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.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	QHD04
Development Phase:	Phase II
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	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
Version and Date of the SAP core body part:	Version 2.0, 04JULY2019

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List of Abbreviations

Ab	Antibody
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CI	confidence interval
CRB	case report book
CSR	clinical study report
D	day
DB	database lock
DM	Data Management
df	degree of freedom
dil	dilution
EDC	electronic data capture
ESDR	Early Safety Data Review
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GM	geometric mean
GMT	geometric mean titer
GMTR	geometric mean titer ratio
HA	hemagglutinin
HAI	hemagglutination inhibition
IAS	immunogenicity analysis set
IM	intramuscular
IRT	interactive response technology
LLOQ	lower limit of quantification
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
µg	microgram
ml	milliliters
NA	Not Applicable
NM	non-measurable
NT	neutralization test
PT	preferred term

QIV	quadrivalent influenza vaccine
QIV-HD	high-dose quadrivalent influenza vaccine
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SMT	Safety Management Team
SN	seroneutralization
SOC	system organ class
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
TLF	table(s), listing(s), and figure(s)
ULOQ	upper limit of quantification
US	United States
V	visit
WHO	World Health Organization

1 Introduction

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. 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 (1) (2) (3).

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 (4). 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, Australia, Brazil, and the United Kingdom to improve immune responses to influenza vaccine and vaccine efficacy in adults 65 years of age and older (5).

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 (6). To overcome the problem of B-strain selection and improve protection of the population against seasonal influenza virus strains, Sanofi Pasteur has been transitioning the Fluzone influenza vaccine portfolio from trivalent to quadrivalent formulations. The quadrivalent formulations contain 1 Victoria lineage B strain and 1 Yamagata lineage B strain. Thus, the issue of having to choose a strain from only one B lineage for the seasonal influenza vaccine and the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage is eliminated (7).

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 higher in children 6 months to 17 years of age compared with adults as seen in the most recent data from the 2015-2016 US influenza season (59.3% in children versus 41.7% in adults) (4). 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.

This statistical analyses plan (SAP) is developed based on the Food and Drug Administration (FDA) guideline for Industry of clinical data needed to support the licensure of seasonal inactivated influenza vaccines (8).

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.

Immunogenicity

- 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 methods.
- 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.

3 Description of the Overall Trial Design and Plan

3.1 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 to 17 years of age to evaluate the safety and immunogenicity of 3 dosages of QIV-HD administered by intramuscular (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 3 dose formulations (ie, 30 µg, 45 µg, and 60 µg 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 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 of the protocol, respectively. The study flow chart is outlined in Figure 3.1, Figure 3.2, and Figure 3.3. 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:

- 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 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).

[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 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 3.1: 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 (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

Stage (Country)	Age Group (Vaccination Status*)	Study Group	N	Vaccine	Vaccine Dosage (µg HA/strain/dose) †
	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 3.1: Study design flow chart for subjects 6 months to < 5 years of age

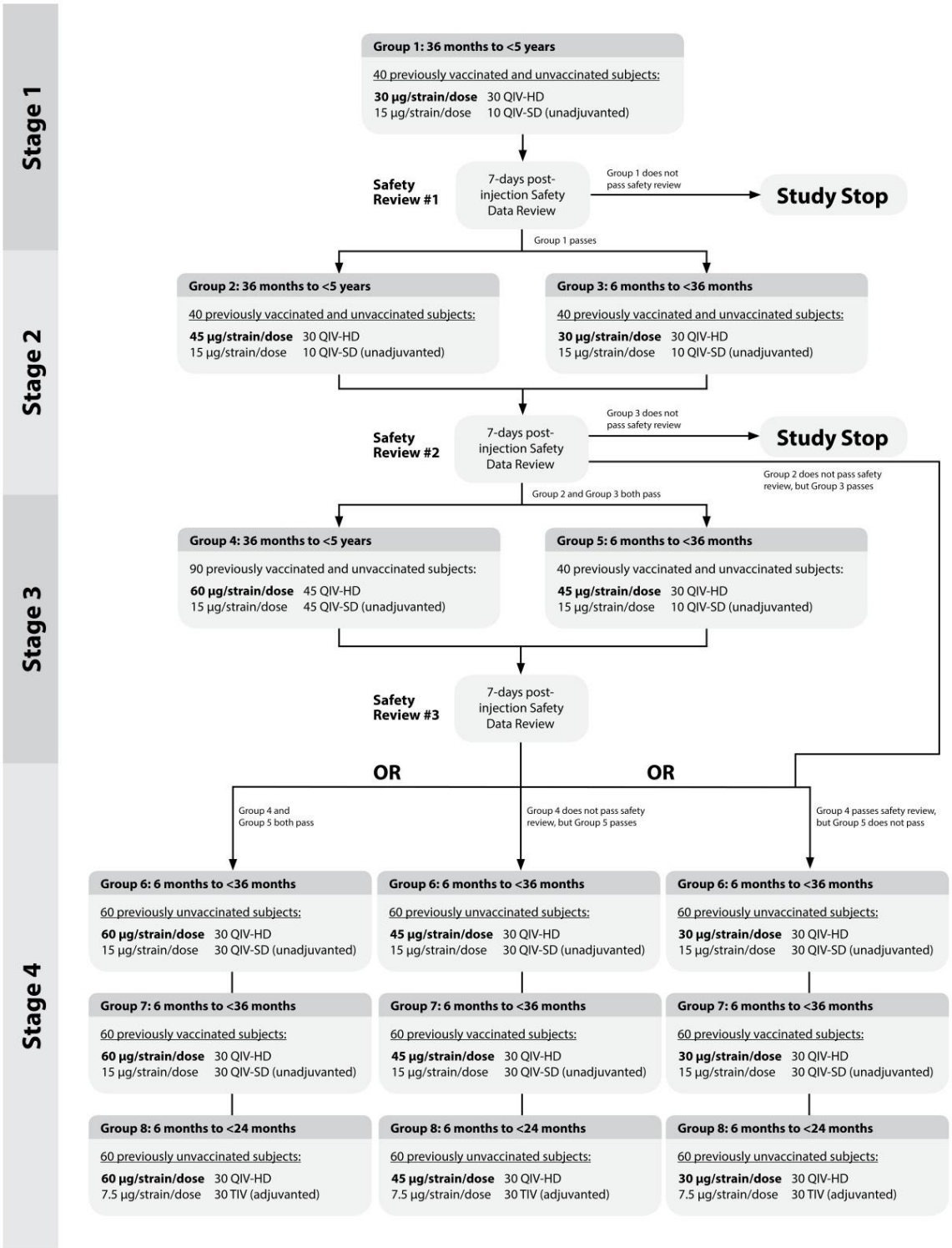


Figure 3.2: Study design flow chart for subjects 5 to 8 years of age

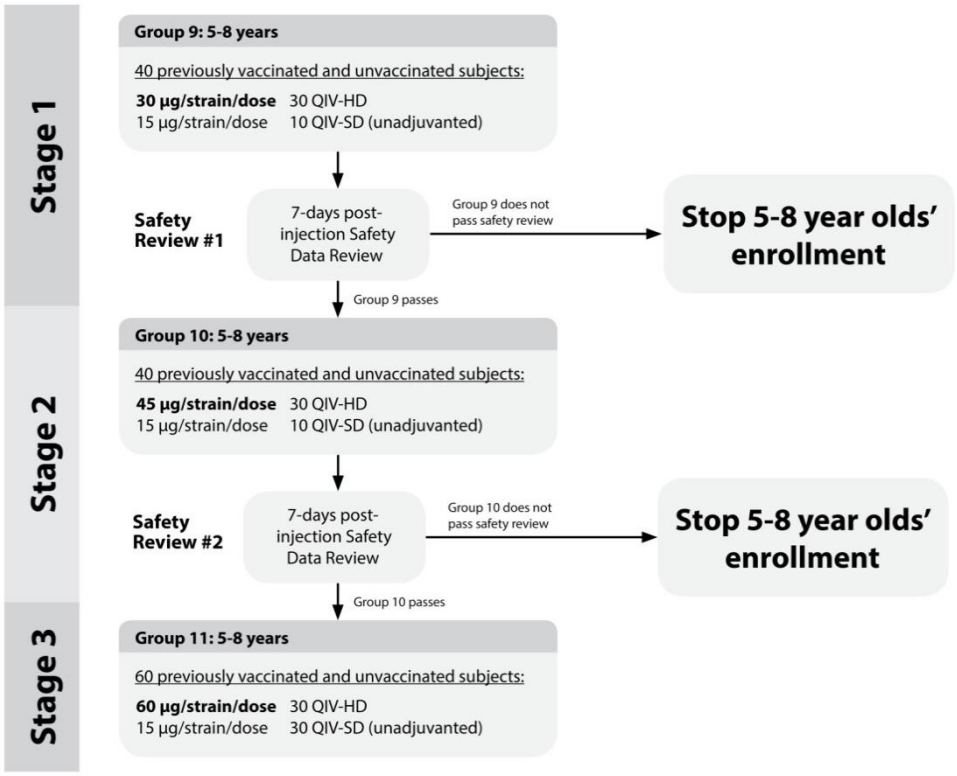
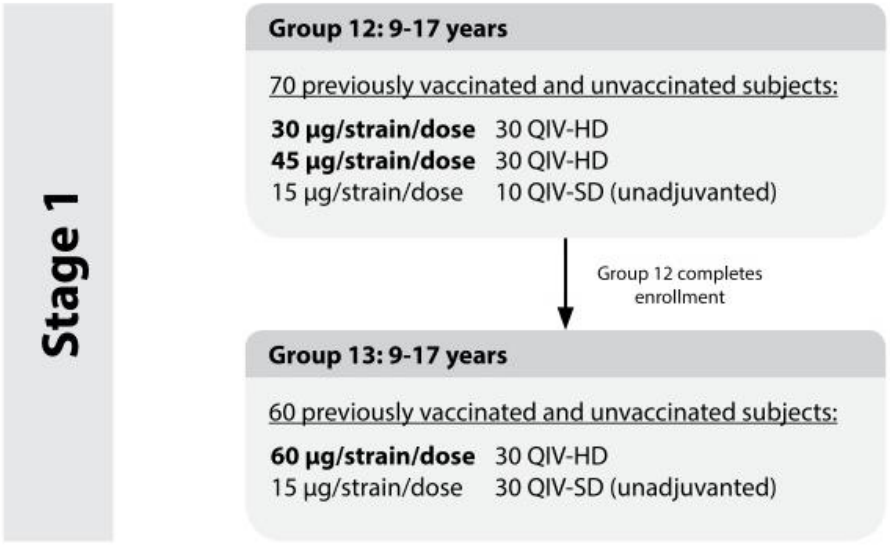


Figure 3.3: Study design flow chart for subjects 9 to 17 years of age



3.2 Study Plan

The study plan is summarized in the Table of Study Procedures (Table 3.2, Table 3.3, and Table 3.4).

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. SAEs and 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 (+2 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 3.1. 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 Safety Management Team (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 of the protocol.

Table 3.2: 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 3.3: 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)		+2	+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	
Safety follow-up phone call based on MA information§§				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 phone 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 3.4: 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)		+2	+7	+2	+7	+14
Informed consent form 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	
Safety follow-up phone call based on MA information‡‡						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.

* 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 phone 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.

4 Endpoints and Assessment Methods

4.1 Safety

See Section 9.1 of the protocol.

4.2 Immunogenicity

See Section 9.2 of the protocol.

4.3 Efficacy

No clinical efficacy data will be obtained in the study.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

For measurable injection site reactions (Erythema/Swelling/Induration/Bruising):

- For subjects 6 months to 11 years of age

  Grade 1: > 0 to < 25 mm

  Grade 2: ≥ 25 to < 50 mm

  Grade 3: ≥ 50 mm

- For subjects 12 to 17 years of age

  Grade 1: ≥ 25 to ≤ 50 mm

  Grade 2: ≥ 51 to ≤ 100 mm

  Grade 3: > 100 mm

For measurable systemic reactions (Fever):

- For subjects 6 months to < 36 months of age

  Grade 1: ≥ 38.0℃ to ≤ 38.5℃ , or ≥ 100.4℉ to ≤ 101.3℉

Grade 2: > 38.5℃ to ≤ 39.5℃ , or > 101.3℉ to ≤ 103.1℉

Grade 3: > 39.5°C, or > 103.1°F

- For subjects 3 to 17 years of age

  Grade 1: ≥ 38.0℃ to ≤ 38.4℃ , or ≥ 100.4℉ to ≤ 101.1℉

  Grade 2: ≥ 38.5℃ to ≤ 38.9℃ , or ≥ 101.2℉ to ≤ 102.0℉

  Grade 3: ≥ 39.0℃ , or ≥ 102.1℉

For the derivation of daily intensities the following sequential steps will be applied:

Solicited reactions (except Fever/Pyrexia) with an investigator occurrence recorded as "No" and with all daily records missing then all daily intensities will be derived as "None".

For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm in 12 to 17 years of age).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.4.1.1.2 Maximum Intensity

Maximum intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Occurrence

Occurrence is derived from the maximum intensity on the period considered:

- None: No occurrence
- Grade 1, Grade 2, or Grade 3: Occurrence
- Missing: Missing occurrence

Subjects with at least one non-missing occurrence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing occurrence will not be included in the analysis of the endpoint.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (ie, reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Table 4.1: Categories for time of onset

Injection Site Reactions (D0-D7)	Systemic Reactions (D0-D7)
D0-D3	D0-D3
D4-D7	D4-D7

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence during the solicited period with a specified intensity may also be derived.

Table 4.2: Categories for number of days of occurrence during the solicited period

Injection Site Reactions (D0-D7)	Systemic Reactions (D0-D7)
1-3 days	1-3 days
4-7 days	4-7 days
8 days	8 days

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1.

If the stop date is missing or incomplete (containing missing data [MD]), the overall number of days of occurrence will be considered as Missing.

Table 4.3: Categories for overall number of days of occurrence

Injection Site Reactions	Systemic Reactions
1-3 days	1-3 days
4-7 days	4-7 days
≥ 8 days	≥ 8 days
Missing	Missing

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

Note: a reaction could be derived as not ongoing for the analysis despite being considered as ongoing by the investigator (eg, when the maximum measurement after D7 is > 0 mm but < 25 mm for 12 to 17 years of age). If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

Unsolicited AEs include non-serious unsolicited AEs and SAEs. This subsection only covers the endpoints for unsolicited non-serious AEs.

4.4.1.2.1 Occurrence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event. Grade 0 events should be included in the listing "Unsolicited non-serious adverse events not included in the safety analysis."

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious AE will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited non-serious AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule as the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Note: the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm for 12 to 17 years of age). Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the CRB.

The maximum intensity corresponds to the highest intensity for a unique term.

4.4.1.2.3 Vaccination

Last vaccination before an unsolicited non-serious AE is derived from the visit numbers provided in the clinical database and is calculated as follows:

- If an unsolicited non-serious AE has a non-missing visit number, the visit number should be used to determine the last vaccination before the unsolicited non-serious AE.
- If the visit number is missing, then the start date should be used to determine the last vaccination before the unsolicited non-serious AE.

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

- Start date of the unsolicited non-serious AE – date of vaccination.

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited non-serious AEs will be analyzed "Within 28 days", which corresponds to AEs with a time of onset between 0 and 28 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number (See Section 4.4.1.2.3), so will be included in these tables.

Note: Unsolicited non-serious AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above (> 28 days) will not be included in analysis, but will be listed separately.

Time of onset will be displayed as follows:

- D0-D3
- D4-D7
- D8-D14
- ≥ D15
- Missing

4.4.1.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

- Stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

Duration will be displayed by period as following:

- 1-3 days

- 4-7 days
- 8-14 days
- ≥ 15 days
- Missing

4.4.1.3 SAEs

4.4.1.3.1 Vaccination

Last vaccination before an SAE is derived from the last visit numbers provided in the clinical database and is calculated as follows:

- If an SAE has a non-missing visit number, the visit number should be used to determine the last vaccination before the SAE
- If the visit number is missing, then the start date should be used to determine the last vaccination before the SAE.

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.4.

SAEs will be analyzed throughout the study using the following periods:

- During post-Dose period (within 28 days after any injection)
- During the whole study (ie, all SAEs occurred during the study)

4.4.1.3.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.5.

4.4.1.3.4 Intensity

The intensity for SAE is the same as the intensity for non-serious AE as described in Section 4.4.1.2.2.

4.4.1.4 Other Safety Endpoints

4.4.1.4.1 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.4.1.4.2 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.4.3 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.4.4 Causality

This information will be summarized as collected. An adverse reaction (AR) is defined as an unsolicited non-serious AE or an SAE with causality to the vaccine. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.4.5 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination "adverse event" checked.
- Safety overview table: A subject who has either on the termination form, the reason for early termination "adverse event" checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated. Note: If the Grade is below 1, the AE will be excluded from the list of AEs leading to study discontinuation.
- System organ class (SOC)/Preferred term (PT) table: An event (solicited, unsolicited, or SAE) that has "Cause Study Termination" or "Caused Study Discontinuation" checked that is at least Grade 1 and is within the time period indicated.

4.4.1.4.6 AESIs

AESIs will be collected throughout the study (from the inclusion until the 6 months safety follow-up contact after the last vaccination). AESIs are to be reported as SAEs. Each AESI will be retrieved using the following (as shown in Table 4.4):

Table 4.4: AESI PTs

AESI	PT
Guillain-Barre syndrome (GBS)	Chronic inflammatory demyelinating polyradiculoneuropathy Demyelinating polyneuropathy Guillain-Barre syndrome Miller Fisher syndrome

AESI	PT
Bell's Palsy	Facial paralysis Facial paresis
Encephalitis/Myelitis (including transverse myelitis)	Myelitis Myelitis transverse Encephalitis is using the narrow SMQ term "Noninfectious encephalitis" (Medical Dictionary for Regulatory Activities [MedDRA 20.1])
Optic neuritis	Optic neuritis Optic neuropathy
Brachial Neuritis	Radiculitis brachial Brachial plexopathy Neuralgic amyotrophy
Convulsions	Febrile Convulsion Seizure

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

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

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

For HAI and SN assays, in order to appropriately manage extreme values (<lower limit of quantification [LLOQ] and ≥ upper limit of quantification [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample (BL) drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is ≥ LLOQ and < ULOQ (or ≤ ULOQ), then use the value
- If a value is ≥ ULOQ (or >ULOQ), then use the computed value ULOQ

For immunogenicity values from HAI assay, each BL will provide two values on each strain on each time point (duplicates). In order to appropriately manage replicate values for analysis purposes, the individual geometric mean (GM) of the 2 values will be computed for each BL after managing extreme values as described above. For immunogenicity values from SN assay, each BL will have one value reported for each strain and each time point.

4.4.2.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values which are computed as described in Section 4.4.2.1. The computed value for fold-rise is:

Computed value = Post-vaccination computed value / Baseline computed value.

For HAI assay, if the computed value is ≥ 4-fold rise, then the derived 4-fold rise indicator will be “Yes” for that test, otherwise the corresponding indicators will be "No".

For SN assay, if the computed value is ≥ 2-fold rise or 4-fold rise, then the derived corresponding 2-fold rise or 4-fold rise indicator will be “Yes” for that test, otherwise the corresponding indicators will be "No".

Note: If baseline or post-baseline is missing, then the fold-rise is missing.

4.4.2.3 Seroconversion

For HAI assay, seroconversion is defined as either

- A computed value <10 [1/dil] at D0 and post-injection computed value ≥40 [1/dil] at D28 and D56 (if applicable), or
- A computed value ≥10 [1/dil] at D0 and a ≥ 4-fold rise in computed titer values [1/dil] at D28 and D56 (if applicable) as described in Section 4.4.2.1.

4.4.3 Efficacy

No clinical efficacy data will be obtained in the study.

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

The age of a subject in the study was the calendar age in months for children under 2 years old, and in years for subjects 2 years and older at the time of inclusion. The age calendar was the age computed automatically in the CRB, and presented as an integer.

4.4.4.2 Duration of the Study

The duration of the study is computed in days as follows:

- Maximum (Visit dates, Termination date, safety follow-up date) – minimum (V01 date)+1

The duration of the active phase of the study is computed in days as follows:

- Maximum (latest date of V03 [or V05 for subjects receiving 2 doses], latest date of termination during the active phase) – minimum (V01 date) +1,

The duration of the 6 months safety follow-up phase of the study is computed in days as follows:

- Maximum (date of D180 [or D208 for subjects receiving 2 doses] safety follow-up) – minimum (V03 dates [V05 dates for subjects receiving 2 doses], termination dates of the active phase) +1.

4.4.4.3 Subject Duration

The duration of a subject in the active phase of the trial is computed as follows:

- Maximum (V03 dates [or V05 dates for subjects receiving 2 doses], termination date) – V01 date +1.

The duration of a subject participation in the trial, including the 6 months safety follow-up, is computed as follows:

- Maximum (visit dates, termination date, safety follow-up date) – V01 date + 1.

4.4.4.4 Time Interval

The time interval between two visits/vaccinations/blood samples is computed as follows:

Later date – earlier date.

4.4.4.5 Influenza Vaccination during the Previous Influenza Season

This information will be used as collected. No derivation or imputation will be done.

5 Statistical Methods and Determination of Sample Size

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).

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs] of subjects). Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroconversion, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / data)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (9), ie, using the inverse of the beta integral with SAS®).

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide GMs and their 95% CI.

Rounding rules on descriptive statistics edited will follow the Sanofi Pasteur standard working instruction ("Conventions for the Presentation of Descriptive Statistics"). To present percentages (and 95% CI of percentages), one digit after the decimal place will be used.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for the Objectives

5.1.1.1 Hypotheses

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

5.1.1.2 Statistical Methods

For the cohorts controlled by the non-adjuvanted QIV-SD, results will be described per stage, according to vaccine received, per age group. Age groups will also be pooled within the same vaccine group for the main endpoints. When age groups are pooled, since age distributions between QIV-HD groups and the pooled QIV-SD group are different, the Simpson Paradox might exist. Therefore, each QIV-HD group (30µg, 45µg, and 60µg) will be compared with its corresponding and restricted QIV-SD group (ie, QIV-SD control group restricted to relevant study groups for comparison to QIV-HD at 30 µg, QIV-HD at 45 µg, and QIV-HD at 60 µg respectively) to reduce the potential bias. 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.

For main safety analyses, results will be described based on both "after any vaccination" and "after each vaccination".

For main immunogenicity analyses, results will be described based on both "after last vaccination" and "after each vaccination". Subgroup immunogenicity analyses per previous vaccination status and/or baseline serostatus may be presented when appropriate. Comparison between each QIV-HD group (30µg, 45µg, and 60µg) and the pooled QIV-SD group will also be performed stratified on age groups for immunogenicity endpoints.

5.1.1.2.1 Safety

Safety endpoints will be analyzed descriptively for subjects in safety analysis set (SafAS). 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) (9).

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] 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.

5.1.1.2.2 Immunogenicity

Immunogenicity endpoints, which are described in Section 4.4.2.1, will be summarized with 95% CIs. The 95% CIs for the geometric mean titers (GMTs) and the geometric means of titer ratios (GMTRs) will be calculated using normal approximation of log-transformed titers. The 95% CIs for the single proportions will be based on the Clopper-Pearson method. When age stratification is not considered, the ratios of GMTs (GMT ratios) 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 (10). 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.

The details about the calculations of the 95% CI for the GMT ratio between 2 groups are as following:

Logarithmic transformation of the individual titers will be calculated first. Assuming that individual $\log_{10}$ (titer) is normally distributed, the 95% CI for the difference in $\log_{10}$ (GMT) between group i and group j will be in the form:

$$\bar{X}_i - \bar{X}_j \pm t(1-\alpha/2, n_i + n_j - 2) \cdot S\sqrt{1/n_i + 1/n_j}$$

where $\bar{X}_i = \log_{10}(\text{GMT})$ is the mean of $\log_{10}$(titer) of Group *i*,

$S^2 = [(n_i - 1)\, S_i^2 + (n_j - 1)\, S_j^2] / (n_i + n_j - 2)$ is the pooled sample variance,

n_i and S_i^2 are the sample size and sample variance of Group i,

$t(1\text{-}\alpha/2,\ n_i + n_j - 2)$ is the 100(1-α/2) percentile of the *t*-distribution with degrees of freedom $(df) = n_i + n_j - 2$.

The 2-sided 95% CI of the difference in proportions will be computed using the Wilson Score method without continuity correction, quoted by Newcombe (10) as follows:

Let $\hat{\theta} = \pi_A - \pi_B$, then $L = \hat{\theta} - \delta$ and $U = \hat{\theta} + \varepsilon$ are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{0.025}\sqrt{\left\{\frac{l_1(1-l_1)}{n_1} + \frac{u_2(1-u_2)}{n_2}\right\}}$$

$$\varepsilon = Z_{0.025}\sqrt{\left\{\frac{l_2(1-l_2)}{n_2} + \frac{u_1(1-u_1)}{n_1}\right\}}$$

l_1 and u_1 are calculated from the CI of the single proportion in Group A given by:

$$\frac{(2n_1 p_A + Z_{0.025}^2 \pm Z_{0.025}\sqrt{(Z_{0.025}^2 + 4n_1 p_A(1-p_A))})}{2(n_1 + Z_{0.025}^2)}$$

l_2 and u_2 are calculated from the CI of the single proportion in Group B given by:

$$\frac{(2n_2 p_B + Z_{0.025}^2 \pm Z_{0.025}\sqrt{(Z_{0.025}^2 + 4n_2 p_B(1-p_B))})}{2(n_2 + Z_{0.025}^2)}$$

where $Z_{0.025}$ is the upper 97.5th percentile of the standard normal distribution.

When age stratification is considered, the age-stratified GMT ratio between each QIV-HD group (30µg, 45µg, and 60µg) and the pooled QIV-SD group will be reported. The corresponding 95% CIs of GMT ratios will be calculated using an analysis of variance (ANOVA) model of $\log_{10}$-transformed titers considering vaccine group as the main effect and age group as a covariate.

The 95% CI of the difference in seroconversion rates between each QIV-HD group (30µg, 45µg, and 60µg) and the pooled QIV-SD group will also be stratified on age effect and calculated using the Wald method (normal approximation). Weighted average of the difference over strata will be calculated using the Minimal Risk weights method (11). The details are as follows.

The 100(1-α)% two-sided CI for the difference in proportions between two groups *A* and *B* using the Minimum Risk Weights will be in the form:

$$\hat{\delta}_w \pm Z_{\alpha/2} \sqrt{\left\{ \sum_{i=1}^{s} w_i^2 \hat{V}(\hat{\delta}_i) \right\}}$$

Where $\hat{\delta}_w = \sum_{i=1}^{s} w_i \delta_i$ is the estimated weighted average of the proportion difference over strata;

$\delta_i = \hat{p}_{iA} - \hat{p}_{iB}$ is the estimated proportion difference between group A and B at stratum *i* (*i*=1,⋯ *s*);

$\hat{V}(\hat{\delta}_i) = \frac{\hat{p}_{iA}(1-\hat{p}_{iA})}{n_{iA}} + \frac{\hat{p}_{iB}(1-\hat{p}_{iB})}{n_{iB}}$ is the estimated variance of proportion difference between group *A* and *B* at stratum *i,* where n_{iA} and n_{iB} are the sample sizes of group *A* and *B* at stratum *i*;

$Z_{\alpha/2}$ is the $100(1-\alpha/2)$th percentile of the standard normal distribution;

w_i is the weight assigned at stratum *i*, where $\sum_{i=1}^{s} w_i = 1$.

The Minimum Risk method computes the weights w_i as follows:

$$w_i = \frac{\beta_i}{\sum_{k=1}^{s} V_k^{-1}} - \left(\frac{\alpha_i V_i^{-1}}{\sum_{k=1}^{s} V_k^{-1} + \sum_{k=1}^{s} \alpha_k \delta_k V_k^{-1}} \right) \left(\frac{\sum_{k=1}^{s} \delta_k \beta_k}{\sum_{k=1}^{s} V_k^{-1}} \right)$$

where $\alpha_i = \delta_i \sum_{k=1}^{s} V_k^{-1} - \sum_{k=1}^{s} \delta_k V_k^{-1}$, $\beta_i = V_i^{-1}\left(1 + \alpha_i \sum_{k=1}^{s} f_k \delta_k\right)$, $V_i = V(\hat{\delta}_i)$, and f_i is the fraction of subjects in the target population that belong in stratum *i* ($\sum_{i=1}^{s} f_i = 1$).

In addition, a sensitivity analysis will be performed with adjustment on the baseline titers. When comparing the GMT ratio between each QIV-HD group (30µg, 45µg, and 60µg) and the pooled QIV-SD group, the 95% CI will be stratified on both age effect and baseline titers and calculated using General Linear Model (GLM). When comparing the GMT ratio between each QIV-HD group and the QIV-SD group per age group, an ANCOVA model will be used when considering the baseline titer as a covariate. Results will be presented in Appendix 15 of the CSR.

5.2 Analysis Sets

Two main analysis sets will be used: IAS and SafAS

5.2.1 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.

5.2.2 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).

5.2.3 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.

5.3 Handling of Missing Data and Outliers

5.3.1 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.

5.3.1.1 Immediate

For unsolicited non-serious systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will remain missing and will not be imputed. Such SAEs will not be considered as immediate.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

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

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and will not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and will not be imputed.

5.3.1.6 Action Taken

Missing action taken will remain missing and will not be imputed.

5.3.2 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 in Section 4.4.2.1. The computed value is then considered the titer for that particular blood sample.

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

5.3.3 Efficacy

Not applicable.

5.4 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 DB has been conducted. A final analysis will be conducted once the 6-month safety data have been collected and the final DB has occurred.

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

5.5 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).

5.6 Data Review for Statistical Purposes

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 3.1 and Figure 3.2).

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.

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 3.1 and Figure 3.2. 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 DB. (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.

A blind review of the data is anticipated through the data review process led by Data Management (DM) before DB. This review of the data includes a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

No significant change occurred during the conduct of the trial not documented in a protocol amendment.

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7 Statistical Analysis Plan Shells - Main Outputs

Main outputs will be presented in the full TLF.