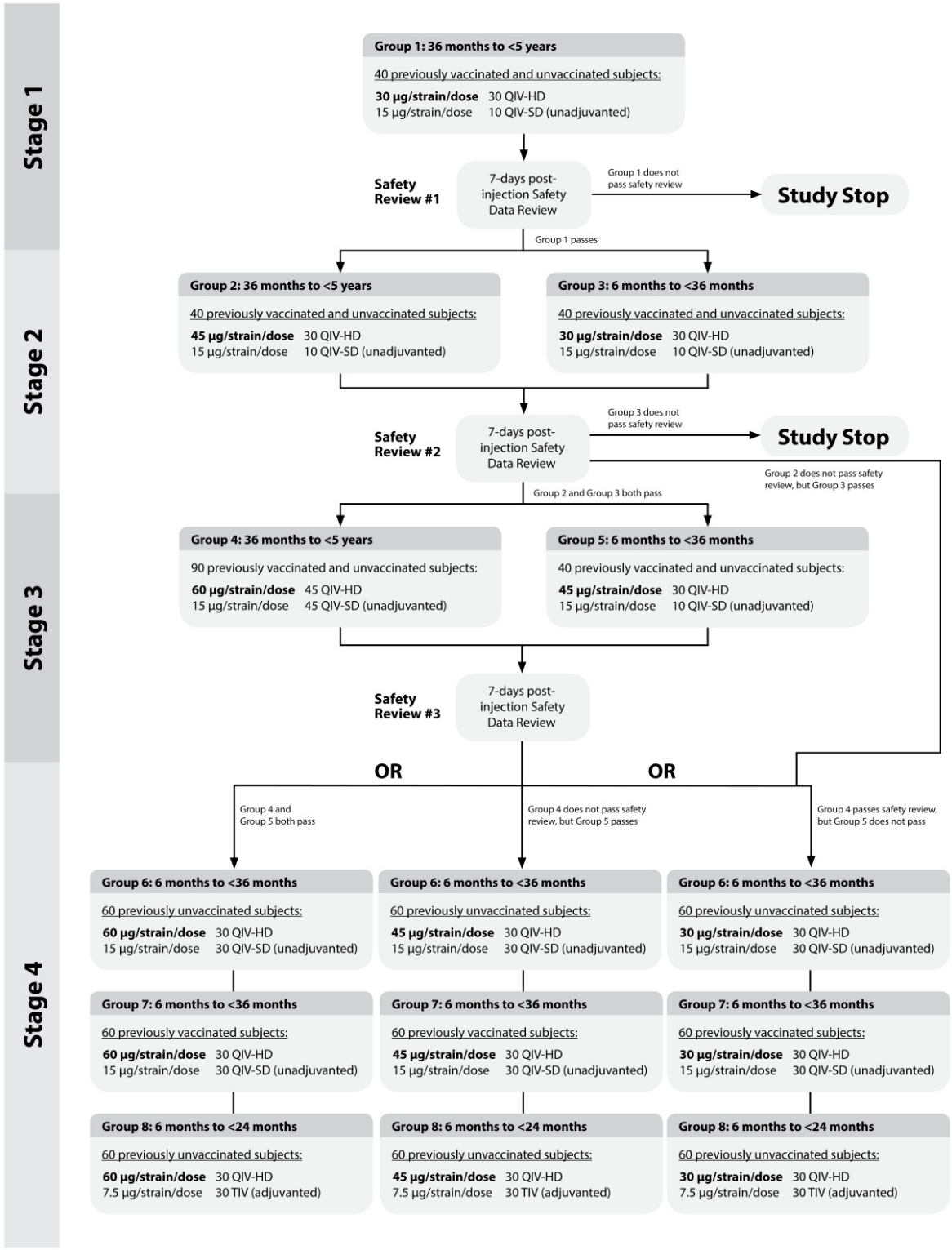


Figure S2: Study design flow chart for subjects 5 to 8 years of age

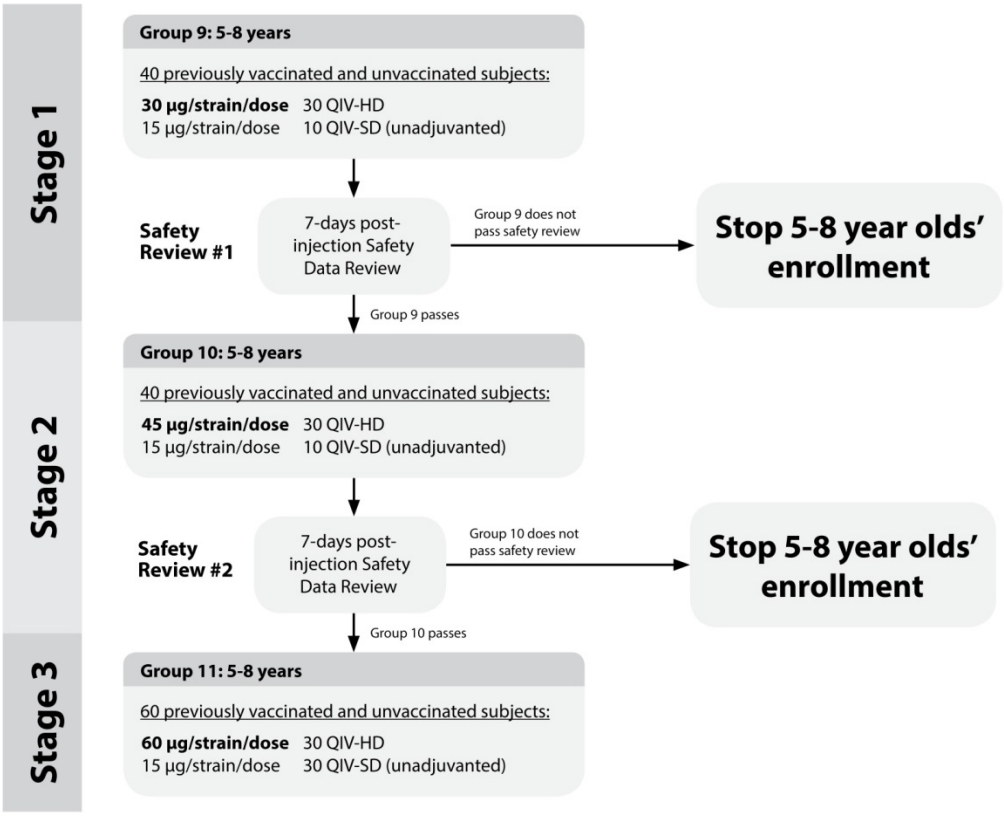
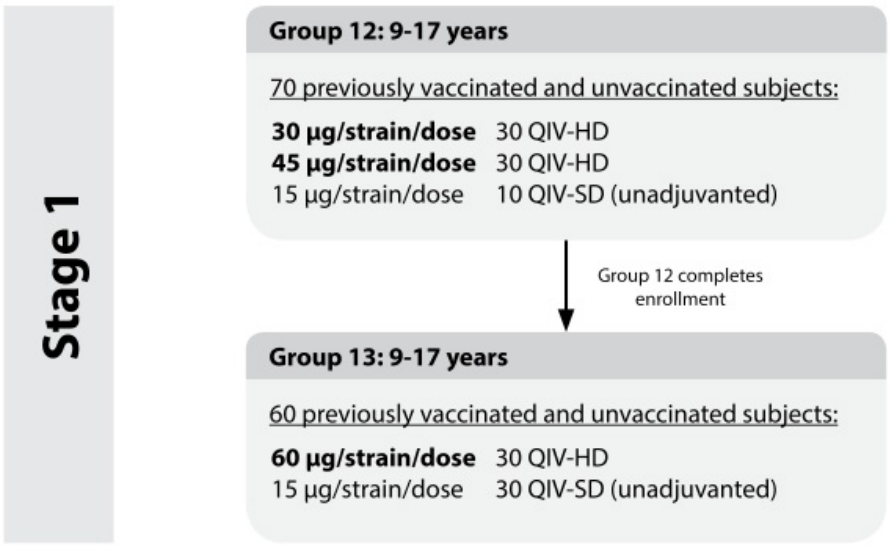


Figure S3: Study design flow chart for subjects 9 to 17 years of age



	Vaccination All eligible subjects will be randomized to receive 1 or 2 doses of either QIV-HD, Fluarix® Quadrivalent (unadjuvanted QIV-SD), or FLUAD Pediatric® (adjuvanted TIV). The dosage of QIV-HD that is administered will depend on both the age of the subject and the stage at which he / she is enrolled. • Previously influenza vaccinated or unvaccinated subjects 9 to 17 years of age (hereafter will be referred to as subjects 9 to 17 years of age) will receive 1 dose of the QIV-HD or the comparator vaccine on D0. • Previously influenza vaccinated subjects 6 months to 8 years of age will receive 1 dose of the QIV-HD or the comparator vaccine on D0. • Previously influenza unvaccinated subjects 6 months to 8 years of age will receive 2 doses of the QIV-HD or the comparator vaccine. Each dose will be administered 28 days apart (at D0 and D28). Of note, the highest dosage with an acceptable safety review in prior stages will determine the dose evaluated in Stage 4. An unblinded administrator at each site will administer the vaccine. ***Blood sampling*** Subjects will provide 2 or 3 blood samples, regardless of the stage of enrollment: Subjects 9 to 17 years of age will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (D28 [+7 days]) for hemagglutination inhibition (HAI) and seroneutralization (SN) testing. Note: Subjects 9 to 17 years of age are scheduled for 2 site visits. However, the second visit is designated as V03 to be consistent with the visits nomenclature of the 6 months to 8 years age groups. Previously influenza vaccinated subjects 6 months to 8 years of age will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (D28 [+7 days]) for HAI and SN testing. Previously influenza unvaccinated subjects 6 months to 8 years of age will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (D28 [+7 days]) and V05 (28 days after V03 [+7 days]) for HAI and SN testing. Note: The blood sample will be taken prior to vaccination during any visit when a subject receives a vaccination. ***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). Solicited reactions will be collected up to 7 days after each vaccination, and unsolicited AEs will be collected up to D28 (V03) for subjects receiving 1 dose and up to D56 (V05) for subjects receiving 2 doses. Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected throughout the study (D0 through approximately 6 months after the last vaccination). It is to be noted that AESIs will be captured as SAEs. These include new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis. Subjects / parents / guardians will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study. The study staff will contact subjects 9 to 17 years of age or the subjects' parents /

	guardians by phone at D8 (+2 days) post-vaccination to identify whether the subject experienced any SAEs not yet reported and will remind the subjects / subjects' parents / guardians to bring the completed diary card with them to V03 (D28 [+7 days]). The study staff will review the D0 to V03 safety data with the subjects at V03. Subjects 6 months to 8 years of age will return to the site at D8 (+3 days) after each vaccination. Staff will review the recorded solicited reactions and unsolicited AEs, and determine whether the subject experienced any SAEs and AESIs not yet reported. Staff will review the safety data with subjects / subjects' parents / guardians at each visit. Staff will also remind the subjects / subjects' parents / guardians to bring the completed diary card with them to the subsequent visit. The interactive response technology (IRT) system will be used to randomly assign subjects to a study product 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. ESDRs will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration. A stepwise dosage ascension approach will be applied to subjects in age group 5 to 8 years (30 µg, 45 µg, and 60 µg HA/strain/dose). A stepwise age de-escalation vaccination approach will be taken for subjects in age group 36 months to < 5 years of age, with an ESDR prior to vaccinating subjects in the age group 6 to < 36 months of age as well as stepwise dosage ascension. The ESDR will be performed following V02 in subjects 6 months to 8 years of age (refer to Figure S1 and Figure S2). The ESDRs for this study are planned after the 6 months to 8 years age groups in each stage have been vaccinated and have provided safety data for Days 0 to 7 post-vaccination, using the data collection methods described in the protocol. ESDR will not be performed for subjects 9 to 17 years of age. During each ESDR, enrollment of subjects will be paused. However, already enrolled subjects 6 months to 8 years of age who require 2 vaccinations because of their previous vaccination status will receive their second dose at D28 as scheduled, which may be prior to the ESDR. Following a satisfactory safety review, enrollment of subjects will resume for the subsequent or appropriate Stage as described in Figure S1 and Figure S2. The study visits according to the Table of Study Procedures will continue to be followed for enrolled subjects within each active Stage (ie, subjects will complete their scheduled visits). The safety data collected will be entered into the CRBs and summarized by the Sponsor in a blinded manner. A review will be performed by the Sponsor during the Safety Management Team (SMT) meetings. 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 early interim safety analysis will continue unchanged.) The following safety parameters will be assessed as part of the early safety review: • Immediate reactions • Solicited injection site and systemic reactions • Unsolicited AEs • SAEs (including AESIs)

	Enrollment will be paused during the review, and 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 decision will be made as to whether enrollment in the study will be allowed to resume. Case unblinding may be performed if necessary.
Interruption of the Study	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Independent Ethics Committees (IECs)/ Institutional Review Boards (IRBs), or the governing regulatory authorities in the US and Canada where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject or subjects' parents / guardians and should assure appropriate subject therapy and/or follow-up.
Objectives:	***Safety*** To describe the safety of each dosage of QIV-HD during the 28 days following each vaccination, and SAEs (including AESIs) throughout the study. ***Immunogenicity*** • To describe the antibody response induced by each dosage of QIV-HD used in the study compared with unadjuvanted QIV-SD by HAI measurement method. • To describe the antibody response induced by each dosage of QIV-HD used in the study compared with unadjuvanted QIV-SD by virus seroneutralization (SN) measurement method. • To describe the antibody response induced by the highest acceptable dosage of QIV-HD compared with adjuvanted TIV by HAI and virus SN measurement methods.
Endpoints:	***Safety*** Safety will be described for all subjects: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after each vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions and systemic reactions occurring up to 7 days after each vaccination. • Occurrence, nature (MedDRA system organ class [SOC] and PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to 28 days after vaccination. • Occurrence, nature (MedDRA SOC and PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the study.

	• Occurrence, nature (MedDRA PT), time to onset, and relationship to vaccination of AESIs throughout the study. ***Immunogenicity by HAI Method*** *For subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age:* • HAI antibody (Ab) titers obtained on D0 and D28 • Individual HAI titers ratio D28/D0 • Seroconversion (titer < 10 [1/dilution {dil}] at D0 and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28) • Percentage of subjects with titers ≥ 40 (1/dil) at D0 and D28 *For previously influenza unvaccinated subjects 6 months to 8 years of age:* • HAI Ab titers obtained on D0, D28, and D56 • Individual HAI titers ratio D28/D0 and D56/D0 • Seroconversion (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil] at D28 and D56, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28 and D56) • Percentage of subjects with titers ≥ 40 (1/dil) at D0, D28, and D56 ***Immunogenicity by SN Method*** *For subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age:* • Individual neutralization test (NT) Ab titer on D0 and D28 • Individual NT Ab titer ratio (fold increase in serum NT post-vaccination relative to D0) at D28 • Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28 • Fold-increase in NT Ab titer [post/pre] ≥2 and ≥ 4 at D28 • Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0 and D28 *For previously influenza unvaccinated subjects 6 months to 8 years of age:* • Individual NT Ab titer on D0, D28, and D56 • Individual NT Ab titer ratio (fold increase in serum NT post-vaccination relative to D0) at D28 and D56 • Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28 and D56 • Fold-increase in NT Ab titer [post/pre] ≥2 and ≥ 4 at D28 and D56 • Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0, D28, and D56

Planned Sample Size:	A total of 700 subjects are planned to be enrolled:
	• Group 1: 40 subjects; 36 months to < 5 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 30 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 2: 40 subjects; 36 months to < 5 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 45 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 3:40 subjects; 6 to < 36 months of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 30 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 4: 90 subjects; 36 months to < 5 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 45 (QIV-HD: 60 µg HA/strain/dose)
	  • n = 45 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 5: 40 subjects; 6 to < 36 months of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 45 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 6: 60 subjects; 6 to < 36 months of age (previously influenza unvaccinated subjects)
	  • n = 30 (QIV-HD: 60 µg, 45 µg, or 30 µg HA/strain/dose)*
	  • n = 30 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 7: 60 subjects; 6 to < 36 months of age (previously influenza vaccinated subjects)
	  • n = 30 (QIV-HD: 60 µg, 45 µg, or 30 µg HA/strain/dose)*
	  • n = 30 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 8: 60 subjects; 6 to < 24 months of age (previously influenza unvaccinated subjects)
	  • n = 30 (QIV-HD: 60 µg, 45 µg, or 30 µg HA/strain/dose)*
	  • n = 30 (adjuvanted TIV: 7.5 µg HA/strain/dose)
	• Group 9: 40 subjects; 5 to 8 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 30 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 10: 40 subjects; 5 to 8 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 45 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 11: 60 subjects; 5 to 8 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 60 µg, 45 µg, or 30 µg HA/strain/dose)*
	  • n = 30 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)

	• Group 12: 70 subjects; 9 to 17 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 30 µg HA/strain/dose)
	  • n = 30 (QIV-HD: 45 µg HA/strain/dose)
	  • n = 10 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	• Group 13: 60 subjects; 9 to 17 years of age (previously influenza vaccinated and unvaccinated subjects)
	  • n = 30 (QIV-HD: 60 µg HA/strain/dose)
	  • n = 30 (QIV-SD [unadjuvanted]: 15 µg HA/strain/dose)
	* The dosage selection will be based on the ESDR by the SMT. The highest dosage with an acceptable safety profile based on the SMT review will be used in Stage 4.

Duration of Participation in the Study:	The duration of each subject's active participation in the study will be approximately 28 days for subjects receiving 1 dose of vaccine and approximately 56 days for subjects receiving 2 doses of vaccine. There will be a safety follow-up contact at 6 months after the last vaccination (approximately 180 days for subjects receiving 1 dose of vaccine and 208 days for subjects receiving 2 doses of vaccine).
Investigational Product 1:	High-Dose Quadrivalent Influenza Vaccine, (inactivated, Split Virus) 2018–2019 Strains (QIV-HD), provided in a pre-filled single-dose syringe
Form:	Suspension
Composition:	Each 0.35 milliliter (mL) dose of QIV-HD will contain: *Strains are based on World Health Organization (WHO) (Vaccines and Related Biological Products Advisory Committee [VRBPAC] in the US) recommendations for the 2018-2019 Northern Hemisphere (NH) influenza season.* ***Active Substances:*** A/Michigan/45/2015 X-275 (H1N1) 30 microgram (µg) HA A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) 30 µg HA B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 30 µg HA B/Phuket/3073/2013 (Yamagata lineage) 30 µg HA ***Excipients:*** Buffered saline solution quantity sufficient (qs) to appropriate volume Octylphenol Ethoxylate (Triton X-100®) not more than 175 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 Number:	UD20382 (US sites); UD20523 (Canadian sites)

Investigational Product 2:	High-Dose Quadrivalent Influenza Vaccine, (inactivated, Split Virus) 2018–2019 Strains (QIV-HD), provided in a pre-filled single-dose syringe
Form:	Suspension
Composition:	Each 0.52 mL dose of QIV-HD will contain: *Strains are based on WHO (VRBPAC in the US) recommendations for the 2018-2019 NH influenza season.* ***Active Substances:*** A/Michigan/45/2015 X-275 (H1N1) 45 µg HA A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) 45 µg HA B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 45 µg HA B/Phuket/3073/2013 (Yamagata lineage) 45 µg HA ***Excipients:*** Buffered saline solution qs to appropriate volume Octylphenol Ethoxylate (Triton X-100) not more than 260 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 Number:	UD20383 (US sites); UD20522 (Canadian sites)
Investigational Product 3:	High-Dose Quadrivalent Influenza Vaccine, (Zonal Purified, Split Virus) 2018–2019 Strains (QIV-HD), provided in a pre-filled single-dose syringe
Form:	Suspension
Composition:	Each 0.7 mL dose of QIV-HD will contain: *Strains are based on WHO (VRBPAC in the US) recommendations for the 2018-2019 NH influenza season.* ***Active Substances:*** A/Michigan/45/2015 X-275 (H1N1) 60 µg HA A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) 60 µg HA B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 60 µg HA B/Phuket/3073/2013 (Yamagata lineage) 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 Number:	UD20384 (US sites); UD20524 (Canadian sites)

Control Product 1:	**Fluarix Quadrivalent** Influenza vaccine, inactivated, non-adjuvanted, presented in a pre-filled syringe (unadjuvanted QIV-SD) (GlaxoSmithKline Biologicals, Dresden, Germany)
Form:	Liquid solution
Composition:	Each 0.5 mL dose contains 15 µg of hemagglutinin (HA) for each of the following strains: *Strains are based on WHO (VRBPAC in the US) recommendations for the 2018-2019 NH influenza season.* ***Active Substances:*** A/Singapore/GP1908/2015 IVR-180 (H1N1) (A/Michigan/45/2015 [H1N1] pdm09-like virus) 15 µg HA A/Singapore/INFIMH-16-0019/2016 NIB-104 (H3N2) 15µg HA B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 15 µg HA B/Phuket/3073/2013 (Yamagata lineage) 15 µg HA ***Excipients:*** Octylphenol-10 (Triton X-100) ≤ 0.115 milligram (mg) α-Tocopheryl hydrogen succinate ≤ 0.135 mg Polysorbate 80 (Tween 80) ≤ 0.550 mg Fluarix Quadrivalent 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 Number:	Commercial batch: HJ9MN
Control Product 2:	**FLUAD Pediatric**: Influenza vaccine, adjuvanted, presented in a pre-filled syringe (Seqirus UK Limited, Maidenhead, UK) (adjuvanted TIV))
Form:	Liquid solution
Composition:	Each 0.25 mL dose contains 7.5 µg of HA for each of the following strains: *Strains are based on WHO (National Advisory Committee on Immunization [NACI] in Canada) recommendations for the 2018-2019 NH influenza season.* ***Active Substances:*** A/Singapore/GP1908/2015 IVR-180 (H1N1) (A/Michigan/45/2015 [H1N1] pdm09-like virus) 7.5 µg HA A/Singapore/INFIMH-16-0019/2016, IVR-186 (H3N2) 7.5 µg HA B/Maryland/15/2016 (B/Colorado/06/2017-like virus,Victoria lineage) 7.5 µg HA ***Excipients:*** Sodium chloride 2.00 mg Potassium chloride 0.05 mg Potassium dihydrogen phosphate 0.05 mg Disodium phosphate dehydrate 0.335 mg Magnesium chloride hexahydrate 0.025 mg Calcium chloride dihydrate 0.03 mg Water for injection qs to appropriate volume

	FLUAD Pediatric is formulated with the adjuvant MF59, an oil-in-water emulsion of squalene oil. FLUAD Pediatric 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 Number:	Commercial batch: 253774
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Aged 6 months to 17 years on the day of inclusion. 2) Assent form has been signed and dated by the subject (7 to 17 years of age) and 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) For subjects aged < 24 months: Born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 2.5 kg.
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be pre-menarche. 2) 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. 3) Receipt of any vaccine in the 30 days preceding the first study vaccination, or planned receipt of any vaccine before Visit 3 for subjects receiving 1 dose of influenza vaccine or Visit 5 for subjects receiving 2 doses of influenza vaccine. 4) For previously influenza vaccinated subjects: Previous vaccination against influenza in the preceding 6 months with either the study vaccine or another vaccine. 5) For previously influenza unvaccinated subjects: Any influenza vaccination (from birth to the day of inclusion) with either the study vaccine or another influenza vaccine. 6) For previously influenza unvaccinated subjects: Any previous laboratory confirmed influenza infection (from birth to the day of inclusion). 7) Receipt of immune globulins, blood or blood-derived products in the past 3 months. 8) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months). 9) 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. 10) Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on Investigator's judgement.

	11) Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntary. 12) Current alcohol abuse or drug addiction. 13) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion. 14) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 15) Identified as an immediate family member (ie, spouse, natural or adopted child, grandchild, nephew, or niece) of the Investigator or employee with direct involvement in the proposed study. 16) Personal history of GBS. 17) 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. 18) Personal history of clinically significant development delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder. 19) Known seropositivity for hepatitis B or hepatitis C.
Statistical Methods:	No hypotheses for safety and immunogenicity are planned. All analyses are descriptive. For the cohorts controlled by the non-adjuvanted QIV-SD, results will be described per stage, according to vaccine received and per age group. Age groups will also be pooled within the same vaccine group for the main endpoints. The descriptive results may also be presented by the pooled QIV-HD group (60 µg) in the two countries. Subgroup immunogenicity analyses according to previous vaccination status and/or baseline serostatus may be presented when appropriate. If any of the stages are not completed, analyses for the higher dose or next stage will not be performed. For the cohort controlled by the adjuvanted TIV, results will be described according to vaccine received. **Safety** The main parameters will be described by the 95% confidence interval (CI) based on the Clopper-Pearson method. The safety analysis set (SafAS) will be used for the safety analyses. **Immunogenicity** Immunogenicity endpoints will be summarized 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 2-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). The immunogenicity analysis set (IAS) will be used for the main immunogenicity analyses. Details of the above analyses will be described in a Statistical Analysis Plan (SAP).

	Calculation of Sample size The sample size is not powered.

Table of Study Procedures 1 (subjects 9 to 17 years of age)

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

Visit/Contact	**V01**	**Telephone Call**	**V03 (Second Visit)***	**Telephone Call**
Study timelines (days)	D0	D8	D28	180 days after V01
Time windows (days)		+2	+7	+14
Informed consent form / assent form signed and dated	X			
Inclusion / exclusion criteria	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)†	X			
History of seasonal influenza vaccination	X			
Medical history	X			
Collection of reportable concomitant medications	D0-D28			
Physical examination‡	X			
Randomization / allocation of subject number and unique dose number§	X			
Blood sampling (BL), 5 mL	BL0001**		BL0002	
Vaccination	X			
Immediate surveillance (30 min)	X			
DC provided††	DC1			
DC reviewed and collected			DC1	
Reporting of solicited injection site and systemic reactions	D0-D7			
Collection of unsolicited adverse events	D0-D28			
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; BL, blood sampling; D, day; DC, diary card; MA, memory aid; SAE, serious adverse event; V, visit.

* Visit 2 is designated as Visit 3 to be consistent with the visits nomenclature of the 6 months to 8 years age groups.

† For females of childbearing potential. The urine pregnancy test must be performed before vaccination. The pregnancy test must be negative for enrollment.

‡ Targeted physical examination based on medical history will be performed at V01. Targeted physical examination may also be performed at the second visit (designated as V03), if necessary.

§ Before blood sampling and vaccine injection.

** Collection of the blood sample before vaccination.

†† Subjects / 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 the second visit (designated as V03).

‡‡ Subjects / parents / guardians will use this MA to collect information on SAEs and AESIs from V03 (D28 [+7 days]) 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 to bring the completed diary card to the second visit (designated as V03).

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

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

Table of Study Procedures 2 (previously influenza vaccinated subjects 6 months to 8 years of age)

Phase II Study, 3 Visits, 1 Telephone Call, 1 Vaccination, 2 Blood Samples, approximately 180 Days' Duration per Subject

Visit/Contact	**V01**	**V02**	**V03**	**Telephone Call**
Study timelines (days)	D0	D8	D28	180 days after V01
Time windows (days)		+3	+7	+14
Informed consent form / assent form (if applicable*) signed and dated	X			
Inclusion / exclusion criteria	X			
Collection of demographic data	X			
History of seasonal influenza vaccination	X			
Medical history	X			
Collection of reportable concomitant medications	D0-D28			
Physical examination†	X			
Randomization / allocation of subject number and unique dose number‡	X			
Blood sampling (BL), 5 mL	BL0001§		BL0002	
Vaccination	X			
Immediate surveillance (30 min)	X			
DC provided**	DC1			
DC reviewed and recorded††		DC1		
DC collected			DC1	
Reporting of solicited injection site and systemic reactions	D0-D7			
Collection of unsolicited adverse events	D0-D28			
MA provided‡‡			X	
Study active phase termination record			X	
Follow-up telephone call§§				X
Reporting of 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; MA, memory aid; SAE, serious adverse event; V, visit.

* For children 7 to 8 years of age.

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

‡ Before blood sampling and vaccine injection.

§ Collection of the blood sample before vaccination.

** Subjects / 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 V03.

†† During V02, staff will review and record D0 to D7 data in the CRB, will find out whether the subject experienced any SAEs and AESIs not yet reported, and will remind the subjects to bring the completed diary card to V03.

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

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

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

Table of Study Procedures 3 (previously influenza unvaccinated subjects 6 months to 8 years of age)

Phase II Study, 5 Visits, 1 Telephone Call, 2 Vaccinations, 3 Blood Samples, approximately 208 Days' Duration per Subject

Visit/Contact	**V01**	**V02**	**V03**	**V04**	**V05**	**Telephone Call**
Study timelines (days)	D0	D8	D28	8 days after V03	28 days after V03	180 days after V03
Time windows (days)		+3	+7	+3	+7	+14
Informed consent form / assent form (if applicable*) signed and dated	X					
Inclusion / exclusion criteria	X					
Collection of demographic data	X					
History of seasonal influenza vaccination	X					
Medical history	X					
Collection of reportable concomitant medications	D0-D56					
Physical examination†	X		X			
Randomization / allocation of subject number and unique dose number‡	X					
Allocation of unique dose number			X			
Temporary and definitive contraindications			X			
Blood sampling (BL), 5 mL	BL0001§		BL0002§		BL0003	
Vaccination	X		X			
Immediate surveillance (30 min)	X		X			
DC provided§**	DC1		DC2			
DC reviewed and recorded††		DC1		DC2		
DC collected			DC1		DC2	
Recording of solicited injection site and systemic reactions	D0-D7		D28-D35			
Collection of unsolicited adverse events	D0-D28			D28-D56		
MA provided‡‡					X	
Study active phase termination record					X	
Follow-up telephone call§§						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; V, visit.

* For children 7 to 8 years of age.

† Targeted physical examination based on medical history will be performed at V01. Targeted physical examination may also be performed at V03 or V05, if necessary.

‡ Before blood sampling and vaccine injection

§ Collection of the blood sample before 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 from D28 to D35) and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V03 and D36 to V05.

†† During V02 and V04, staff will review and record D0 to D7 and D28 to D35 data in the CRB, will find out whether the subject experienced any SAEs and AESIs not yet reported, and will remind the subjects to bring the completed diary card to their next scheduled visit.

‡‡ Subjects / parents / guardians will use this MA to collect information on SAEs and AESIs from V05 to the end of the 6-month safety follow-up period.

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

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

List of Abbreviations

µg	microgram
Ab	antibody
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
ALRI	acute lower respiratory infections
AR	adverse reaction
BL	blood sampling
CDC	Centers for Disease Control and Prevention
CDM	Clinical Data Management
CI	confidence interval
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CRO	contract research organization
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	day
DC	diary card
dil	dilution
DP	drug product
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ESDR	early safety data review
FVFS	first visit, first subject
FVLS	first visit, last subject
GMT	geometric mean titer
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
GSK	GlaxoSmithKline
GSO	Global Safety Officer
HA	hemagglutinin

HAI	hemagglutination inhibition
HAU	hemagglutination unit
IAS	immunogenicity analysis set
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
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 quantitation
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MDCK	Madin-Darby canine kidney
MA	memory aid
mg	milligram
mL	milliliter
NACI	National Advisory Committee on Immunization
NT	neutralization test
NH	Northern Hemisphere
NMT	not more than
NSAID	non-steroidal anti-inflammatory drug
PT	preferred term
QIV	quadrivalent influenza vaccine
QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
qs	quantity sufficient
RBC	red blood cell
RMO	Responsible Medical Officer
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SN	seroneutralization
SMT	Safety Management Team
SOC	system organ class

TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
TMF	trial master file
ULOQ	upper limit of quantitation
US	United States
V	visit
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 Introduction

1.1 Background

This study will evaluate the safety and immunogenicity of 3 different dosages of quadrivalent influenza vaccine (QIV) in subjects 6 months to 17 years of age.

Influenza is a highly contagious, acute viral respiratory disease caused by influenza type A and type B viruses. Influenza can be a serious illness impacting millions of people each year. In the United States (US), for example, an average of over 200,000 people are hospitalized, and 23,000 people die from influenza-related respiratory and circulatory complications each year (1). During the 2015-2016 influenza season, the Centers for Disease Control and Prevention (CDC) reported an estimated 24.5 million Americans had influenza and close to 12,000 Americans died from pneumonia- and influenza-related deaths (2).

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. Members of high risk groups (eg, infants, younger children, adults 65 years of age and older, and children and adults 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 (3) (4) (5).

According to the CDC, seasonal flu-related hospitalizations have ranged from 7000 to 26,000 among children younger than 5 years in the US since 2010 (6). In a meta-analysis which estimated the global incidence of influenza associated with acute lower respiratory infections (ALRI) and the resultant mortality in children aged less than 5 years, 90 million (95% confidence interval [CI]: 49-162 million) new cases of influenza episodes, 20 million (95% CI: 13-32 million) cases of influenza-associated ALRI, and 1 million (95% CI: 1-2 million) cases of influenza-associated severe ALRI were calculated for this age group, causing 27,800 (95% CI: 7400-48,000) deaths worldwide in 2008 (7). In the US, 110 pediatric deaths due to influenza were reported during the 2016-2017 influenza season (8). In Canada, the Public Health Agency of Canada reported 6546 influenza-associated hospitalizations and 388 influenza-associated deaths during the 2016-2017 influenza season (9).

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, such as children less than 5 years, should receive an annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (10) (11) (12).

While influenza affects all age groups, 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. Vaccine coverage rates are high in children 6 months to 17 years of age as seen in the most recent data from the 2015-2016 US influenza season (59.3% in children versus 41.7% in adults) (13). However, data from the US Flu Vaccine Effectiveness Network during the same season showed a lower vaccine effectiveness rate against medically-attended influenza in younger

children 6 months to 8 years of age versus children 9 to 17 years of age. Therefore, an increase in antigen dose may improve protection against influenza in certain pediatric populations.

Thus, the goal of this Phase II study is to generate safety and immunogenicity data for 3 different dosages of high-dose quadrivalent influenza vaccine (QIV-HD) in order to select the appropriate vaccine dosage for advancement into the Phase III clinical development.

1.2 Background of the Investigational Product

Standard-dose trivalent influenza vaccines (TIV-SDs) contain 15 micrograms (µg) hemagglutinin (HA) of each of the 3 virus strains recommended by the WHO for use in that hemisphere's upcoming influenza season, for a total of 45 µg of HA antigen per dose. The immune response to a TIV-SD (15 µg HA/strain/dose) is lower in adults 65 years of age and older than in younger healthy adults (13). 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 TIV-SD, for a total of 180 µg of HA antigen per dose) was developed by Sanofi Pasteur and subsequently licensed in the US, Canada, and Australia to improve immune responses to influenza vaccine and vaccine efficacy in adults 65 years of age and older (14).

Previously, influenza vaccines contained a single influenza B strain. Two distinct genetic lineages of influenza B virus (the Victoria and the Yamagata lineages) have been co-circulating worldwide; both are responsible for influenza illnesses. However, the B strain included in seasonal influenza vaccines has not been the dominant circulating B lineage (mismatched strains) in approximately 25% of the seasons between 2000 and 2013 (15). To overcome the problem of B-strain selection and improve protection of the population against seasonal influenza virus strains, Sanofi Pasteur has been transitioning the Fluzone influenza vaccine portfolio from trivalent to quadrivalent formulations. The quadrivalent formulations contain 1 Victoria lineage B strain and 1 Yamagata lineage B strain. Thus, the issue of having to choose a strain from only one B lineage for the seasonal influenza vaccine and the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage is eliminated (16).

QIV-HD is produced using the same drug substance and drug product (DP) manufacturing processes as TIV-HD, except for the DP formulation and filling, which increases the fill volume up to 0.7 milliliter (mL) at a maximum in order to include the second influenza B strain at the same HA content as the other 3 strains. Since three different dosages of QIV-HD will be used in this dose exploration study (30 µg, 45 µg, and 60 µg of HA/strain/dose) to determine the appropriate vaccine dosage for the Phase III study, the volume will be reduced when obtaining dosages lower than 60 µg HA/strain/dose. Thus, the decrease in the amount of HA content corresponds to a decrease in the fill volume (injection volume) and each of the 3 QIV-HD dosages will have a different fill volume (injection volume).

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects enrolled in Study QHD04 will receive an influenza vaccine which will be either 1 of the 3 investigational QIV-HD, which differ by the amount of HA per strain, or one of the 2 licensed comparator vaccines, QIV-SD or adjuvanted TIV. Therefore, they will be vaccinated against the influenza viruses recommended by the WHO (Vaccines and Related Biological Products Advisory Committee [VRBPAC] in the US) for the 2018-2019 Northern Hemisphere (NH) influenza season. These children may be protected against those strains and may be less likely to catch influenza or develop complications during the 2018-2019 influenza season.

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) (17).

These reactions usually begin 6 to 12 hours after vaccination and usually resolve within 3 days. Results from a previous study of children 6 to 36 months of age demonstrated the safety of influenza vaccination in this age group (18).

Immediate allergic reactions (eg, hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component.

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 (19).

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 (20).

The potential risks listed here are not exhaustive; refer to the package inserts of the marketed vaccines (Fluarix® Quadrivalent and FLUAD Pediatric®) for additional information regarding potential risks (21) (22).

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

There is no post-marketing experience for QIV-HD as it has not been licensed yet. However, QIV-HD has been given to adults 65 years of age and older in 2 clinical studies, and no safety risks have been identified.

Post-marketing experience with QIV-SD and TIV-HD has not identified any events other than those described below, which were spontaneously reported during the post-approval use of TIV-SD, for addition to the QIV-SD package insert (23).

The following events have been spontaneously reported during the post-approval use of TIV-SD and TIV-HD (24). These events are reported voluntarily from a population of uncertain size, consequently it is not always possible to reliably estimate the frequency of the events or establish a causal relationship to vaccine exposure. Adverse events (AEs) were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to TIV-SD:

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

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

- *General Disorders and Administration Site Conditions*: pruritus, asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders*: vomiting

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

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

1.4 Rationale for the Study

While influenza affects all age groups, 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. Therefore, following a similar rationale that has been applied for adults 65 years of age and older, children may benefit from an increased antigen dose. Thus, this Phase II study will evaluate if an increased antigen dose in the QIV-HD investigational product is safe and will improve immune responses in the pediatric population aged 6 months to 17 years compared to currently licensed standard-dose quadrivalent influenza vaccines (QIV-SD) (15 µg HA/strain). The goal of QHD04 is to select the appropriate vaccine dosage for advancement to Phase III clinical development.

QHD04 is planned to be conducted during the 2018-2019 NH influenza season in approximately 700 children 6 months to 17 years of age and will evaluate 3 different dosages of QIV-HD in this pediatric population. The comparator vaccine will be Fluarix Quadrivalent which is a unadjuvanted QIV-SD and is manufactured by GlaxoSmithKline (GSK). Furthermore, another comparator vaccine, FLUAD Pediatric, which is an adjuvanted TIV and manufactured by Seqirus, will also be evaluated since FLUAD Pediatric is the only licensed pediatric vaccine which has been evaluated in relative efficacy studies. FLUAD Pediatric is only licensed for the pediatric indication (6 months to < 2 years of age) in Canada.

2 Study Objectives

Safety

To describe the safety of each dosage of QIV-HD used in the study during the 28 days following each vaccination, and serious adverse events (SAEs) (including adverse events of special interest [AESIs]) throughout the study.

The endpoints for the safety objective are presented in Section 9.1.2

I***mmunogenicity***

- To describe the antibody response induced by each dosage of QIV-HD used in the study compared with unadjuvanted QIV-SD by hemagglutination inhibition (HAI) measurement method.
- To describe the antibody response induced by each dosage of QIV-HD used in the study compared with unadjuvanted QIV-SD by virus seroneutralization (SN) measurement method.

- To describe the antibody response induced by the highest acceptable dosage of QIV-HD compared with adjuvanted TIV by HAI and virus SN measurement methods.

The endpoints for the immunogenicity objective are presented in Section 9.2.1

3 Investigators and Study Organization

This study will be conducted in 16 centers in the US and Canada. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the study centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" document.

Safety Management Team

An internal safety management team (SMT) will perform an analysis of safety data during the conduct of the study after the first vaccination (Early Safety Data Review [ESDR]).

Monitoring, Data Management, and Statistical Analysis

Biostatistics, data management, monitoring, and medical writing will either be subcontracted to a Contract Research Organization (CRO) or performed in-house by the Sponsor.

Laboratory Analysis

Testing will be performed at Sanofi Pasteur's Global Clinical Immunology (GCI) department or at an outsourced laboratory under the supervision of GCI.

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] Clinical Team Leader (CTL).

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form (ICF), the assent form, 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 SAEs occurring during the study that are

related to the product administered will be reported to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

QHD04 will be a Phase II, randomized, staged, modified double-blind, active-controlled, multi-center study to be conducted in 700 children 6 months 17 years of age to evaluate the safety and immunogenicity of 3 dosages of QIV-HD administered by IM route versus QIV-SD or adjuvanted TIV.

The study will be divided into 13 groups and will enroll in 4 stages. The study will use a stepwise age de-escalation and dose ascension design for children 6 months to < 5 years of age. Children 5 to 8 years of age will also undergo a dose ascension design and begin enrollment in Stage 1. Children 9 to 17 years of age will be enrolled in Stage 1 and randomized to receive all three dose formulations (ie, 30 µg, 45 µg, and 60 µg HA/strain/dose). An ESDR will be conducted after Visit (V) 02 (at Day [D] 8 post-vaccination) of Stages 1, 2, and 3 for children 6 months to < 5 years of age and Stages 1 and 2 for children 5 to 8 years of age. The ESDR for children 6 months to < 5 years of age will be independent of the ESDR for children 5 to 8 years of age. Enrollment of subjects in the next stage will be initiated if the safety review results are satisfactory.

The 13 study groups are divided according to:

- Age (9 to 17 years[a], 5 to 8 years[b], 36 months to < 5 years, 6 to < 36 months, or 6 to < 24 months)
- Influenza vaccination history (previously influenza vaccinated, previously influenza unvaccinated, or both)
- Administered vaccines (QIV-HD dosages [30 µg, 45 µg, or 60 µg HA/strain/dose], unadjuvanted QIV-SD, and adjuvanted TIV).

The study design and the safety reviews are described in Table 5.1 and Section 5.1.6, respectively. The study flow chart is outlined in Figure 5.1, Figure 5.2, and Figure 5.3. The details of the study design are described below.

Stage 1 will include 3 age groups (36 months to < 5 years, 5 to 8 years, and 9 to 17 years) and will be conducted in the US:

[a] "9 to 17 years" means from the 9th birthday to the day before the 18th birthday.

[b] "5 to 8 years" means from the 5th birthday to the day before the 9th birthday.

- Previously influenza vaccinated and unvaccinated subjects 36 months to < 5 years of age (Group 1) will be randomized to receive either QIV-HD at 30 µg HA/strain/dose or the unadjuvanted QIV-SD. Based on the early safety data review, the study will either stop (Group 1 does not pass safety review) or continue into Stage 2 .
- Previously influenza vaccinated and unvaccinated subjects 5 to 8 years of age (Group 9), will be randomized to receive either QIV-HD at 30 µg HA/strain/dose or the unadjuvanted QIV-SD. Based on the early safety data review, the enrollment of this age group will either stop (Group 9 does not pass safety review) or continue into Stage 2.
- Previously influenza vaccinated and unvaccinated subjects 9 to 17 years of age (hereafter will be referred to as subjects 9 to 17 years of age) will be divided into 2 groups (Group 12 and Group 13). Group 12 will be enrolled first and will be randomized to receive either QIV-HD at 30 µg, or 45 µg HA/strain/dose or the unadjuvanted QIV-SD. Once the enrollment of Group 12 is complete, subjects in Group 13 will be randomized to receive either QIV-HD at 60 µg or the unadjuvanted QIV-SD. Subjects 9 to 17 years of age will not undergo an ESDR.

Stage 2 will include 3 age groups (6 to < 36 months, 36 months to < 5 years, and 5 to 8 years) and will be conducted in the US:

- Previously influenza vaccinated and unvaccinated subjects 36 months to < 5 years of age (Group 2) will receive either QIV-HD at 45 µg HA/strain/dose or the unadjuvanted QIV-SD and previously influenza vaccinated and unvaccinated subjects 6 to < 36 months of age (Group 3) will receive either QIV-HD at 30 µg HA/strain/dose or the unadjuvanted QIV-SD. Based on the early safety data review, the study will either stop (Group 3 does not pass safety review), continue and skip to Stage 4 (Group 2 does not pass safety review), or continue to Stage 3 (Group 2 and Group 3 both pass the safety review).
- Previously influenza vaccinated and unvaccinated subjects 5 to 8 years of age (Group 10), will be randomized to receive either QIV-HD at 45 µg HA/strain/dose or the unadjuvanted QIV-SD. Based on the early safety data review, the enrollment of this age group will either stop (Group 10 does not pass safety review) or continue into Stage 3.

Stage 3 will include 3 age groups (6 to < 36 months, 36 months to < 5 years, and 5 to 8 years) and will be conducted in the US:

- Previously influenza vaccinated and unvaccinated subjects 36 months to < 5 years of age (Group 4) will receive either QIV-HD at 60 µg HA/strain/dose or the unadjuvanted QIV-SD; and previously influenza vaccinated and unvaccinated subjects 6 to < 36 months of age (Group 5) will receive either QIV-HD at 45 µg HA/strain/dose or the unadjuvanted QIV-SD. Based on the early safety data review, the highest dosage with an acceptable safety review will be determined and used in Stage 4.
- Previously influenza vaccinated and unvaccinated subjects 5 to 8 years of age (Group 11) will be randomized to receive either QIV-HD at 60 µg HA/strain/dose or the unadjuvanted QIV-SD.

Stage 4 will include 2 age groups (6 to < 36 months and 6 to < 24 months) and will be conducted in the US (subjects 6 to < 36 months) and Canada (subjects 6 to < 24 months):

- Previously influenza unvaccinated subjects 6 to < 36 months of age (Group 6) and previously influenza vaccinated subjects 6 to < 36 months of age (Group 7) will be randomized to receive either the highest dosage of QIV-HD with an acceptable safety review or the unadjuvanted QIV-SD.
- Previously influenza unvaccinated subjects 6 to < 24 months of age (Group 8) will receive either the highest dosage of QIV-HD with an acceptable safety review or the adjuvanted TIV.

Table 5.1: Description of study design

Stage (Country)	Age Group (Vaccination Status*)	Study Group	N	Vaccine	Vaccine Dosage (µg HA/strain/dose)†
1 (US)	9 to 17 years (previously vaccinated and unvaccinated)	12	30	QIV-HD	30
			30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
	9 to 17 years (previously vaccinated and unvaccinated)	13	30	QIV-HD	60
			30	unadjuvanted QIV-SD	15
	5 to 8 years (previously vaccinated and unvaccinated)	9	30	QIV-HD	30
			10	unadjuvanted QIV-SD	15
	36 months to < 5 years (previously vaccinated and unvaccinated)	1	30	QIV-HD	30
			10	unadjuvanted QIV-SD	15
2 (US)	5 to 8 years (previously vaccinated and unvaccinated)	10	30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
	36 months to < 5 years (previously vaccinated and unvaccinated)	2	30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
	6 to < 36 months (previously vaccinated and unvaccinated)	3	30	QIV-HD	30
			10	unadjuvanted QIV-SD	15
3	5 to 8 years	11	30	QIV-HD	60

Stage (Country)	Age Group (Vaccination Status*)	Study Group	N	Vaccine	Vaccine Dosage (µg HA/strain/dose)†
(US)	(previously vaccinated and unvaccinated)		30	unadjuvanted QIV-SD	15
	36 months to < 5 years (previously vaccinated and unvaccinated)	4	45	QIV-HD	60
			45	unadjuvanted QIV-SD	15
	6 to < 36 months (previously vaccinated and unvaccinated)	5	30	QIV-HD	45
			10	unadjuvanted QIV-SD	15
4 (US)	6 to < 36 months (previously unvaccinated)	6	30	QIV-HD	30, 45, or 60†
			30	unadjuvanted QIV-SD	15
	6 to < 36 months (previously vaccinated)	7	30	QIV-HD	30, 45, or 60†
			30	unadjuvanted QIV-SD	15
4 (Canada)	6 to < 24 months (previously unvaccinated)	8	30	QIV-HD	30, 45, or 60†
			30	adjuvanted TIV	7.5

Abbreviations: HA, hemagglutinin; QIV-SD, standard-dose quadrivalent influenza vaccine;TIV, trivalent influenza vaccine; µg, microgram.

* Vaccination status is determined by information provided by the parent / guardian.

† Dosage selection will be based on the ESDR of the prior Stages. The highest dosage with an acceptable safety review from prior Stages will determine the dose evaluated in Stage 4.

Figure 5.1: Study design flow chart for subjects 6 months to < 5 years of age

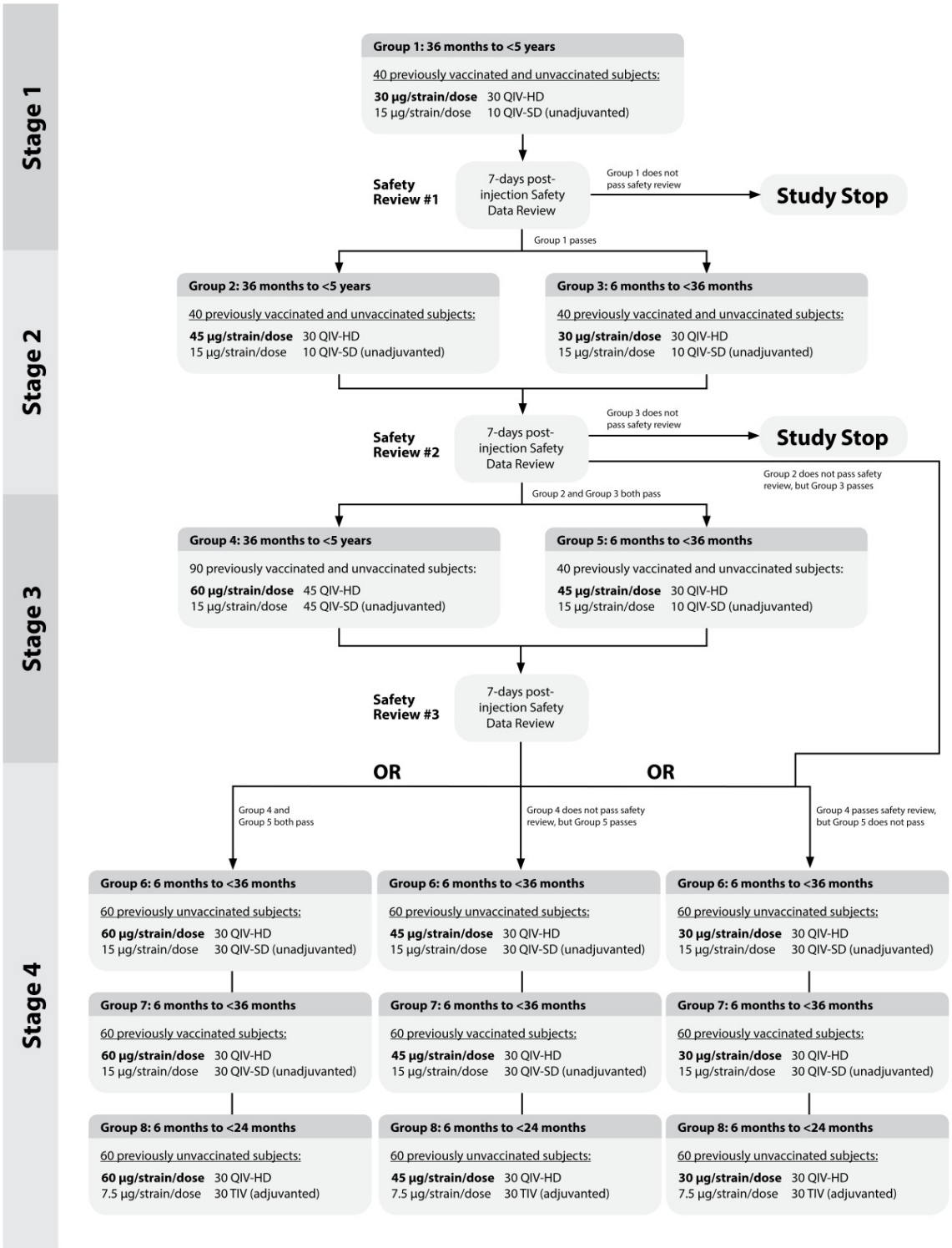


Figure 5.2: Study design flow chart for subjects 5 to 8 years of age

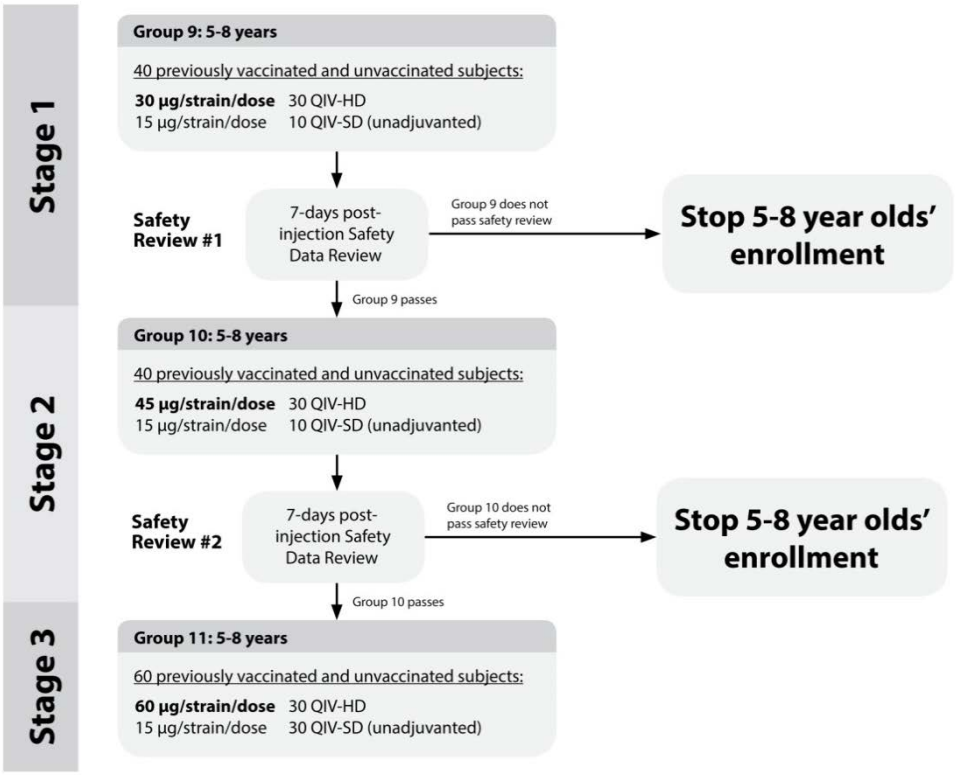
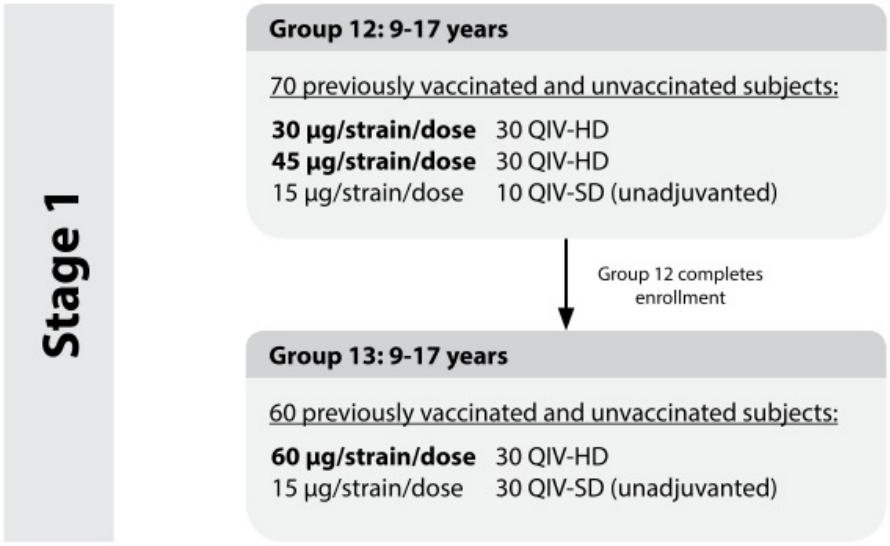


Figure 5.3: Study design flow chart for subjects 9 to 17 years of age



5.1.2 Justification of the Study Design

QHD04 study will describe the safety of the 3 different dosages of QIV-HD in children 6 months to 17 years of age. The study will also describe the immunogenicity of the different dosages of QIV-HD compared to a unadjuvanted QIV-SD (Fluarix Quadrivalent, licensed in the US) in all stages of the study and compared to an adjuvanted TIV (FLUAD Pediatric, licensed in Canada) during Stage 4 after the highest acceptable dosage of QIV-HD is established. Both comparators will be obtained commercially and will be used according to the approved indication.

Given the different volumes in the 3 different dosages of the QIV-HD and the comparator vaccines, QHD04 will be a staged, modified double-blind study with an unblinded administrator used at each study site. The administrator will not be involved in any of the blinded study assessments (eg, safety).

Since this is the first time that the QIV-HD will be administered to the pediatric population, an ESDR will be performed for subjects 6 months to 8 years of age prior to dosage ascension (30, 45, and 60 µg HA/strain/dose).

Given the matured immune system in children 9 to 17 years of age, no ESDR will occur for subjects 9 to 17 years of age prior to dosage ascension. Subjects 9 to 17 years of age will be randomized to receive the 30 and 45 µg HA/strain/dose vaccines separately from subjects 9 to 17 years of age who receive the 60 µg HA/strain/dose formulation in order to maintain the randomization ratio across all age groups and thus allow for pooling of the 30, 45, and 60 µg HA/strain/dose formulations across all age groups as well.

The comparison of the QIV-HD that will be used in Stage 4 (highest dosage with acceptable safety) to the adjuvanted TIV will be an indicator in terms of expected vaccine efficacy since FLUAD Pediatric is the only licensed pediatric vaccine with studies evaluating both HAI immunogenicity and relative efficacy data.

5.1.3 Study Plan

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

Vaccination

All eligible subjects will be randomized to receive 1 or 2 doses of either QIV-HD, Fluarix® Quadrivalent (unadjuvanted QIV-SD), or FLUAD Pediatric® (adjuvanted TIV). The dosage of QIV-HD that is administered will depend on both the age of the subject and the stage at which he / she is enrolled.

- Subjects 9 to 17 years of age will receive 1 dose of the QIV-HD or the comparator vaccine on D0.
- Previously influenza vaccinated subjects 6 months to 8 years of age will receive 1 dose of the QIV-HD or the comparator vaccine on D0.
- Previously influenza unvaccinated subjects 6 months to 8 years of age will receive 2 doses of the QIV-HD or the comparator vaccine. Each dose will be administered 28 days apart (at D0 and D28).

Of note, the highest dosage with an acceptable safety review in prior stages will determine the dose evaluated in Stage 4.

An unblinded administrator at each site will administer the vaccine.

Blood sampling

Subjects will provide 2 or 3 blood samples, regardless of the stage of enrollment:

- Subjects 9 to 17 years of age will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (D28 [+7 days]) for HAI and SN testing.

  Note: Subjects 9 to 17 years of age are scheduled for 2 site visits. However, the second visit is designated as V03 to be consistent with the visits nomenclature of the 6 months to 8 years age groups.

- Previously influenza vaccinated subjects 6 months to 8 years of age will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (D28 [+7 days]) for HAI and SN testing.

- Previously influenza unvaccinated subjects 6 months to 8 years of age will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (D28 [+7 days]) and V05 (28 days after V03 [+7 days]) for HAI and SN testing.

Note: The blood sample will be taken prior to vaccination during any visit when a subject receives a vaccination.

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).

Solicited reactions will be collected up to 7 days after each vaccination, and unsolicited AEs will be collected up to D28 (V03) for subjects receiving 1 dose and up to D56 (V05) for subjects receiving 2 doses. Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected throughout the study (D0 through approximately 6 months after the last vaccination). It is to be noted that AESIs will be captured as SAEs. These include new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

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

The study staff will contact subjects 9 to 17 years of age or the subjects' parents / guardians by phone at D8 (+2 days) post-vaccination to identify whether the subject experienced any SAEs not yet reported and will remind the subjects / subjects' parents / guardians to bring the completed diary card with them to V03 (D28 [+7 days]). The study staff will review the D0 to V03 safety data with subjects at V03.

Subjects 6 months to 8 years of age will return to the site at D8 (+3 days) after each vaccination. Staff will review the recorded solicited reactions and unsolicited AEs, and determine whether the subject experienced any SAEs and AESIs not yet reported. Staff will review the safety data with

subjects / subjects' parents / guardians at each visit. Staff will also remind the subjects / subjects' parents / guardians to bring the completed diary card with them to the subsequent visit.

The interactive response technology (IRT) system will be used to randomly assign subjects to a study product and to assign subject numbers in each of the groups.

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

Review of safety data

The study will be divided into 4 stages as described in Section 5.1.1. An ESDR will be conducted for subjects 6 months to 8 years of age. The ESDR will occur following the collection of the safety data at V02 (approximately 8 days post-vaccination) of Stages 1, 2, and 3 by the SMT. Enrollment of subjects in the next stage will be initiated if the safety review results are satisfactory. The details of the safety reviews are described in Section 5.1.6.

5.1.4 Visit Procedures

Visit 1 (Day 0): Inclusion, Randomization, Blood sample, and Vaccination – for all subjects

The Investigator or delegate will:

1) Give the subject and / or subject's parent / guardian information about the study.
2) Obtain informed consent and assent (for subjects 7 to 17 years of age) and answer any questions to ensure that the subjects and/or subject's parent / guardian have been informed of all aspects of the study that are relevant to their decision to participate.
3) Date and sign the ICF (and assent form for subjects 7 to 17 years of age) after it has been signed and dated by the subject or subject's parent / guardian. Retain the original and give a signed copy to the subject or subject's parent / guardian.
4) Check all inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively) through physical examination and medical interview of the subject and / or 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) For females of childbearing potential, conduct a urine pregnancy test.
7) Obtain verbal information on medical history.
8) Obtain information on seasonal influenza vaccination and any influenza diagnosis as follows:
   - For previously influenza unvaccinated subjects, confirm that the subject has not been vaccinated with any seasonal influenza vaccine since birth and has never had a known influenza diagnosis.
     Note: For the US sites, in following the Advisory Committee on Immunization Practices (ACIP) Guidelines, this study will consider subjects 6 months to 8 years of age who have never been vaccinated against influenza or who have not received at least 2 doses of seasonal influenza vaccine in a prior influenza season as "previously influenza unvaccinated subjects" when enrolling and thus these subjects will receive 2 doses of study vaccine at least 28 days apart. Subjects whose vaccination history is unknown will

also be considered as "previously influenza unvaccinated subjects" when enrolling and also receive 2 doses of study vaccine at least 28 days apart.
For the Canadian sites, in following the National Advisory Committee on Immunization (NACI) recommendations, this study will consider subjects 6 months to less than 24 months of age who have never been vaccinated against influenza in a prior influenza season as "previously influenza unvaccinated subjects" when enrolling and thus these subjects will receive 2 doses of study vaccine at least 28 days apart. Subjects who have received at least one dose of any influenza vaccine in the past will not be considered "previously influenza unvaccinated subjects".

- For previously influenza vaccinated subjects, obtain the date (month and year) when the subject was last vaccinated with a seasonal influenza vaccination.
  Note: For the US sites, in following the ACIP Guidelines, this study will consider subjects 6 months to 8 years of age who have received at least 2 doses of seasonal influenza vaccine in prior influenza seasons as "previously influenza vaccinated subjects" when enrolling and thus these subjects will receive only 1 dose of study vaccine.

9) For subjects 6 to 12 months of age, obtain information on influenza vaccination during the mother's pregnancy and breastfeeding routines, if any.

10) Collect any reportable concomitant medications (see Section 6.7).

11) Perform and document a targeted physical examination per standard site-specific immunization practices and record temperature[a] in the source documents.

12) Call the IRT for assignment of the 12-digit subject number, randomization, and allocation of a dose number (see Section 6.5).

13) 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.

<u>The unblinded qualified study staff member will:</u>

14) 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).

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

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

The Investigator or delegate will:

16) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any AE in the source documents.
17) Give the subject or subject's parent / guardian the diary card (DC) 1 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.
18) 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.
19) Remind the subject or subject's parent / guardian to bring back the DC1 when they return for V02. For subjects 9 to 17 years of age, schedule the D8 telephone call.
20) 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.
21) Complete the relevant CRB forms for this visit.

Telephone call (8 [+2] days after Visit 1): Collection of Safety Information – for subjects 9 to 17 years of age

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 or subject's parent / guardian to do the following:
   - Complete the remaining pages of the DC1 and bring the completed diary to V03 (D28 [+7 days]).
   - Notify the site in case of an SAE.

Visit 2 (8 [+3] days after Visit 1): Collection of Safety Information – for subjects 6 months to 8 years of age

Note: If Visit 2 falls on a weekend or a holiday, the visit may be scheduled on the next business day.

The Investigator or delegate will:

1) Review (for clarity, content, and completeness) the information in the DC1 with the subject or subject's parent / guardian and clarify with the subject or subject's parent / guardian, if required, any AEs, medications (see Section 6.7), or SAE that occurred since V01. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Record the D0 to D7 safety data in the CRB.
3) Remind the subject or subject's parent / guardian to do the following:
   - Complete the remaining pages of the DC1 and bring the completed diary to V03
   - Notify the site in case of an SAE.

Visit 3 (28 [+7] days after Visit 1) – for subjects 9 to 17 years of age and for previously influenza vaccinated subjects 6 months to 8 years of age

Note: Subjects 9 to 17 years of age are scheduled for 2 site visits. However, the second visit is designated as V03 to be consistent with the visit nomenclature of the 6 months to 8 years age groups.

The Investigator or delegate will:

1) Review (for clarity, content, and completeness) and collect the DC1 information with the parent / guardian and clarify with the parent / guardian if required any AEs, medications (see Section 6.7), or SAE that occurred since the telephone call (for subjects 9 to 17 years of age) or V02 (for previously vaccinated subjects 6 months to 8 years of age). If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Draw approximately 5 mL of blood sample. Process the blood sample as specified in the "Management of Samples" section (see Section 7).
   Note: If 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.
   Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), the parent / guardian should be given the opportunity to bring his / her child to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRB. In this case, the subject will be followed for safety in the study.
3) Provide the subject / parent / guardian with a memory aid (MA) and review the directions for its use.
4) Remind the subject / parent / guardian to promptly notify the site in case of an SAE that may occur at any time during the study.
5) Schedule the 6-month safety follow-up phone call
6) Record all applicable information obtained into the CRB
7) Complete the termination record of the CRB.

Visit 3 (28 [+7] days after Visit 1) – for previously influenza unvaccinated subjects 6 months to 8 years of age

The Investigator or delegate will:

1) Review (for clarity, content, and completeness) and collect the DC1 information with the parent / guardian and clarify with the parent / guardian if required any AEs, medications (see Section 6.7), or SAE that occurred since V02. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Conduct a targeted physical examination, if necessary.
3) Review temporary and definitive contraindications to vaccination.
4) 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).
   Note: If 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.

Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), the parent / guardian should be given the opportunity to bring his / her child to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRB. In this case, the subject will remain in the study and should be vaccinated after all the attempts to collect blood are complete.

The unblinded qualified study staff member will:

5) Call the IRT to obtain a 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 (the vaccine must be administered on the side opposite to that of the blood sampling).
7) Record the injection site / side / route / dose number in the source documents and affix the detachable corresponding label in the source document.

The Investigator or delegate will:

8) Keep the subject under medical surveillance for at least 30 minutes after the injection and report the occurrence or non-occurrence of any AE in the source documents.
9) Give the subject / parent / guardian the DC2 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.
10) Remind the subject / parent / guardian to bring back the DC2 when they return for V04.
11) Remind the subject / parent / guardian to promptly notify the site in case of an SAE that may occur at any time during the study.
12) Complete the relevant CRB forms for this visit.

Visit 4 (8 [+3] days after Visit 3) – for previously influenza unvaccinated subjects 6 months to 8 years of age

The Investigator or delegate will:

1) Review (for clarity, content, and completeness) the information in the DC2 with the subject / parent / guardian and clarify with the parent / guardian, if required, any AEs, medications (see Section 6.7), or SAE that occurred since V03. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Record the D28-D35 safety data in the CRB.
3) Remind the subject / parent / guardian to do the following:
    - Complete the remaining pages of the DC2 and bring them to V05
    - Notify the site in case of an SAE.

Visit 5 (28 [+7] days after Visit 3) – for previously influenza unvaccinated subjects 6 months to 8 years of age

The Investigator or delegate will:

1) Review (for clarity, content, and completeness) and collect the DC2 information with the parent / guardian and clarify with the subject / parent / guardian if required any AEs, medications (see Section 6.7), or SAE that occurred since V04. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) 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.
   Note: If the attempt(s) to collect blood is (are) unsuccessful (3 attempts), the parent / guardian should be given the opportunity to bring his / her child to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRB. In this case, the subject will remain in the study.
3) Provide the subject / parent / guardian with a MA and review the directions for its use.
4) Remind the subject / parent / guardian to promptly notify the site in case of an SAE that may occur at any time during the study.
5) Schedule the 6-month safety follow-up phone call
6) Record all applicable information obtained into the CRB
7) Complete the termination record of the CRB.

Safety Follow-up Telephone Call – approximately 6 months after the last vaccination: Collection of SAEs

1) Inquire about new occurrences of SAEs and perform follow-up on SAEs. If an SAE has occurred, inquire if the subject has received any vaccinations or other medications since the last contact.
2) Explain that this will be the last contact with the site for this study (except for subjects with SAEs that need further follow-up, as stated below).

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

The exceptions for the final phone calls are:

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

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

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

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

5.1.5 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject; phone call at the end of the 6-months follow up period): 10 October 2018 – 15 October 2019

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

- Stage 1[a]: 10 October 2018 – 19 October 2018
- Stage 2: 05 November 2018 – 09 November 2018
- Stage 3: 29 November 2018 – 10 December 2018
- Stage 4: 03 January 2019 – 28 February 2019

Planned study period (active phase) – FVFS to LVLS (last visit, last subject):

- Stage 1: 10 October 2018 – 21 November 2018
- Stage 2: 05 November 2018 – 11 January 2019
- Stage 3: 29 November 2018 – 11 February 2019
- Stage 4: 03 January 2019 – 02 May 2019

Planned end of study (LCLS; phone call at the end of the 6-months follow up period): 15 October 2019

Planned date of final clinical study report: 05 March 2020

5.1.6 Early Safety Data Review

The safety of the investigational product will be continuously monitored by the Sponsor. ESDRs will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration. A stepwise dosage ascension approach will be applied to subjects in age group 5 to 8 years (30 µg, 45 µg, and 60 µg HA/strain/dose). A stepwise age de-escalation vaccination approach will be taken for subjects in age group 36 months to < 5 years of age, with an ESDR prior to vaccinating subjects in the age group 6 to < 36 months of age as well as stepwise dosage ascension. The ESDR will be performed following V02 in subjects 6 months to 8 years of age (refer to Figure 5.1 and Figure 5.2).

The ESDRs for this study are planned after the 6 months to 8 years age groups in each stage have been vaccinated and have provided safety data for Days 0 to 7 post-vaccination, using the data collection methods described in the protocol. ESDR will not be performed for subjects 9 to 17 years of age.

[a] Enrollment of subjects 9 to 17 years of age may be extended

During each ESDR, enrollment of subjects will be paused. However, already enrolled subjects 6 months to 8 years of age who require 2 vaccinations because of their previous vaccination status will receive their second dose at D28 as scheduled, which may be prior to the ESDR. Following a satisfactory safety review, enrollment of subjects will resume for the subsequent or appropriate Stage as described in Figure 5.1 and Figure 5.2. The study visits according to the Table of Study Procedures will continue to be followed for enrolled subjects within each active Stage (ie, subjects will complete their scheduled visits).

The safety data collected will be entered into the CRBs and summarized by the Sponsor in a blinded manner. A review will be performed by the Sponsor during the SMT meetings. 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 early interim safety analysis will continue unchanged.)

The following safety parameters will be assessed as part of the early safety review:

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

Enrollment will be paused during the review, and 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 decision will be made as to whether enrollment in the study will be allowed to resume.

Case unblinding may be performed if necessary.

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 / 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 addition to the ICF, subjects that are 7 years of age and older will be asked to review and sign a separate assent form.

In accordance with GCP, prior to signing and dating the consent form, the subject's parent / guardian must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate and must have sufficient time and opportunity to ask any questions. A subject whose parent / guardian cannot read will not be included in the study.

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 / subject's parent's / 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 / subject's parent / guardian.

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

5.2.3 Screening Criteria

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

5.2.4 Inclusion Criteria

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

1) Aged 6 months to 17 years on the day of inclusion[a].
2) Assent form has been signed and dated by the subject (7 to 17 years of age) and 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) For subjects aged < 24 months: Born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 2.5 kg.

5.2.5 Exclusion Criteria

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

[a] "6 months to 17 years" means from the 6th month after birth to the day before the 18th birthday.

1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be pre-menarche[a].
2) 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.
3) Receipt of any vaccine in the 30 days preceding the first study vaccination, or planned receipt of any vaccine before Visit 3 for subjects receiving 1 dose of influenza vaccine or Visit 5 for subjects receiving 2 doses of influenza vaccine.
4) For previously influenza vaccinated subjects: Previous vaccination against influenza in the preceding 6 months with either the study vaccine or another vaccine[b].
5) For previously influenza unvaccinated subjects: Any influenza vaccination (from birth to the day of inclusion) with either the study vaccine or another influenza vaccine[c].
6) For previously influenza unvaccinated subjects: Any previous laboratory confirmed influenza infection (from birth to the day of inclusion).
7) Receipt of immune globulins, blood or blood-derived products in the past 3 months.
8) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).
9) 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].

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[a] Pre-menarche females will declare by themselves that they have not yet started menstruation. If a young female subject reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward.

[b] For the US sites, in following the ACIP Guidelines, this study will consider subjects 6 months to 8 years of age who have received at least 2 doses of seasonal influenza vaccine in prior influenza seasons as “previously influenza vaccinated subjects” when enrolling and thus these subjects will receive only 1 dose of study vaccine.

[c] For the US sites, in following the ACIP Guidelines, this study will consider subjects 6 months to 8 years of age who have never been vaccinated against influenza or who have not received at least 2 doses of seasonal influenza vaccine in a prior influenza season as “previously influenza unvaccinated subjects” when enrolling and thus these subjects will receive 2 doses of study vaccine at least 28 days apart. Subjects whose vaccination history is unknown will also be considered as “previously influenza unvaccinated subjects” when enrolling and also receive 2 doses of study vaccine at least 28 days apart.
For the Canadian sites, in following the NACI’s recommendations, this study will consider subjects 6 months to less than 24 months of age who have never been vaccinated against influenza in a prior influenza season as “previously influenza unvaccinated subjects” when enrolling and thus these subjects will receive 2 doses of study vaccine at least 28 days apart. Subjects who have received at least 1 dose of any influenza vaccine in the past will not be considered “previously influenza unvaccinated subjects”.

10) Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on Investigator's judgement.
11) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.
12) Current alcohol abuse or drug addiction.
13) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[b].
14) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
15) Identified as an immediate family member (ie, spouse, natural or adopted child, grandchild, nephew, or niece) of the Investigator or employee with direct involvement in the proposed study.
16) Personal history of GBS.
17) 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.
18) Personal history of clinically significant development delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.
19) Known seropositivity for hepatitis B or hepatitis C.

5.2.6 Medical History

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

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

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

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

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[a] The components of QIV-HD are listed in Section 6.1 and in the Investigator's Brochure and the components of the comparator products are listed in Section 6.1 and in the package inserts.

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

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

5.2.7 Contraindications for Subsequent Vaccination

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 one of the conditions 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.

- Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment.

5.2.7.2 Definitive Contraindications

The following criteria are applicable to subjects who had never received any influenza vaccine before the start of the study and who will be receiving 2 influenza vaccine injections during the study (1 at V01 and 1 at V03). Should a subject experience 1 of the conditions listed below, the Investigator will discontinue vaccination.

- D01: An anaphylactic or other significant allergic reaction to the previous dose of vaccine
- D02: Receipt of any immune globulins, blood, or blood-derived products between V01 and V03.
- D03: Known or suspected congenital or acquired immunodeficiency; 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).
- D04: Thrombocytopenia or bleeding disorder, which may be a contraindication for IM vaccination, based on Investigator's judgement.
- D05: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion.
- D06: Development of any condition that in the opinion of the Investigator would pose a health risk to the subject or could interfere with the evaluation of the study vaccine (including GBS, clinically significant developmental delay, neurologic disorder, seizure disorder, hepatitis B, or hepatitis C).
- D07: Any SAE related to the study vaccines following the previous study vaccination, based on investigator's judgement.

Subjects with a definitive contraindication will not be vaccinated at V03, but will continue to be followed up for the study-defined safety 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

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

- At the discretion of the Investigator or Sponsor due to safety concerns 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 / parent / guardian (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (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 CRB and in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.1.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the investigator and returned unsigned, and the subject or 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 noncompliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is a protocol deviation. • The subject or the 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 or Parent / Guardian	To be used: • When the subject or parent/guardian indicated unwillingness to continue in the study • When the subject or parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject or parent / guardian of any subject who has prematurely terminated the study because of an AE, a protocol deviation, or loss of eligibility, including definitive contraindications. The follow-up duration in the event of discontinuation is 6 months after the last vaccination.

For subjects where the reason for early termination was lost to follow-up or if the subject / 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 or 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.

5.2.12 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy, and if at least 1 dose of the study

vaccine(s) has been administered, the subject will not be discontinued from the study. However, the subject will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

All pregnancy cases should be reported if they occurred during the study and during the 6 month follow up period. To report the pregnancy case, the Investigator must fill out Pregnancy Reporting forms in the electronic data capture (EDC) system and inform the Sponsor within 1 month of identifying a pregnancy case.

If the EDC system is not available, the investigator must fill out a paper Pregnancy Reporting Form (provided by the Sponsor at the start of the study) and inform the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome (i.e., details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, blighted ovum, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the Global Pharmacovigilance (GPV) Department regardless of when the SAE occurs (eg, even after the end of the study).

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 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 (refer to Section 10).

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

5.4 Modification of the 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. Administrative changes do not require IEC / IRB approval; however, the IEC / IRB must be notified whenever one is made.

The Investigator is responsible for ensuring that changes to an approved 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 the applicable regulatory requirements. The Investigator shall promptly inform the subjects / subjects' parents / guardians and should assure appropriate subject therapy and/or follow-up.

6 Vaccines Administered

6.1 Identity of the Investigational Products

6.1.1 Identity of Study Product 1

The investigational QIV-HD is a split virion quadrivalent influenza vaccine (30 µg HA/strain) containing virus strains chosen by the WHO (VRBPAC in the US) for the NH 2018-2019 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 120 µg HA antigen per 0.35 mL dose provided in sterile suspension for IM injection.

QIV-HD vaccine is thimerosal-free and prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.1.1 Composition

Each 0.35 mL dose of vaccine contains the following components:

(*Strains are based on WHO [VRBPAC in the US] recommendations for the 2018-2019 NH influenza season):*

Active substances:

- A/Michigan/45/2015 X-275 (H1N1) 30 µg HA

- A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) 30 µg HA
- B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 30 µg HA
- B/Phuket/3073/2013 (Yamagata lineage) 30 µg HA

Excipients:

- Buffered saline solution quantity sufficient (qs) to appropriate volume
- Octylphenol Ethoxylate (Triton X-100®) not more than (NMT) 175 µg

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

Batch number: UD20382 (US sites); UD20523 (Canadian sites)

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.

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

Subjects must be kept under observation for 30 minutes after 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 9 to 17 years of age.

6.1.2 Identity of Study Product 2

The investigational QIV-HD is a split virion quadrivalent influenza vaccine (45 µg HA/strain) containing virus strains chosen by the WHO (VRBPAC in the US) for the NH 2018-2019 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 180 µg HA antigen per 0.52 mL dose provided in sterile suspension for IM injection.

QIV-HD vaccine is thimerosal-free and prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.2.1 Composition

Each 0.52 mL dose of vaccine contains the following components:

(*Strains are based on WHO [VRBPAC in the US] recommendations for the 2018-2019 NH influenza season):*

Active substances:

- A/Michigan/45/2015 X-275 (H1N1) 45 µg HA
- A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) 45 µg HA
- B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 45 µg HA
- B/Phuket/3073/2013 (Yamagata lineage) 45 µg HA

Excipients:

- Buffered saline solution qs to appropriate volume
- Octylphenol Ethoxylate (Triton X-100) NMT 260 µg

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

Batch number: UD20383 (US sites); UD20522 (Canadian sites)

6.1.2.2 Preparation and Administration

The procedures for preparing and administering study product 2 are the same as those described for study product 1 in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

The dose selection and timing for the investigational product 2 are the same as those described for the investigational product 1 in Section 6.1.1.3

6.1.3 Identity of Study Product 3

The investigational QIV-HD is a split virion quadrivalent influenza vaccine (60 µg HA/strain) containing virus strains chosen by the WHO (VRBPAC in the US) for the NH 2018-2019 influenza season. The vaccine contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages). Each pre-filled syringe contains a total of 240 µg HA antigen per 0.7 mL dose provided in sterile suspension for IM injection.

QIV-HD vaccine is thimerosal-free and prepared from influenza viruses propagated in embryonated chicken eggs.

6.1.3.1 Composition

Each 0.7 mL dose of vaccine contains the following components:

(*Strains are based on WHO [VRBPAC in the US] recommendations for the 2018-2019 NH influenza season):*

Active substances:

- A/Michigan/45/2015 X-275 (H1N1) 60 µg HA
- A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) 60 µg HA
- B/Maryland/15/2016 BX-69A (B/Colorado/6/2017-like virus, Victoria lineage) 60 µg HA
- B/Phuket/3073/2013 (Yamagata lineage) 60 µg HA

Excipients:

- Buffered saline solution qs to appropriate volume
- Octylphenol Ethoxylate (Triton X-100) NMT 350 µg

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

Batch number: UD20384 (US sites); UD20524 (Canadian sites)

6.1.3.2 Preparation and Administration

The procedures for preparing and administering study product 3 are the same as those described for study product 1 in Section 6.1.1.2.

6.1.3.3 Dose Selection and Timing

The dose selection and timing for the investigational product 3 are the same as those described for the investigational product 1 in Section 6.1.1.3

6.1.4 Identity of Control Product 1

Fluarix Quadrivalent: Influenza vaccine, Inactivated (GlaxoSmithKline Biologicals, Dresden, Germany)

- Form: Liquid solution
- Dose: 0.5 mL
- Route: IM
- Batch number: HJ9MN (commercial product to be provided to the sites by the Sponsor)

6.1.4.1 Composition

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

Strains are based on WHO (VRBPAC in the US) recommendations for the 2018-2019 NH influenza season.

Active Substances:

- A/Singapore/GP1908/2015 IVR-180 (H1N1) (A/Michigan/45/2015 [H1N1] pdm09-like virus) 15 µg HA
- A/Singapore/INFIMH-16-0019/2016 NIB-104 (H3N2) 15µg HA
- B/Maryland/15/2016 NYMC BX-69A (B/Colorado/06/2017-like virus, Victoria lineage) 15 µg HA
- B/Phuket/3073/2013 (Yamagata lineage) 15 µg HA

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

Fluarix Quadrivalent does not contain a preservative.

6.1.4.2 Preparation and Administration

Fluarix Quadrivalent will be prepared and administered according to manufacturer's package insert (21).

6.1.4.3 Dose Selection and Timing

Fluarix Quadrivalent will be administered to a randomized set of subjects in Groups 1 through 7 and Groups 9 through 13 as a single 0.5 mL dose at V01 for subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age and at V01 and V03 for previously influenza unvaccinated subjects 6 months to 8 years of age.

6.1.5 Identity of Control Product 2

FLUAD Pediatric: Influenza vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1 (Seqirus UK Limited, Maidenhead, UK)
- Form: Liquid solution
- Dose: 0.25 mL
- Route: IM
- Batch number: 253774 (commercial product to be provided to the sites by the Sponsor)

6.1.5.1 Composition

Each 0.25 mL dose contains 7.5 µg of HA for each of the following strains:

Strains are based on WHO (NACI in Canada) recommendations for the 2018-2019 NH influenza season.

Active substances:
- A/Singapore/GP1908/2015 IVR-180 (H1N1) (A/Michigan/45/2015 [H1N1] pdm09-like virus) 7.5 µg HA
- A/Singapore/INFIMH-16-0019/2016, IVR-186 (H3N2) 7.5 µg HA
- B/Maryland/15/2016 (B/Colorado/06/2017-like virus, Victoria lineage) 7.5 µg HA

Excipients
- Sodium chloride 2.00 mg
- Potassium chloride 0.05 mg
- Potassium dihydrogen phosphate 0.05 mg
- Disodium phosphate dehydrate 0.335 mg
- Magnesium chloride hexahydrate 0.025 mg
- Calcium chloride dihydrate 0.03 mg
- Water for injection qs to appropriate volume

FLUAD Pediatric is formulated with the adjuvant MF59, an oil-in-water emulsion of squalene oil.

FLUAD Pediatric does not contain a preservative.

6.1.5.2 Preparation and Administration

FLUAD Pediatric will be prepared and administered according to manufacturer's product monograph (22).

6.1.5.3 Dose Selection and Timing

FLUAD Pediatric will be administered to a randomized set of subjects in Group 8 as a single 0.25 mL dose at V01 and V03.

6.2 Identity of Other Products

Not applicable

6.3 Product Logistics

6.3.1 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 3 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 vaccines, Fluarix Quadrivalent and FLUAD Pediatric, will be supplied in single dose syringes with the manufacturer label on the syringes and an investigational label on the carton. The carton label will also have a detachable label for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

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

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

6.3.3 Replacement Doses

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

6.3.4 Disposal of Unused Products

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

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

The study is designed as a staged, modified double-blind study with the following measures to ensure to ensure the integrity of the data:

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

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

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

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

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

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

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

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

In any case, the code will be broken after the first database lock, for the primary statistical analysis planned to analyze the data collected within the 28 days (for subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age) and 56 days (for previously influenza unvaccinated subjects 6 months to 8 years of age) following the vaccination,

but the randomization list will not be provided to Investigators and will be kept internally until the end of the statistical analyses after the final database lock.

6.5 Randomization and Allocation Procedures

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

The study will be randomized and modified double-blinded for all study groups. On the day of enrollment, subjects who meet the inclusion / exclusion criteria and complete the informed consent process will be randomly assigned to receive:

- either QIV-HD at 30 µg or 45 µg HA/strain/dose or Fluarix Quadrivalent in a 3:3:1 ratio for previously influenza vaccinated and unvaccinated subjects 9 to 17 years of age enrolled during Stage 1 in the US.
- either QIV-HD at 60 µg HA/strain/dose or Fluarix Quadrivalent in a 1:1 ratio for previously influenza vaccinated and unvaccinated subjects 9 to 17 years of age enrolled during Stage 1 in the US.
- either QIV-HD at 30 µg HA/strain/dose or Fluarix Quadrivalent in a 3:1 ratio for previously influenza vaccinated and unvaccinated subjects 36 months to 8 years of age enrolled during Stage 1 in the US.
- either QIV-HD at 45 µg HA/strain/dose or Fluarix Quadrivalent in a 3:1 ratio for previously influenza vaccinated and unvaccinated subjects 36 months to 8 years of age enrolled during Stage 2 in the US.
- either QIV-HD at 30 µg HA/strain/dose or Fluarix Quadrivalent in a 3:1 ratio for previously influenza vaccinated and unvaccinated subjects 6 to < 36 months of age enrolled during Stage 2 in the US.
- either QIV-HD at 60 µg HA/strain/dose (highest dosage of QIV-HD) or Fluarix Quadrivalent in a 1:1 ratio for previously influenza vaccinated and unvaccinated subjects 36 months to 8 years of age enrolled during Stage 3 in the US.
- either QIV-HD at the highest dosage with acceptable safety review or Fluarix Quadrivalent in a 1:1 ratio for previously vaccinated subjects 6 to 36 months of age enrolled in Stage 4 in the US.
- either QIV-HD at the highest dosage with acceptable safety review or Fluarix Quadrivalent in a 1:1 ratio for previously unvaccinated subjects 6 to 36 months of age enrolled in Stage 4 in the US.
- either QIV-HD at the highest dosage with acceptable safety review or FLUAD Pediatric in a 1:1 ratio for previously unvaccinated subjects 6 to < 24 months of age enrolled in Stage 4 in Canada.

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. Stratified randomization will be applied for all

subjects enrolled in each group stratified by previous influenza vaccination status and country. Site will not be a strata for randomization due to the small sample size in each group. The allocation ratios between investigational HD vaccines to the comparators are: 3:1 ratio in groups 1, 2, 3, 5, 9, and 10; 3:3:1 ratio in group 12; and 1:1 ratio in groups 4, 6, 7, 8, 11, and 13. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier [840 for the US and 124 for Canada], a 4-digit study site identifier, and a 5-digit subject identifier). For example, Subject 840000100005 is the fifth subject enrolled in Center Number 1 in the US.

Subject numbers should not be reassigned for any reason.

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

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

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

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

Reportable medications will be collected in the CRB from the day of first vaccination to the end of the solicited and unsolicited follow-up period (from D0 to D28 for subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age and from D0 to D56 for previously influenza unvaccinated subjects 6 months to 8 years of age).

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

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs]).

- Category 2: medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors).
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, steroids/corticosteroids)

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

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

Dosage and administration route; homeopathic medication; topical, nasal, ophthalmic, otic, and inhaled steroids; as well as other topical, ophthalmic, and ear treatments will not be recorded.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF. Details will be recorded in the concomitant medication CRF only if the medication(s) received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at V01 and V03 (D28 [+7 days]) for subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age, and at V01, V03, and V05 for the previously influenza unvaccinated subjects 6 months to 8 years of age. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At V01 and V03 (D28 [+7 days]) for subject 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age, and at V01, V03, and V05 for the previously influenza unvaccinated subjects 6 months to 8 years of age, 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; will verify the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

Note: if 5 mL of blood sample cannot be drawn, a volume less than 5 mL can be obtained.

7.2 Sample Preparation

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

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 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.

7.3 Sample Storage and Shipment

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

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to GCI at Sanofi Pasteur. The address is provided in the Operating Guidelines.

7.4 Future Use of Stored Serum Samples for Research

Subjects' parents / guardians 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, pregnancy tests, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

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

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

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

9 Endpoints and Assessment Methods

9.1 Safety

9.1.1 Safety Definitions

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

Adverse Event (AE):

An AE is any untoward medical occurrence in a 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.

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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.

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) prelisted in the protocol and CRB (eg, injection site pain or headache occurring between D0 and D7 post-vaccination).

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

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

Unsolicited AE / AR:

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

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

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

9.1.2 Safety Endpoints

The endpoints for the evaluation of safety are:

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

9.1.3 Safety Assessment Methods

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

At V03 (D28 [+7 days]), and / or V05, as applicable, the Investigator or a delegate may perform a targeted clinical or medically-driven physical examination, as necessary, and will ask the subject / 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.

9.1.3.1 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 and recorded in the CRB, as follows:

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

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

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

After each vaccination, subjects / parents / guardians 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, D0 to D7) until resolution:

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

  The action(s) taken by the subject / parent / 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 9.1, Table 9.2, Table 9.3, Table 9.4, and Table 9.5 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 9.1: Solicited injection site reactions for infants and toddlers aged < 36 months: 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.
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is mobilized, 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, swelling, hardening, and bruising, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: Solicited injection site reactions for children aged 3 to 11 years: terminology, definitions, and intensity scales

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

Intensity scale*	Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	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 pain, parents / guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness, swelling, hardening, and bruising, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.3: Solicited injection site reactions for children aged 12 to 17 years: terminology, definitions, and intensity scales

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

Intensity scale*	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

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

Table 9.4: Solicited systemic reactions for infants and toddlers aged < 36 months: 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.

Table 9.5: Solicited systemic reactions for children aged 3 to 17 years: terminology, definitions, and intensity scales

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

	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

* For all reactions but fever, subjects / 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 / parents / guardians are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is rectal for subjects 6 months to < 4 years of age and oral for subjects 4 years of age and older. However, axillary is also acceptable for subjects 6 months of age and older if 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.

9.1.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects / parents / guardians will be instructed to record any other medical events that may occur during the 28-day period after each vaccination. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from inclusion until 6 months after the last vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Death/Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). 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 9.1, Table 9.2, Table 9.3, Table 9.4, and Table 9.5).

  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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.1.3.5.
- Action taken for each AE (eg, medication)

  The action(s) taken by the subject / parent / 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

9.1.3.4 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 (25) (26) (27).

9.1.3.5 Assessment of Causality

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

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.

9.2 Immunogenicity

9.2.1 Immunogenicity Endpoints

9.2.1.1 Immunogenicity by HAI Method

The endpoints for the evaluation of immunogenicity by HAI method are:

For subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age*:*

- HAI antibody (Ab) titers obtained on D0 and D28
- Individual HAI titers ratio D28/D0
- Seroconversion (titer < 10 [1/dilution {dil}] at D0 and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28)
- Percentage of subjects with titers ≥ 40 (1/dil) at D0 and D28

For previously influenza unvaccinated subjects 6 months to 8 years of age:

- HAI Ab titers obtained on D0, D28, and D56
- Individual HAI titers ratio D28/D0 and D56/D0
- Seroconversion (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil] at D28 and D56, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28 and D56)
- Percentage of subjects with titers ≥ 40 (1/dil) at D0, D28, and D56

9.2.1.2 Immunogenicity by Virus SN Method

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

For subjects 9 to 17 years of age and previously influenza vaccinated subjects 6 months to 8 years of age*:*

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

For previously influenza unvaccinated subjects 6 months to 8 years of age:

- Individual NT Ab titer on D0, D28, and D56
- Individual NT Ab titer ratio (fold increase in serum NT post-vaccination relative to D0) at D28 and D56
- Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28 and D56
- Fold-increase in NT Ab titer [post/pre] ≥2 and ≥ 4 at D28 and D56
- Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0, D28, and D56

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

Influenza Virus Neutralization Test

Assays will be performed by the Sponsor's laboratory (GCI, Swiftwater, PA, USA).

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

To measure NT, serially diluted, heat-inactivated human serum samples will be pre-incubated with a fixed amount of challenge virus prior to the addition of Madin-Darby canine kidney (MDCK) cells. After overnight incubation, the viral nucleoprotein production in infected MDCK cells is measured by enzyme-linked immunosorbent assay (ELISA), using monoclonal Ab specific to either influenza A nucleoprotein or influenza B nucleoprotein. Since serum neutralizing Abs to the influenza virus inhibits the viral infection of MDCK cells, the ELISA optical density results are inversely proportional to the titers of neutralizing Ab present in the serum. The LLOQ is set at the reciprocal of the lowest dilution used in the assay, ie, 10 (1/dil). Titers below this level are reported as < 10 (1/dil). The highest titer that would be reported is 10239 (1/dil). Anything ≥ 10240 (1/dil) will be pre-diluted, retested, and end point titers will be reported.

9.3 Efficacy

No clinical efficacy data will be obtained in the study.

10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor 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 products. 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 Death/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 Death/Safety Complementary

Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the CTL with relevant SAE information details.

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

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

- By fax, to the following number: +1 570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: SanofiPasteurPharmaco@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 5.2.12.

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 Death/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 products, or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.1.3.5.

Following this, the Sponsor's Global Safety Officer (GSO) 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 (Lee-Jah Chang, MD, CTL) will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.1.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1, Table 9.2, Table 9.3, Table 9.4, and Table 9.5) as well as areas for free text to capture additional safety information or other relevant details. Subjects / parents / guardians 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 / parents / guardians on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects / parents / guardians over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A memory aid will be provided to the subjects at the preceding 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 / parents / guardians 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 and Pregnancy Data

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) and pregnancy data (reported by the Investigator on ePregnancy Forms) 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 GSO 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.

12.1.1 Hypotheses and Statistical Methods for the Objectives

12.1.1.1 Hypotheses

No hypotheses for safety and immunogenicity are planned. All analyses are descriptive.

12.1.1.2 Statistical Methods

For the cohorts controlled by the non-adjuvanted QIV-SD, results will be described per stage, according to vaccine received, and per age group. Age groups will also be pooled within the same vaccine group for the main endpoints. The descriptive results may also be presented by the pooled QIV-HD group (60 µg) in the two countries. Subgroup immunogenicity analyses per previous vaccination status and/or baseline serostatus may be presented when appropriate. If any of the stages are not completed, analyses for the higher dose or next stage will not be performed.

For the cohort controlled by the adjuvanted TIV, results will be described according to vaccine received.

Safety

Safety endpoints will be analyzed descriptively for subjects in SafAS who received the QIV-HD. Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and

AESIs will be summarized. The main parameters will be described by single proportions with the 95% CI (Clopper-Pearson method) (28).

- ***Immunogenicity***

Immunogenicity endpoints will be summarized 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 2-sided 95% CIs by the Wilson-Score method without continuity correction (29). 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).

The immunogenicity analysis set (IAS) will be used for the main immunogenicity analyses. Details of the above analyses will be described in a SAP.

12.2 Analysis Sets

Two main analysis sets will be used: the IAS and the Safety Analysis Set (SafAS).

12.2.1 Immunogenicity Analysis Set

The IAS is defined as the subset of randomized subjects who received 1 dose of a study vaccine (for subjects 9 to 17 years of age and for previously influenza vaccinated subjects 6 months to 8 years of age) or 2 doses of a same study vaccine (for previously influenza unvaccinated subjects 6 months to 8 years of age) and had a post-vaccination blood sample. Subjects will be analyzed as treated.

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccines[a].

All subjects will have their safety analyzed as following:

- After each dose, according to the vaccine they actually received at the dose considered
- After any dose, according to the vaccine received at the first dose. In case the second dose received is different, safety data recorded at V04 and V05 will be excluded from this analysis and listed separately.

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

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

12.2.3 Populations Used in Analyses

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

The safety analyses will be performed on the SafAS.

The immunogenicity analyses from HAI assay and SN assay will both be performed on the IAS.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

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

12.3.2 Immunogenicity

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

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

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

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

12.4 Interim / Preliminary Analysis

For Stages 1, 2, and 3, there will be an early blinded look at the 7-day safety data for subjects 6 months to 8 years of age to determine whether the next group will be enrolled. No statistical adjustment is necessary because no hypotheses will be tested.

A limited statistical analysis of the unblinded safety and immunogenicity data obtained up to D28 or D56 may be conducted once data are available and an interim database lock has been conducted. A final analysis will be conducted once the 6-month safety data have been collected and the final database lock has occurred.

No statistical adjustment is necessary because no hypotheses will be tested.

12.5 Determination of Sample Size and Power Calculation

QHD04 is a Phase II study to describe the safety and immunogenicity of 3 different dosages of QIV-HD. The sample size is not powered. The study will include a total of approximately 700 subjects that will be divided into 13 groups as follows:

- Groups 1, 2, 3, 5, 9, and 10 will each include 40 subjects (previously influenza vaccinated or previously influenza unvaccinated) in a 3:1 ratio (QIV-HD: QIV-SD).
- Group 4 will include 90 subjects (previously influenza vaccinated or previously influenza unvaccinated) in a 1:1 ratio (QIV-HD: QIV-SD).
- Groups 7 will include 60 subjects who are previously influenza vaccinated in a 1:1 ratio (QIV-HD: QIV-SD).
- Groups 6 and 8 will each include 60 subjects who are previously influenza unvaccinated in a 1:1 ratio (QIV-HD: QIV-SD or TIV).
- Group 11 and 13 will each include 60 subjects (previously influenza vaccinated or previously influenza unvaccinated) in a 1:1 ratio (QIV-HD: QIV-SD).
- Group 12 will include 70 subjects (previously influenza vaccinated or previously influenza unvaccinated) in a 3:3:1 ratio (QIV-HD: QIV-HD: QIV-SD).

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.

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 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 the Food and Drug Administration in the US (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 which 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.

[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.

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

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the 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 CTA 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 / 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

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