NCT number: NCT02451358

Immunogenicity and Safety of a Single Dose or Two Doses Given 28 Days Apart of a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 6 Months or Older in India

Open-label, multi-center, Phase-III study in healthy subjects aged 6 months or older in India

Clinical Trial Protocol, Amendment 2

Health Authority File Number:	Not applicable
WHO Universal Trial Number (UTN):	U1111-1143-8370
Trial Code: QIV06	**Development Phase:** Phase III
Sponsor:	Sanofi Pasteur SA 2, avenue Pont Pasteur, 69367 Lyon cedex 07, France
Investigational Product:	Quadrivalent Inactivated Influenza Vaccine, No Preservative
Form / Route:	Liquid/Intramuscular
Indication For This Study:	Prophylaxis of influenza in subjects aged 6 months or older
Manufacturer:	Same as Sponsor
Investigators	This is a multi-center trial with multiple investigators.
Sponsor's Responsible Medical Officer:	[redacted]
Medical Director:	[redacted]
Projects Manager and Study Leader	[redacted]
Product Safety Officer:	[redacted]
Regional Clinical Trial Manager:	[redacted]
Version and Date of the Protocol:	Version 5.0 dated 30 September 2015

This protocol version 5.0 is the second amendment to the initial trial protocol version 3.0 dated 09 September 2013. It is preceded by amendment 1, protocol version 4.0 dated 22 December 2014.

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	Quadrivalent Inactivated Influenza Vaccine, No Preservative
Active Substances:	Split influenza virus, inactivated, containing antigens equivalent to the following strains: A/H1N1-like, A/H3N2-like, B-like (Yamagata lineage), B-like (Victoria lineage) strains
Title of the Trial:	Immunogenicity and Safety of a Single Dose or Two Doses Given 28 Days Apart of a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 6 Months or Older in India
Development Phase:	Phase III
Coordinating Investigator:	This will be a multi-center trial with multiple investigators.
Trial Centers:	This will be a multi-center trial conducted at approximately 9 sites in India. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	July 2015 to January-February 2017
Trial Design and Methodology:	This will be an open-label, multi-center trial. A total of 400 subjects aged 6 months or older will be included in 4 age groups: 6 to 35 months, 3 to 8 years, 9 to 17 years, and 18 years or older (100 subjects per age group). Subjects will be sequentially enrolled as follows: • Per requirement from New Drug Advisory Committee (NDAC) / Subject Expert Committee (SEC) and approval letters from the Drug Controller General of India (DCGI) dated 22 July 2014, 15 May 2015, and 17 August 2015, the following recruitment will be performed: 100 adult subjects (18 years and older) will be enrolled first to receive the Quadrivalent influenza vaccine (QIV). • The safety events (line listings) with an occurrence within 28 days after vaccination will be submitted to the DCGI for evaluation by SEC experts. • When the DCGI gives the Go decision, the younger age groups will be sequentially enrolled, as follows: firstly the 100 subjects from the 9 to 17 years group, secondly the 100 subjects from the 3 to 8 years group, and thirdly the 100 subjects from the 6 to 35 months group. Safety events (line listings) with an occurrence within 28 days after vaccination for subjects aged 9 to 17 years and 28 days after the first vaccination for subjects aged 3 to 8 years will be reviewed by the Sponsor, and then submitted to the DCGI for information before moving to each of the younger age groups (3 to 8 years and 6 to 35 months). All subjects will be vaccinated with QIV (split-virion, inactivated) formulation recommended by the World Health Organization (WHO) Northern Hemisphere (NH) or Southern Hemisphere (SH) according to the study timelines, by the intramuscular (IM) route. The vaccination regimen will be as follows: • 100 previously unvaccinated* subjects aged 6 to 35 months will receive 2 injections 4 weeks apart (28 days) of QIV 7.5µg hemagglutinin (HA)/strain (0.25 milliliters [mL]) • 100 previously unvaccinated* subjects aged 3 to 8 years will receive 2 injections at least 4 weeks apart (28 days) of QIV 15µg HA/strain (0.5 mL)

	• 200 subjects aged 9 years or older (i.e., 100 adolescents aged 9 to 17 years and 100 adults aged 18 years or older) will receive 1 injection of QIV 15µg HA/strain (0.5 mL) * "previously unvaccinated": a child aged 6 months to 8 years not adequately primed, e.g., if he / she has not been vaccinated with 2 doses (with an approximate interval of 4 weeks) for at least 1 previous influenza season, then 2 doses of influenza vaccine will be administered Immunogenicity of the vaccine will be assessed at baseline (Day 0 [D0]) and 28 days after the last injection. Safety data will be collected up to 28 days after each vaccination. Serious adverse events (SAEs), including adverse events of special interest (AESIs) will be collected throughout the trial (i.e., up to 28 days after the final vaccination).

Early Safety Data Review:	Three early safety data reviews for this trial are planned, as follows:
	• When the 100 adult subjects have been vaccinated and have provided safety data from D0 to D28 post-vaccination, using the data collection methods described in the protocol. The safety data collected will be entered into the electronic case report forms (CRFs), and will be reviewed by SEC experts. It is understood that this review is based on preliminary data that have not been subject to 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 early safety review conducted by SEC experts will focus on the following adverse events (AEs) occurring within 28 days post-vaccination:
	  • Immediate reactions
	  • Solicited injection site and systemic reactions
	  • Unsolicited non-serious AEs
	  • SAEs
	• When the 100 adolescent subjects aged 9 to 17 years have been vaccinated and have provided safety data from D0 to D28 post-vaccination, using the data collection methods described in the protocol. The safety data collected will be entered into the CRFs, will be reviewed by the Sponsor, and then submitted to the NDAC. It is understood that this review is based on preliminary data that have not been subject to database lock
	• Similarly, when the 100 children subjects aged 3 to 8 years have been vaccinated and have provided safety data from D0 to D28 post-first vaccination. The safety data collected will be reviewed by the Sponsor, and then submitted to the NDAC.
	Apart from the early safety reviews, the trial may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs)/ Institutional Review Boards (IRBs), or the governing regulatory authorities in India where the trial is taking place.
	If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the trial subjects / subjects' parents/guardians and should assure appropriate therapy and follow-up.

Objectives:	• To describe in each age group the immune response induced by a single injection (subjects aged 9 years or older) or 2 injections (subjects aged 6 months to 8 years) of QIV • To describe in each age group the safety profile of QIV

Endpoints:	Immunogenicity Endpoints:
	Immunogenicity will be evaluated before and 28 days after the final vaccination (D56 for subjects aged 6 months to 8 years, and D28 for subjects aged 9 years or older) using the hemagglutination inhibition (HAI) technique. For each vaccine strain, serum hemagglutinin (HA) antibody titers will be expressed as geometric mean (GM) of HAI titers obtained in duplicates for pre- (D0) and post-vaccination (28 days after the final vaccination).
	The derived endpoints will be:
	• Individual geometric mean of duplicate titers (GM of titers) pre- and post-vaccination
	• Detectable HAI titer ≥ 10 (1/dilution [1/dil]) on pre- and post-vaccination
	• Individual titer ratio post-vaccination/pre-vaccination
	• Seroprotection status: titer ≥ 40 (1/dil) pre- and post-vaccination
	• Seroconversion or significant increase status:
	  • Seroconversion status: pre-vaccination titer < 10 (1/dil) and post-vaccination titer ≥ 40 (1/dil)
	  • Significant increase status: pre-vaccination titer ≥ 10 (1/dil) and ≥ 4-fold increase of post-vaccination titer
	Safety Endpoints
	• Occurrence of unsolicited AEs reported in the 30 minutes after each / any injection
	• Occurrence of solicited (prelisted in the subject diary card [DC],and CRF) injection site reactions and systemic reactions within 7 days following each / any injection
	• Occurrence of unsolicited (spontaneously reported) AEs within 28 days following each / any injection
	• Occurrence of SAEs (including AESIs) throughout the trial (i.e., from D0 through end of the study)
	Other endpoints recorded or derived will be described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, Grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.
	Note: The following AESIs, considered as important medical events are to be considered as SAEs and reported to the Sponsor. These include new onset of Guillain-Barré syndrome (GBS), Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and febrile seizures

Planned Sample Size:	A total of 400 subjects are planned to be enrolled: • Infants, toddlers, and children aged 6 to 35 months: n = 100 • Children aged 3 to 8 years: n = 100 • Adolescents aged 9 to 17 years: n = 100 • Adults aged 18 years or older: n = 100 In each age group, the enrollment will be controlled to maintain a minimum number of subjects in each age subgroup (6 to 23 months, 24 to 35 months, 3 to 8 years, 9 to 11 years, 12 to 17 years, 18 to 64 years, and 65 years or older) according to safety data collection needs, and to balance the inclusion of adults (18 to 64 years) and elderly (65 years or older) subjects.

Schedule of Study Procedures:	Vaccination Depending on their age, the subjects will receive 1 or 2 doses of QIV: • Subjects aged 6 to 35 months will receive 2 injections 28 days apart of QIV 7.5µg HA/strain (0.25 mL) • Subjects aged 3 to 8 years will receive 2 injections 28 days apart of QIV 15µg HA/strain (0.5 mL) • Subjects aged 9 years or older will receive 1 injection of QIV 15µg HA/strain (0.5 mL) Blood sampling All subjects will provide 2 blood samples including a pre-vaccination blood sample at D0. Subjects who are to receive 1 injection will provide a post-vaccination blood sample on D28. Subjects who are to receive 2 injections will provide a post-vaccination blood sample on D56 (28 days after the second injection). Collection of safety data Subjects / subjects' parents / legally acceptable representatives will use a DC to record information about solicited reactions from D0 to D7 post-injection(s) and unsolicited AEs up to 28 days after injection(s). Information on SAEs, including AESIs, will be collected throughout the study (i.e., up to 28 days for adolescents and adults and up to 56 days for toddlers and children) using DCs.
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be approximately: • 1 month for subjects aged 9 years or older • 2 months for subjects aged 6 months to 8 years
Investigational Product:	QIV, No Preservative
Form:	Liquid
Composition:	The formulation used will be as per World Health Organization (WHO) recommendations. Each 0.25-mL dose of vaccine contains 7.5 µg HA and each 0.5-mL dose contains 15 µg HA of: • A/ (H1N1) • A/ (H3N2) • B1/ (Victoria lineage) • B2/ (Yamagata lineage)
Route:	IM into the deltoid muscle or anterolateral aspect of the thigh: • The preferred site is the anterolateral aspect of the thigh in infants 6 months through 11 months of age • The preferred site is the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age • The preferred site is the deltoid muscle in persons ≥ 36 months of age
Batch Number:	To be determined

Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Aged 6 months or older on the day of inclusion 2) *For subjects aged 6 to 35 months only*: born at full term of pregnancy (≥ 37 weeks) or birth weight ≥ 2.5 kg or both 3) Informed consent form has been signed and dated by the subjects / subjects' parent(s) or another legally acceptable representative and by an independent witness, if required by local regulations. For subjects aged 7 to 17 years of age, assent form has been signed and dated by the subject 4) Subjects / subjects' parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) *For subjects aged 9 years or older only*: subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at least 4 weeks after vaccination) 2) Participation at the time of study enrollment (or in the 4 weeks preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 3) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks following any trial vaccination (except Oral Poliomyelitis Vaccine [OPV] received during national immunization days) 4) *For subjects aged 9 years or older only*: previous vaccination against influenza (in the previous 9 months) with any influenza vaccine 5) *For subjects aged 6 months to 8 years only*: previous priming with any influenza vaccine (i.e., subjects who received 2 doses for at least 1 previous influenza season) 6) Receipt of immune globulins, blood or blood-derived products in the past 3 months 7) 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) 8) Self-reported history of seropositivity for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C, after questioning 9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances 10) Self-reported thrombocytopenia or as reported by the parent/legally acceptable representative, contraindicating intramuscular vaccination 11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination 12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 13) *For subjects aged 9 years or older only*: current alcohol abuse or drug addiction

	14) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion 15) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (axillary temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided 16) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

Statistical Methods:	***Immunogenicity***
	The following parameters will be presented with their 95% confidence interval (CI) for each age group:
	• GM of titers pre- and post-vaccination
	• GM of individual titer ratio (GMTR) post-vaccination/pre-vaccination
	• Detectable HAI titer ≥ 10 (1dil) on D0 and D28/D56
	• Seroprotection rate (titer ≥ 40 [1/dil]) pre- and post-vaccination
	• Seroconversion or significant increase rate from pre- to post-vaccination
	  • Seroconversion: pre-vaccination titer < 10 (1/dil) and post-vaccination titer ≥ 40 (1/dil)
	  • Significant increase: pre-vaccination titer ≥ 10 (1/dil) and ≥ 4-fold increase of post-vaccination titer
	<u>Geometric Mean and 95% CI Computation</u>
	Assuming that $\log_{10}$ transformation of the measurements follows a normal distribution, at first, the mean and 95% CI will be calculated on $\log_{10}$ measurements using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, in order to provide GM and their 95% CIs.
	The 95% CIs will be computed using the normal approximate method for GM of titers and GMTRs, and the exact binomial distribution for percentages (Clopper-Pearson's method, quoted by Newcombe).
	HAI (1/dil) antibody titers against each strain will be graphically represented by a reverse cumulative distribution curve by visit and age group.
	Safety
	All analyses will be descriptive; no hypotheses will be tested. For the main parameters, 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions.
	Sample size determination
	The sample size was set to 100 subjects per age group.
	A 5% drop-out rate can be anticipated; therefore, 95 subjects per age group are expected to be evaluable for immunogenicity. With this sample size, the immunogenicity assessment in terms of percentages of subjects will have 95% CI widths of less than 21% (as shown in Table 1).

Table 1: 95% Confidence intervals for proportions (Exact method)

n/N	% subjects observed	95% CI
45/95	47.40%	(37.0;57.9)
50/95	52.60%	(42.1;63.0)
55/95	57.90%	(47.3;68.0)
70/95	73.70%	(63.6;82.2)
90/95	94.70%	(88.1;98.3)
95/95	100.00%	(96.2;100.0)

For the safety assessment, a sample size of 100 subjects vaccinated will allow detecting with 0.95 probability an AE with a frequency of 3%.

Table of Study Procedures for Subjects Aged 6 Months to 8 Years[a]

Phase III Trial, 3 Visits, 2 Vaccinations, 2 Blood Samples

Visit	V01	Phone Call or Home Visit	V02	Phone Call or Home Visit	V03
Trial timelines (days)	**D0**	**V01 + 3 days**	**V01 + 28 days**	**V02 + 3 days**	**V02 + 28 days**
Trial windows (days)	**-**	**+2**	**± 2**	**+2**	**± 2**
Indicative Months (M)			**M1**		**M2**
Informed consent / assent forms signed and dated	X				
Inclusion / exclusion criteria	X				
Demographics	X				
History of seasonal influenza vaccination / history of influenza diagnosis*	X				
Significant medical history	X				
Physical examination	X		X		X
Temperature (axillary)	X		X		
Temporary and definitive contraindications			X		
Assign subject number	X				
Blood sampling (3 mL)	BL1†				BL2
Vaccine injection	VAC1		VAC2		
30-minute surveillance period	X		X		
Diary Card (DC): **Provided** **Collected**	DC1		DC2 DC1		DC2
Contact with Subjects‡		X		X	
Recording of solicited injection site & systemic reactions			X		X
Recording of unsolicited non-serious adverse events			X		X
Reportable concomitant medication	X		X		X
Termination record					X
Serious adverse events§	Collected throughout the trial				

* History of seasonal influenza vaccination and influenza diagnosis will be collected within the past 3 years or since birth for subjects aged 6 to 35 months

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

‡ Telephone Calls or Home Visits:: trial personnel will ensure correct completion of DC, ask the subjects / subject's parent(s) / legally acceptable representative(s) whether the subject experienced any SAEs not yet reported, confirm the next visit and remind the subjects / subject's parent(s) / legally acceptable representative(s) that the DC should be brought to the trial center at the next visit

§ Including all AESIs

[a] '6 months to 8 years' means from the day of the 6th month after birth to the day before the 9th birthday

Table of Study Procedures for Subjects Aged 9 Years or older[a]

Phase III Trial, 2 Visits, 1 Vaccination, 2 Blood Samples

Visit	**V01**	**Phone Call or Home Visit**	**V02**
Trial timelines (days)	**D0**	**Visit 1 + 3 days**	**Visit 1 + 28 days**
Trial windows (days)	**-**	**+2**	**± 2**
Indicative Months (M)			**M1**
Informed consent / assent forms signed and dated	X		
Inclusion / exclusion criteria	X		
Demographics	X		
History of seasonal influenza vaccination / history of influenza diagnosis*	X		
Significant medical history	X		
Physical examination	X		X
Temperature (axillary)	X		
Urine pregnancy test†	X		
Assign subject number	X		
Blood sampling (3 or 5 mL‡)	BL1§		BL2
Vaccine injection	VAC1		
30-minute surveillance period	X		
Diary Card (DC) **Provided** **Collected**	DC1		DC1
Contact with Subjects**		X	
Recording of solicited injection site & systemic reactions			X
Recording of unsolicited non-serious adverse events			X
Reportable concomitant medication	X		X
Termination record			X
Serious adverse events††	Collected throughout the trial		

* History of seasonal influenza vaccination and influenza diagnosis will be collected within the past 3 years

† For women of childbearing potential, the urine pregnancy test is to be performed before vaccination.

‡ 3 mL for subjects aged 9 to 11 years and 5 mL for subjects aged 12 years or older

§ Collection of the first blood sample (BL1) will be before vaccination

** Telephone Calls or Home Visit: trial personnel will ensure correct completion of DC, ask the subjects / subject's parent(s) / legally acceptable representative(s) whether the subject experienced any SAEs not yet reported, confirm the next visit and remind the subjects / subject's parent(s) / legally acceptable representative(s) that the DC should be brought to the trial center at the next visit

†† Including all AESIs

[a] '9 years or older' means from the day of the 9th birthday

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse events of special interest
AF	assent form
ALRI	influenza-associated acute lower respiratory infections
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	confidence interval
CRA	Clinical Research Associate
CRF	electronic case report form
CRO	Contract Research Organization
CSR	clinical study report
CTA	clinical trial agreement
D	day
DC	diary card
DCGI	Drug Controller General of India
dil	dilution
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
FVFS	first visit first subject
FVLS	first visit last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	geometric mean
GMTR	geometric mean of titer ratio
GPV	Global PharmacoVigilance
HA	hemagglutinin
HAI	hemagglutination inhibition
HAU	hemagglutination units
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICF	informed consent form

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
LCLS	last contact last subject
LLOQ	lower limit of quantitation
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NA	neuraminidase
NDAC	New Drug Advisory Committee
NH	Northern Hemisphere
NSAID	non-steroidal anti-inflammatory drugs
OPV	oral poliomyelitis vaccine
PSO	Product Safety Officer
PPAS	per protocol analysis set
QIV	Quadrivalent influenza vaccine
RBC	red blood cell
RME	Regional Medical Expert
RMO	Responsible Medical Officer
RNA	ribonucleic acid
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SEC	Subject Expert Committee
SH	Southern Hemisphere
TIV	trivalent influenza vaccine
TMF	trial master file
ULOQ	upper limit of quantitation
WHO	World Health Organization

1 Introduction

1.1 Background

Influenza is a highly contagious, acute viral respiratory disease. It is typically characterized by the rapid onset of fever, myalgia, sore throat, and non-productive cough. Influenza can cause severe malaise, which lasts for several days. While influenza affects all age groups, the very young, older adults and persons with underlying health problems are at increased risk for complications. Members of high-risk groups who become ill with influenza are more likely than the general population to require hospitalization (1). Complications of influenza include primary viral pneumonia, secondary bacterial pneumonia, and exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and congestive heart failure.

Influenza in Humans can be caused by influenza type A and type B viruses. Influenza viruses types A and B belong to the genus *Orthomyxoviridae* and are characterized as enveloped, negative strand, segmented ribonucleic acid (RNA) viruses. The viral envelope contains 2 virus-coded glycoprotein spikes, the hemagglutinin (HA) and neuraminidase (NA) proteins, which are key antigens in the host response to influenza virus in both natural infection and vaccination. Antigenic variation is an important feature of the influenza virus. The viral HA and NA surface antigens are subject to continuous and sequential evolution within immune or partially immune populations. *Antigenic drift* results from mutation(s) affecting the RNA segment coding for either HA or NA, but more commonly HA. As a result, there is alteration in protein structure involving one or a few amino acids, resulting in minor changes in antigenicity. Antigenic variants within a subtype (e.g., H1 or H3) emerge and through natural selection gradually become the more predominant circulating virus strain, while the preceding antigenic variant is suppressed by a specific immunity in the population. In contrast to antigenic drift, *antigenic shift* represents the emergence of completely new subtypes, typically through gene reassortment with other circulating strains and acquisition of antigenically different gene sequences. Antigenic shift occurs at irregular intervals and may lead to pandemics.

Although influenza A accounts for the majority of circulating influenza viruses in most countries and seasons, influenza B circulates every year, late in the season in comparison to influenza A viruses, and accounts for 20% of all influenza isolates worldwide since 1990 (2). Based on the current knowledge, the epidemiology of influenza B is characterized by a major annual epidemic every 2 to 4 years. It causes infections in all age groups, most prominent among older children and young adults (3) (4). Influenza B infection is also prominent among older adults, which leads to excess mortality in some annual epidemics. In general, the burden of disease from influenza B is less than A/H3N2 but greater than A/H1N1 (4). It is a significant cause of absenteeism, clinic visits, hospitalizations, and deaths (5) (6) (7).

In temperate regions of the world, influenza occurs in winter season, whereas in tropical countries like India, peak influenza activity is seen during rainy season with some activity throughout the year. In a multisite surveillance study conducted in India from 2004 – 2008, seasonality of influenza was observed to vary with the geographical location of the site (8). North India demonstrated peak activity in winter and rainy seasons, Eastern and Western India demonstrated highest activity during rains and limited activity in winter and South India demonstrated a peak in the cooler season during rains. Studies conducted in India showed that, pandemic influenza A

(H1N1), A (H3N2), and type B virus co-circulated in different regions of the country with no dominance of any particular subtype (9) (10) (11). Even among influenza type-B subtypes, co-circulation of Yamagata-like and Victoria-like strains was observed in eastern India from 2006 to 2009 (12).

Although influenza is recognized as an important cause of acute respiratory illness, little is known about the prevalence and burden of influenza in India (9) (13) (14). In an active surveillance study by Chadha et al. conducted in Pune (West India) from May 2009 to April 2011, 20% of all hospital admissions due to acute medical illness or acute exacerbation of chronic disease had influenza positivity during the peak monsoon period. Out of all influenza-related hospitalizations, 340 (51%) were due to pandemic A (H1N1) and 327 (49%) were seasonal, including A/H3 (16%), A/H1 (3%) and influenza B (30%) (9).

Vaccination is currently the most effective protection against influenza (15) (16). Current vaccines induce serum anti-HA antibody for prevention of subsequent infection and illness from natural influenza. Serum anti-HA antibody is the most consistent correlate of immunity to influenza, in that serum hemagglutination-inhibition (HAI) titer correlates inversely with frequency of influenza illnesses among vaccinated persons (17). Annual vaccination is recommended for the elderly population as well as for all adults at higher risk for influenza complications or in close contacts of persons at higher risk. Moreover, vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others. Influenza vaccination of the elderly reduces the risk of serious complication or death by 70-85% (18) (19) (20). In 2003, the World Health Assembly urged Member States with influenza vaccination policies to increase vaccination coverage of all people at high risk and to aim a vaccination coverage of elderly people of at least 50% by 2006 and 75% by 2010 (21).

Children aged < 5 years, and particularly those < 2 years of age, have a high burden of influenza. A systematic review of the global disease burden of influenza in children, representing studies on a total of around 8 million children < 5 years of age, estimated that in 2008, there were 90 million (95%, confidence interval [CI] 49–162 million) new cases of seasonal influenza, 20 million (95% CI: 13–32 million) cases of influenza-associated acute lower respiratory infections (ALRI), and 1 to 2 million cases of influenza associated severe ALRI, including 28,000 to 111,500 deaths. The great majority of deaths from influenza occurred in developing countries. However, sufficient data to estimate precisely the contribution of influenza to childhood mortality, especially in developing countries, are not available (22).

1.2 Background of the Investigational Product

The Trivalent Influenza Vaccine (TIV) (Vaxigrip®) has been registered in India since 1996, and since 2011 both the Northern Hemisphere (NH) and Southern Hemisphere (SH) variations (as per the World Health Organization [WHO] recommendations) are available in India.

Antigenic variation is an important feature of the influenza virus. To accommodate for this variation, since 1978, the use of TIVs containing 1 H1N1 strain, 1 H3N2 strain and 1 B strain has been the norm. Fluzone® (Influenza Virus Vaccine), an inactivated TIV, has been used in the US since 1947, first as a whole virus preparation, and since 1980 as a split virus preparation, with a very good safety profile. In addition, several studies have demonstrated the efficacy and effectiveness of Fluzone vaccine (23) (24) (25) (26) (27) (28) (29) (30).

Although in general, influenza B viruses are more genetically stable than influenza A viruses, there is variation from season to season with respect to the circulating B strain. In recent years, 2 distinct lineages of influenza B have co-circulated worldwide, the B/Victoria/2/87-lineage (Victoria-lineage) prominent during the 1980s and, subsequently, the B/Yamagata/16/88-lineage (Yamagata-lineage) circulating during the 1990s, neither providing good cross-protection against the other. The Victoria-lineage continued to circulate in China and South-East Asia, but no isolation was reported in other parts of the world from 1991 until 2001 when they re-emerged in Canada and the United States (31). Since then, both Victoria and Yamagata-lineages have been circulating worldwide with varying intensity. Unfortunately, the ability to predict with acceptable accuracy which B lineage will be dominant during an upcoming season has been unsatisfactory, with frequent mismatches between the lineage chosen for inclusion in the vaccine and the predominant lineage in circulation. Indeed, for 6 of the past 12 influenza seasons (the 2000-2001 through 2011-2012 seasons), the B-lineage strain chosen for inclusion in TIV did not match the predominant B-lineage strain that actually circulated (32).

Consequently, there seems to be growing evidence among regulators, industry, and academic advisors that the time has come to move toward a Quadrivalent influenza vaccine (QIV), which would add an additional alternate-lineage B strain to the current TIV. Through modeling, the Centers for Disease Control and Prevention demonstrated that in some years, QIV would have led to a reduction in morbidity and mortality during seasons in which the B strain contained in TIV did not match the circulating B strain (33).

In this context, Sanofi Pasteur has developed an inactivated QIV containing 15 µg of HA of the two A strains (A/H1N1 and A/H3N2) and 15 µg of the two B strains (from the Victoria lineage and from the Yamagata lineage), based on the same manufacturing process as Fluzone manufactured by Sanofi Pasteur, US for active vaccination of subjects from 6 months of age (a pediatric formulation containing 7.5 µg of HA has been also developed).

Sanofi Pasteur conducted 3 studies (GRC43, QIV03, and QIV04) to evaluate the safety and immunogenicity of vaccination with QIV in adults and children (from 6 months of age). In these clinical trials, QIV demonstrated non-inferiority of antibody responses for each of the common 3 strains as compared to TIVs in each age group. QIV also demonstrated superiority of antibody response to the TIV groups which did not contain corresponding B strain in each age group. In addition, the overall safety profiles were similar in Fluzone® Quadrivalent and Fluzone groups in all age groups tested.

On June 7, 2013, US Food and Drug Administration (FDA) approved Sanofi Pasteur request to supplement the biologics license application for Influenza Virus Vaccine to include a Quadrivalent influenza virus vaccine formulation (Fluzone Quadrivalent) for use in persons 6 months of age and older (34).

This Quadrivalent vaccine is currently marketed in the US, Canada, Guatemala, Mexico, Panama, Venezuela, Hong Kong, and Malaysia. This vaccine is planned to be marketed during SH 2015 influenza season in some other countries in Latin America and Asia.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects will receive the QIV; therefore all subjects may be protected against the strains contained in the vaccine they will receive. These strains are the ones recommended by WHO as being the most likely strains anticipated to circulate during the influenza season.

Based on data generated in individuals as young as 6 months of age (studies GRC43, QIV03, and QIV04), it is anticipated that all subjects would be immunized against influenza B of both lineages simultaneously and may develop wider protection against influenza B.

1.3.2 Potential Risks to Subjects

The most frequent side effect of influenza vaccination is soreness at the injection site that lasts up to 2 days. Injection site reactions are generally mild and rarely interfere with the ability to conduct usual daily activities.

Systemic findings such as fever, shivering, malaise, and other side effects can occur following vaccination and most often affect persons who have had no prior exposure to the vaccine antigens (e.g., young children). These reactions begin 6 to 12 hours after vaccination and can persist for 1 to 2 days. Placebo-controlled trials suggest that in both older and healthy young adults, split-virus influenza vaccine is not associated with higher rates of systemic symptoms when compared with placebo injection (35).

Immediate allergic reactions occur rarely after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component; the majority is most likely related to residual egg protein (1).

Guillain-Barré syndrome (GBS) is a very rare, acute, and frequently severe polyneuropathy characterized by ascending fulminant muscle paralysis. The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was < 10 cases/1,000,000 persons vaccinated. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for such a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10 to 20 cases per 1,000,000 adults and stretches the limits of epidemiologic investigation.

The reasons why swine flu vaccine triggered GBS in 1976 to 1977 have never been discovered. In subsequent annual flu vaccine programs in the US, from 1991 to 1997, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of the studies. However, in a study of the 1992–1993 and 1993–1994 seasons, the overall relative risk for GBS was 1.7 (95% CI=1.0–2.8; P = 0.04) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS for each 1,000,000 persons vaccinated. The combined number of GBS cases peaked 2 weeks after vaccination. Thus, investigations to date indicate that there is no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976) and that, if influenza vaccine

does pose a risk, it is probably about one additional case per 1,000,000 persons vaccinated. Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately one additional case/1,000,000 persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination in all age groups, especially and chiefly persons ≥ 65 years of age and those who are at increased risk for complications from influenza.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported. However, no cause and effect has been established. Almost all persons affected were adults, and the described clinical reactions began as soon as a few hours and as late as 2 weeks after vaccination. Full recovery was almost always reported.

Cases of demyelinating disorders (e.g., incident multiple sclerosis in adults, acute disseminated encephalomyelitis, transverse myelitis), have been reported following influenza virus vaccines, although the Institute of Medicine concluded that the evidence is inadequate to accept or reject a causal relationship.

Cases of vasculitis have been reported following influenza immunization. A cause-and-effect relationship has not been determined.

There may be some discomfort or bruising from the needle stick.

There may be other risks not yet identified.

1.4 Rationale for the Trial

Sanofi Pasteur is committed to fulfilling its public health mission and is therefore willing to satisfy the requirements of Indian Health Authorities enabling the registration of the QIV to protect the Indian population against influenza. The aim of the present study is to generate immunogenicity and safety data in the whole population, i.e., infants, toddlers, children, adolescents, and adults to support registration of the QIV in India, offering the possibility of protection against 2 influenza B lineages simultaneously.

2 Trial Objectives

2.1 Immunogenicity Objective

- To describe in each age group the immune response induced by a single injection (subjects aged 9 years or older) or 2 injections (subjects aged 6 months to 8 years) of QIV

The endpoints for the immunogenicity objective are presented in Section 9.1.1.

2.2 Safety Objective

- To describe in each age group the safety profile of QIV

The endpoints for the safety objective are presented in Section 9.2.2.

3 Investigators and Trial Organization

This trial will be conducted in approximately 9 centers in India. Details of the trial centers, the Investigators at each center are provided in the "List of Investigators and Centers Involved in the Trial" document.

Development activities for data management, conduct of the data management activities and statistical analysis will be conducted by a contract research organization (CRO) under the responsibility of Sanofi Pasteur SA.

No independent data monitoring committee is planned for this trial as no safety concerns emerged during the clinical trials conducted with the QIV.

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

The country medical director is [redacted].

4 Independent Ethics Committee / Institutional Review Board

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

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

The Investigator with Sponsor's support will submit written summaries of the status of the trial to the IEC / IRB annually, or more frequently as per IEC / IRB standard operating procedure. All serious adverse events (SAEs) occurring during the trial will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Trial Design and Plan

5.1.1 Trial Design

This will be an open-label multi-center trial. A total of 400 subjects aged 6 months or older will be included in 4 age groups: 6 to 35 months, 3 to 8 years, 9 to 17 years, and 18 years or older (100 subjects per age group).

Subjects will be sequentially enrolled as follows:

- Per requirement from New Drug Advisory Committee (NDAC) / Subject Expert Committee (SEC) and approval letter from the Drug Controller General of India (DCGI) dated 22 July 2014, 15 May 2015, and 17 August 2015, the following recruitment will be performed: 100 adult subjects (18 years and older) will be enrolled first to receive QIV injection.
- The safety events (line listings) with an occurrence within 28 days after vaccination will be submitted to the DCGI for evaluation by SEC experts.

  When the DCGI gives the Go decision, the younger age groups will be sequentially enrolled, as follows: firstly the 100 subjects from the 9 to 17 years group, secondly the 100 subjects from the 3 to 8 years group, and thirdly the 100 subjects from the 6 to 35 months group. Safety events (line listings) with an occurrence within 28 days after vaccination for subjects aged 9 to 17 years and 28 days after the first vaccination for subjects aged 3 to 8 years will be reviewed by the Sponsor, and then submitted to the DCGI for information before moving to each of the younger age groups (3 to 8 years and 6 to 35 months).

All subjects will be vaccinated with the QIV (split-virion, inactivated) formulation recommended by the WHO NH or SH according to the study timelines, by the intramuscular (IM) route.

The vaccination regimen will be as follows:

- 100 previously unvaccinated[a] subjects aged 6 to 35 months will receive 2 injections 4 weeks apart (28 days) of QIV 7.5µg HA/strain (0.25 milliliters [mL])
- 100 previously unvaccinated[a] subjects aged 3 to 8 years will receive 2 injections at least 4 weeks apart (28 days) of QIV 15µg HA/strain (0.5 mL)
- 200 subjects aged 9 years or older (i.e., 100 adolescents aged 9 to 17 years and 100 adults aged 18 years or older) will receive 1 injection of QIV 15µg HA/strain (0.5 mL)

Immunogenicity of the vaccine will be assessed at baseline (Day 0 [D0]) and 28 days after the last injection. Safety data will be collected up to 28 days after each vaccination. SAEs, including adverse events of special interest (AESIs) will be collected throughout the trial (i.e., up to 28 days after the final vaccination).

[a] "previously unvaccinated": a child aged 6 months to 8 years not adequately primed, e.g., if he / she has not been vaccinated with 2 doses (with an approximate interval of 4 weeks) for at least 1 previous influenza season, then 2 doses of influenza vaccine will be administered

5.1.2 Justification of the Trial Design

Subjects will not be randomized since the trial will not be controlled. All included subjects will receive the same investigational vaccine but at different doses and regimens depending on their age. Subjects who will meet the eligibility criteria will be allocated a subject identifier (8-digit number) and then be vaccinated.

A sequential enrollment will be used: first, adult subjects from 18 years or older will be enrolled followed by the adolescents subjects aged 9 to 17 years, children aged 3 to 8 years, and then infants and toddlers aged 6 to 35 months.

Despite the fact that the investigational QIV was previously administered to humans in GRC43, QIV03, and QIV04 studies, and safety data support the enrollment of populations of children in this Phase III trial, 3 early safety data reviews are planned as per requirement from NDAC experts. Furthermore, its manufacturing process is based on Sanofi Pasteur's current manufacturing process for production of the IM licensed seasonal TIV manufactured by Sanofi Pasteur, US (see Section 1.2). Finally, the safety profile of this vaccine is very similar to the licensed TIV and it is not anticipated that the addition of a second influenza B virus strain to the final product would modify the current safety profile of this product. In addition, on June 7, 2013, the US FDA approved Sanofi Pasteur's request to supplement the biologics license application for Influenza Virus Vaccine to include a Quadrivalent influenza virus vaccine formulation (Fluzone Quadrivalent) for use in persons 6 months of age and older (34).

5.1.3 Trial Plan

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

Recruitment and information of subjects / parents / legally acceptable representatives:

Prior to enrollment, the investigator or a designee will inform subjects / parents / legally acceptable representatives of potentially eligible subjects about the trial. They will explain to subjects / parents / legally acceptable representatives that they may have to first sign an AF and/or ICF for Audio-Video Recording, if required by local regulation.

Then, candidates will be given a verbal description of the trial design, including but not limited to, the potential risks and benefits, discomforts, and subject responsibilities. Subjects / parents / legally acceptable representatives must voluntarily sign an ICF prior to enrollment in the trial. AFs may be voluntarily signed by the subject in accordance with local EC requirements or local regulations.

Trial description and enrollment of subjects:

After the subjects / parents / legally acceptable representatives (if applicable) have signed the ICF and, if applicable after the subject has signed the AF, and following confirmation by the Investigator that the subject has satisfied all inclusion / exclusion criteria, eligible subjects will be included in the study. They will provide their first blood sample (BL) and will be vaccinated with QIV.

Sequential approach

Per requirement from NDAC and approval from DCGI, adult subjects (18 years and older) will be enrolled first to receive QIV injection and will be followed for safety assessment. The younger age groups will then be enrolled sequentially when DCGI gives the Go decision as follows: firstly adolescents aged 9 to 17 years, secondly children aged 3 to 8 years, and then infants and toddlers aged 6 to 35 months (see Section 5.1.1 for more details).

Vaccination

Depending on their age, the subjects will receive 1 or 2 doses of QIV as follows:

- Subjects aged 6 to 35 months will receive 2 injections 28 days apart of QIV 7.5µg HA/strain (0.25 mL)
- Subjects aged 3 to 8 years will receive 2 injections 28 days apart of QIV 15µg HA/strain (0.5 mL)
- Subjects aged 9 years or older will receive 1 injection of QIV 15µg HA/strain (0.5 mL)

Blood sampling

All subjects will provide a pre-vaccination baseline blood sample (3 or 5 mL[a]) at D0 and a second blood sample (3 or 5 mL[a]) 28 days after the last vaccination.

Collection of safety data

Solicited reactions from D0 to D7 and non-serious unsolicited adverse events (AEs) from D0 to D28 will be collected after each vaccination.

Information on SAEs, including AESIs, will be collected throughout the study.

5.1.4 Visit Procedures

Each task performed and any information collected by the site staff will be documented in the subject source document. Some of the following information will also be recorded in the electronic case report form (CRF).

Prior to enrollment of the subject/parent(s) / legally acceptable representative(s), they may have to sign an AF and/or ICF for Audio-Video Recording, and the same should be signed by the Investigator, if required by local regulation.

5.1.4.1 Subjects Aged 6 Months to 8 Years

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

The Investigator or delegate will:

1) Explain the trial to the subject/parent(s) / legally acceptable representative(s), answer any questions and ensure that the subject/parent(s)/legally acceptable representative(s) have been informed of all aspects of the trial that are relevant to his / her decision to participate

[a] 3 mL for subjects aged 6 months to 11 years and 5 mL for subjects aged 12 years or older

2) Conduct the informed consent process and obtain written informed consent from the subject/parent(s)/legally acceptable representative(s) and obtain written assent from subjects if applicable. The Investigator will retain the original of these documents and will give a copy to the parent(s)/legally acceptable representative(s).

3) Check inclusion and exclusion criteria[a] for eligibility, which includes:
   a) Collect demographic data[a]
   b) Obtain verbal medical history about the subject (including history of seasonal influenza vaccination and history of influenza diagnosis)[a]
   c) Collect any reportable concomitant medications or vaccines[a]
   d) Conduct a physical examination (including axillary temperature measurement[a])
   e) If subject satisfies all eligibility criteria, assign a trial inclusion number to the subject (order of inclusion)
   f) Obtain the first blood sample, BL1 (3mL)[a] (see Section 7.1 for detailed instructions regarding the handling of blood samples)

   Note: If the attempt(s) to collect blood is (are) unsuccessful, the subject should be given the opportunity for another attempt, even on another day within the enrollment period. When the subject can be included in the study, the same inclusion number as the one assigned initially will be used, and inclusion and exclusion criteria will be re-checked. If ultimately a blood sample cannot be obtained, the reason will be recorded in the CRF. In this case, the subject will not be vaccinated and will be withdrawn from the study, but the CRF will be created. The subject's number will not be re-allocated to another subject.

4) Administer the first dose of study vaccine by IM into the deltoid muscle or anterolateral aspect of the thigh and record the date, the site, side, the route of injection, and the batch number[a]. Affix the vaccine label(s) into the source documents and the vaccination card (if applicable):
   - The preferred site is the anterolateral aspect of the thigh in infants 6 months through 11 months of age
   - The preferred site is the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age
   - The preferred site is the deltoid muscle in persons ≥ 36 months of age

5) Keep the subject under observation for 30 minutes, and record any AE in the source document

6) Give the parent(s)/legally acceptable representative(s) the first diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use

7) Remind the parent(s)/legally acceptable representative(s) that they will be called or visited 3 days after vaccination and that they have to bring back the DC1 when they return for Visit 2 at a specified date and time and to notify the site in case of an SAE

8) Complete the relevant CRF forms for this visit

[a] To be recorded in the CRF

Phone Call/Home Visit 1 (3 [+2D] days after Visit 1)

1) Remind the parent(s)/legally acceptable representative(s) to fill out solicited injection site and systemic reactions from D0 to D7 post-vaccination in the DC provided
2) Remind the parent(s)/legally acceptable representative(s) to bring back the DC when they return for the next visit at a specified date and time
3) Ask parent(s)/legally acceptable representative(s) if the subject experienced any SAEs not yet reported

Visit 2 (28 [±2D] days after Visit 1)

The Investigator or delegate will:

1) Collect and review (for clarity, content, and completeness) the DC1 information with the subject/parent(s)/legally acceptable representative(s) and clarify with the subject/parent(s)/legally acceptable representative(s), if required, any AEs, reportable medications (see Section 6.7), or SAE that occurred since the previous visit[a]. If an SAE occurred, the SAE reporting process should be followed (see Section 10).
2) Check contraindications to subsequent vaccination
3) Conduct a physical examination (including axillary temperature measurement)
4) Administer the second dose of study vaccine by IM into the deltoid muscle or anterolateral aspect of the thigh and record the date, the site, side, the route of injection, and the batch number[a]. Affix the vaccine label(s) into the source documents and the vaccination card (if applicable):
   - The preferred site is the anterolateral aspect of the thigh in infants 6 months through 11 months of age
   - The preferred site is the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age
   - The preferred site is the deltoid muscle in persons ≥ 36 months of age
5) Keep the subject under observation for 30 minutes, and record any AE in the source document
6) Give the parent(s)/legally acceptable representative(s) the DC2, a new thermometer and ruler[b], and go over the instructions for their use
7) Remind the parent(s)/legally acceptable representative(s) that they will be called or visited 3 days after vaccination and that they have to bring back the DC2 when they return for Visit 3 at a specified date and time and to notify the site in case of an SAE
8) Complete the relevant CRF for this visit

Phone Call/Home Visit 2 (3 [+2D] days after Visit 2)

Please refer to the procedures described for the phone call/home visit performed after Visit 1.

[a] To be recorded in the CRF

[b] Only if thermometer and ruler from Visit 1 are damaged

Visit 3 (28 [±2D] days after Visit 2)

The Investigator or delegate will:

1) Collect and review (for clarity, content, and completeness) the DC2 information with the subject/parent(s)/legally acceptable representative(s) and clarify with the subject/parent(s)/legally acceptable representative(s), if required, any AEs, reportable medications (see Section 6.7), or SAE that occurred since the previous visit[a]. If a SAE occurred, the SAE reporting process should be followed (see Section 10).
2) Conduct a physical examination
3) Obtain BL2 (3mL)[a] (see Section 7.1 for detailed instructions regarding the handling of blood samples)

   If the attempt(s) to collect blood is (are) unsuccessful, the subject should be given the opportunity to return to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRF.
4) Complete all relevant CRF forms for this visit
5) Complete the termination form of the CRF

5.1.4.2 Subjects Aged 9 Years or Older

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

The Investigator or delegate will:

1) Explain the trial to the subject/parent(s)/legally acceptable representative(s) answer any questions and ensure that the subject/parent(s)/legally acceptable representative(s) have been informed of all aspects of the trial that are relevant to his / her decision to participate
2) Conduct the informed consent process and obtain written informed consent from the subject/parent(s)/legally acceptable representative(s) and obtain written assent from subjects if applicable (the Investigator will retain the original of these documents and will give a copy to the subject/parent(s)/legally acceptable representative(s)).
3) Check inclusion and exclusion criteria[a] for eligibility, which includes:
   a) Collect demographic data[a]
   b) Obtain verbal medical history about the subject (including history of seasonal influenza vaccination and history of influenza diagnosis)[a]
   c) Collect any reportable concomitant medications or vaccines[b]
   d) Conduct a physical examination (including axillary temperature measurement[a])
   e) Perform a urine pregnancy test (women of childbearing potential[c] only)

[a] To be recorded in the CRF

[b] To be recorded in the CRF for children 9 to 11 years only

[c] To be considered of non-child-bearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at least 4 weeks after vaccination

4) If subject satisfies all eligibility criteria, assign a trial inclusion number to the subject (order of inclusion)

5) Obtain BL1 (3 or 5 mL[a])[a] (see Section 7.1 for detailed instructions regarding the handling of blood samples)

   Note: If the attempt(s) to collect blood is (are) unsuccessful, the subject should be given the opportunity for another attempt, even on another day within the enrollment period. When the subject can be included in the study, the same inclusion number as the one assigned initially will be used, and inclusion and exclusion criteria will be re-checked. If ultimately a blood sample cannot be obtained, the reason will be recorded in the CRF. In this case, the subject will not be vaccinated and will be withdrawn from the study, but the CRF will be created. The subject's number will not be re-allocated to another subject.

6) Administer the study vaccine by IM (into the deltoid muscle area), and record the date, the site, side, the route of injection, and the batch number[a]. Affix the vaccine label(s) into the source documents and the vaccination card (if applicable).

7) Keep the subject under observation for 30 minutes, and record any AE in the source document

8) Give the subjects / parents / legally acceptable representative a DC, a thermometer, and a ruler, and go over the instructions for their use

9) Remind the subject/parent(s)/legally acceptable representative(s) that they will be called or visited 3 days after vaccination and that they have to bring back the DC when they return for Visit 2 at a specified date and time and to notify the site in case of an SAE

10) Complete the relevant CRF for this visit

Phone Call/Home Visit 1 (3 [+2D] days after Visit 1)

1) Remind the subject/parent(s)/legally acceptable representative(s) to fill out solicited injection site and systemic reactions from D0 to D7 post-vaccination in the DC provided

2) Remind the subject/parent(s)/legally acceptable representative(s) to bring back the DC when they return for the next visit at a specified date and time

3) Ask the subject/parent(s)/legally acceptable representative(s) if he/she/the subject experienced any SAEs not yet reported

Visit 2 (28 [±2D] days after Visit 1)

The Investigator or delegate will:

1) Collect and review (for clarity, content, and completeness) the DC information with subject/parent(s)/legally acceptable representative(s) and clarify with the subject/parent(s)/legally acceptable representative(s), if required, any AEs, reportable medications (see Section 6.7), or SAE that occurred since the previous visit[b]. If a SAE occurred, the SAE reporting process should be followed (see Section 10).

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[a] 3 mL for subjects aged 9 to 11 years and 5 mL for subjects aged 12 years or older

[b] To be recorded in the CRF

2) Conduct a physical examination
3) Obtain BL2 (3 or 5 mL[a])[a] (see Section 7.1 for detailed instructions regarding the handling of blood samples)

   If the attempt(s) to collect blood is (are) unsuccessful, the subject should be given the opportunity to return to the study site for another attempt within the visit window. If a blood sample cannot be obtained, the reason will be recorded in the blood sampling page of the CRF.
4) Complete the relevant CRF forms for this visit
5) Complete the termination form in the CRF

5.1.4.3 SAEs and AEs That Are Related to Vaccination or That Led to Discontinuation

At any time during the study, a subject who experiences an SAE or an AE must be followed if *either* of the following is true:

- The SAE or AE is considered by the Investigator to be related to vaccination, and is not resolved by the end of the subject's participation in the trial
- The subject has been discontinued from the trial because of the SAE or AE

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

5.1.5 Planned Trial Calendar

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

Adults Group (18 years or older)

Planned trial period - FVFS[b] to LCLS[c] :	July 2015 to October 2015
Planned inclusion period - FVFS to FVLS[d] :	July 2015 to September 2015

Younger Age Groups (6 months to 17 years)[e]

Planned trial period – FVFS to LCLS	December 2015 to January-February 2017
Planned inclusion period – FVFS to FVLS	December 2015 to November-December 2016
Planned end of trial:	January-February 2017
Planned date of final clinical study report:	July-August 2017

[a] 3 mL for subjects aged 9 to 11 years and 5 mL for subjects aged 12 years or older
[b] First Visit, First Subject
[c] Last Contact, Last Subject
[d] First Visit, Last Subject
[e] Depending on the adult recruitment timelines, both adults and children might be included in the same flu season

5.1.6 Early Safety Data Review

Three early safety data reviews for this trial are planned, as followed:

- When the 100 adult subjects have been vaccinated and have provided safety data from D0 to D28 post-vaccination, using the data collection methods described in the protocol. The safety data collected will be entered into the CRFs, and will be reviewed by SEC experts. It is understood that this review is based on preliminary data that have not been subject to 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 early safety review conducted by SEC experts will focus on the following adverse events (AEs) occurring within 28 days post-vaccination:

  - Immediate reactions
  - Solicited injection site and systemic reactions
  - Unsolicited non-serious AEs
  - SAEs

- When the 100 adolescent subjects aged 9 to 17 years have been vaccinated and have provided safety data from D0 to D28 post-vaccination, using the data collection methods described in the protocol. The safety data collected will be entered into the CRFs, will be reviewed by the Sponsor, and then submitted to the NDAC. It is understood that this review is based on preliminary data that have not been subject to database lock.
- Similarly, when the 100 children subjects aged 3 to 8 years have been vaccinated and have provided safety data from D0 to D28 post-first vaccination. The safety data collected will be reviewed by the Sponsor, and then submitted to the NDAC.

Apart from the early safety reviews, the trial may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in India where the trial is taking place.

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

5.2 Enrollment and Retention of Trial Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator and/or study staff will determine the recruitment strategy to be used for this study (e.g., advertising, database, direct mail, word of mouth referral).

Using the relevant methods they will contact an appropriate pool of potential subjects and invite them to participate in the study. 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

Prior to the inform consent process, subjects / parents / legally acceptable representatives may have to sign first an AF and/or ICF for Audio-Video Recording, if required by local regulation.

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

In addition, children aged 7 to 17 years will be given an AF to sign and date, which will be signed and dated in addition to, not in place of, the ICF signed by the subject's parent(s) or other legally acceptable representative (if applicable). The use of the AF will be in accordance with local EC guidelines or local regulations.

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

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

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

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

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

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

5.2.3 Screening Criteria

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

5.2.4 Inclusion Criteria

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

1) Aged 6 months or older on the day of inclusion
2) ***For subjects aged 6 to 35 months only:*** born at full term of pregnancy (≥ 37 weeks) or birth weight ≥ 2.5 kg or both
3) Informed consent form has been signed and dated by the subject / subjects' parent(s) or another legally acceptable representative(s) and by an independent witness, if required by local regulations. For subjects aged 7 to 17 years of age, AF has been signed and dated by the subject
4) Subject / subjects' parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures

5.2.5 Exclusion Criteria

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

1) ***For subjects aged 9 years or older only***: subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at least 4 weeks after vaccination)
2) Participation at the time of study enrollment (or in the 4 weeks preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
3) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks following any trial vaccination (except oral poliomyelitis vaccine [OPV] received during national immunization days)
4) ***For subjects aged 9 years or older only***: previous vaccination against influenza (in the previous 9 months) with any influenza vaccine
5) ***For subjects aged 6 months to 8 years only***: previous priming with any influenza vaccine (i.e., subjects who received 2 doses for at least 1 previous influenza season)
6) Receipt of immune globulins, blood or blood-derived products in the past 3 months
7) 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)
8) Self-reported history of seropositivity for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C, after questioning
9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances

10) Self-reported thrombocytopenia or as reported by the parent/legally acceptable representative, contraindicating IM vaccination
11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination
12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
13) ***For subjects aged 9 years or older only***: current alcohol abuse or drug addiction
14) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion
15) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (axillary temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided
16) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

5.2.6 Medical History

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

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

5.2.7 Contraindications for Subsequent Vaccinations

Contraindications to subsequent vaccination will be checked in subjects aged 6 months to 8 years.

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 (axillary temperature ≥ 38.0°C) or moderate or severe acute illness / infection on the day of vaccination (36), according to Investigator judgment

5.2.7.2 Definitive Contraindications

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

1) An anaphylactic or other significant allergic reaction to the previous dose of vaccine
2) Receipt of contraindicated medications (blood derived products, anticoagulants…).
3) Participation at the time of study enrollment (or in the 4 weeks preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
4) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks following any trial vaccination (except OPV received during national immunization days)
5) For subjects aged 6 months to 8 years only: previous priming with any influenza vaccine (i.e., subjects who received 2 doses for at least 1 previous influenza season)
6) Receipt immune globulins, blood or blood-derived products in the past 3 months
7) 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)
8) Self-reported history of seropositivity for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C, after questioning
9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances
10) Self-reported thrombocytopenia or as reported by the parent/legally acceptable representative, contraindicating IM vaccination
11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination
12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
13) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion
14) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

15) Any AEs that are considered as a contraindication for further participation in the trial, at the discretion of the Investigator due to safety concerns leading to early termination of the trial.

16) Poor or non-compliance to study protocol by the subject. In case where a subject is outside the recommended visit schedule, the subject may be continued in the study as a protocol violator and will be analyzed accordingly.

Subjects will not be withdrawn from the trial due to contraindication but will be followed up for safety and possibly immunogenicity assessment.

5.2.8 Conditions for Withdrawal

Subjects / Parents / legally acceptable representatives will be informed that they have the right to withdraw or withdraw their child from the trial at any time.

A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission
- At the request of the subject / parent(s) / legally acceptable representative (dropout)

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant non-compliance with the protocol, based on the Investigator's judgment

The reason for a withdrawal or dropout should be clearly documented in the source documents and on the CRF. Withdrawn subjects will not be replaced.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in that case, the reason for discontinuation will be noted as "SAE" or "other AE" as appropriate) or for another reason.

5.2.9 Lost to Follow-up Procedures

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

5.2.10 Classification of Subjects Who Discontinue the Trial

For any subject who discontinues the trial prior to completion, the most significant reason for early termination will be checked in the CRF. Reasons will be listed from the most significant to the least significant as follows:

- **SAE:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an SAE, as defined in Section 9.2.1.
- **Other AE:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an AE other than an SAE, as defined in Section 9.2.1.

- **Non-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow protocol guidelines (e.g., not attending visits, not providing blood samples). This termination category may also be used if it is retrospectively discovered that a subject did not fulfill the eligibility criteria. The Investigator will provide a comment as to the specific cause of non-compliance.
- **Lost to follow-up:** To be used when the Investigator withdraws a subject from the study because of failure to establish contact, as outlined in Section 5.2.9. The Investigator will provide documentation that contact was attempted (i.e., return of unsigned certified mail receipt).
- **Voluntary withdrawal not due to an AE:** To be used when a subject drops out of the study for any reason other than those listed above.

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups with any subject who has prematurely terminated the trial because of an SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definite contraindications.

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

For subjects where the reason for early termination is voluntary withdrawal, the site will attempt to contact them except if they specified that they do not want to be contacted again and it is documented in the source document.

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

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 electronic Pregnancy Reporting Form. 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, 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 (e.g., even after the end of the trial).

5.3 Modification of the Trial and Protocol

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

A non-substantial amendment to a protocol is one that modifies some administrative or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. The IECs / IRBs will either be notified of or will approve non-substantial amendments per their local IEC regulations. Regulatory Authorities need only be notified about administrative changes.

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

5.4 Interruption of the Trial

The trial will include an early safety data review conducted by SEC experts and 2 early safety reviews conducted by the Sponsor (see Section 5.1.6).

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

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

6 Vaccines Administered

All subjects will receive the QIV as follows:

- Subjects 6 to 35 months will receive 2 IM injections of QIV (0.25 mL doses)
- Subjects 3 to 8 years will receive 2 IM injections of QIV (0.5 mL doses)
- Subjects 9 years or older will receive one IM injection of QIV (0.5 mL dose)

6.1 Identity of the Trial Products

6.1.1 Identity of Investigational Product

Vaccine:	QIV (no preservative)
Form:	Liquid
Dose:	0.25 mL – each dose contains 7.5 µg of HA per strain
	0.5 mL – each dose contains 15 µg of HA per strain
Route:	IM injection into the deltoid muscle or into the anterolateral aspect of the thigh depending on the age of the subject (see Section 6.1.1.2 for further details)
Batch number:	To be determined

QIV, single dose, no preservative is a sterile suspension prepared from the allantoic fluid of chicken embryos infected with specific influenza virus strains. The virus-containing fluid is harvested and the virus inactivated with formaldehyde. The influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted producing a split antigen. The split antigen is then suspended in sodium phosphate-buffered isotonic sodium chloride solution. Antibiotics are not used in the manufacture of the vaccine. QIV is essentially clear and slightly opalescent in color.

6.1.1.1 Composition

The formulation used will be as per WHO recommendations.

Each 0.25-mL dose of vaccine contains 7.5 µg HA and each 0.5-mL dose contains 15 µg HA each of:

- A/ (H1N1)
- A/ (H3N2)
- B1/ (Victoria lineage)
- B2/ (Yamagata lineage)

6.1.1.2 Preparation and Administration

QIV is a liquid preparation; as such, no diluent is required. This product is provided in 0.25-mL or 0.5-mL, pre-filled, single-dose syringes. The vaccine will be administered intramuscularly into the deltoid muscle or into the anterolateral aspect of the thigh:

- The preferred site is the anterolateral aspect of the thigh in infants 6 months through 11 months of age
- The preferred site is the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age
- The preferred site is the deltoid muscle in persons ≥ 36 months of age

The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

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. Another 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 CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

QIV will be administered as a single 0.25-mL **or** 0.5-mL dose given on Day 0 at Visit 1 for all subjects. For subjects requiring 2 doses, i.e. subjects aged 6 months to 8 years of age and receiving influenza vaccine for the first time as per Advisory Committee on Immunization Practices (ACIP) guidance, a second dose will be administered at Visit 2 (D28 [± 2 days] days after Visit 1).

6.1.2 Identity of Control Product

Not applicable.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

All study vaccines will be provided by the Sponsor, and will be labeled and packaged in accordance with national regulations.

Each dose of vaccine, in a pre-filled syringe, will be packaged in an individual box. Each pre-filled syringe will bear 1 fixed label and each box will bear 2 detachable labels and 1 fixed label enabling identification and providing information on the study.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

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

the product and send the printout of temperature recorder to the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

The Sponsor's monitoring staff will verify the trial site's product accountability records against the record of administered doses in the CRF.

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

6.3.3 Replacement Doses

If a dose is broken, another dose will be used.

6.3.4 Disposal of Unused Products

Unused or wasted products will be either disposed of upon Sponsor's written authorization or returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the trial period.

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

Not applicable.

6.5 Randomization and Allocation Procedures

Subjects in this trial will not be randomized since they will receive the vaccine according to their age group.

At Visit 1, after collecting a signed informed consent from Subjects/ parents / legally acceptable representatives and checking all inclusion and exclusion criteria, the Investigator will allocate an inclusion number to each subject.

Subjects will be provided with an inclusion number of 8 digits long, with a 3-digit center identifier, and a 5-digit subject identifier. This 5-digit subject identifier will correspond to the chronological order of enrollment in the center (e.g., the 21st subject included in center number 1 will be subject 001-00021).

In each age group, the enrollment will be controlled to maintain a minimum number of subjects in each age subgroup (6 to 23 months, 24 to 35 months, 3 to 8 years, 9 to 11 years, 12 to 17 years, 18 to 64 years and 65 years and older) according to safety data collection needs, and to balance the inclusion of adults (18 to 64 years), and elderly (65 years or older) subjects.

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications or Other Therapies

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

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

Reportable medications will be collected in the CRF from the day of vaccination to the end of the solicited and unsolicited follow-up period in general (i.e., 28 days safety follow-up) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

History of Influenza vaccination within the past 3 years (or since birth for subjects aged 6 to 35 months) prior to inclusion will be collected at enrollment (see Section 5.1.4 and Section 5.2.5).

The “reportable” medications are distributed according to two categories. These are:

- Category 1: antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) corticosteroids, and other immune modulators[a].
- *Note: inhaled and topical steroids should not be captured.*
- Category 2:
  - any vaccine other than the trial vaccines (except OPV received during national immunization days)
  - immune globulins, blood or blood-derived products
  - immunosuppressive therapy
  - anticoagulants

In the present study, protocol-restricted therapies are those of Category 2.

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

- Trade name
- Given as treatment or as prophylaxis[b]
- Medication category
- Start and stop dates

Dosage and administration route will not be recorded. Homeopathic medication will not be recorded. Topical treatment will not be recorded.

Medication given in response to an AE will be captured in the "Action Taken" column of the AE only. No details will be recorded in the concomitant medication module of the CRF unless the medication received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visit 1 (D0) and Visit 2 (D28 [±2 days]) for subjects aged 9 years or older, and at Visit 1 (D0) and Visit 3 (D56 [±2]) for subjects aged 6 months to 8 years. See the Tables of Study Procedures and Section 5.1.3 for details of the sampling schedule.

[a] Immunoglobulins, immunosuppressive therapies and other immune-modifying drugs from Visit 1 up to Visit 2 (for subjects aged 9 or older) or Visit 3 (for subjects aged 6 months to 8 years).

[b] The term "prophylactic" means: medication taken to prevent any AEs that may occur following the administration of the vaccine during the solicited follow-up period.

7.1 Sample Collection

At Visit 1 and Visit 2 or Visit 3, 3 or 5 mL[a] 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 check the assigned subject's number on the pre-printed label that contains the assigned subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of antibody 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 in order to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

The samples are then centrifuged, and 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 date and time for each step (blood draw, storage, centrifugation, aliquoting, and freezing) and the number of aliquots obtained must be documented in the source document.

The labels of the samples are to be stuck on the sample identification list. The date of sampling, the number of aliquots obtained, and the subject's consent for future use of his / her samples (if applicable) are to be specified on a sample identification list. Space is provided on this list for comments on the quality of samples.

7.3 Sample Storage and Shipment

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

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

Samples will be shipped to Global Clinical Immunology (GCI) at Sanofi Pasteur. The address is provided in the Operating Guidelines. Samples will be shipped outside the country only after approval from the relevant authorities.

[a] 3 mL for subjects aged 6 months to 11 years and 5 mL for subjects aged 12 years or older

7.4 Future Use of Stored Serum Samples for Research

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

8 Clinical Supplies

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

The means for performing 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 trial.

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

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines. They must allow at least 6 weeks for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Immunogenicity

The immunogenicity objective is to describe, in each age group, the immune response induced by a single injection (subjects aged > 9 years) or 2 injections (subjects aged 6 months to 8 years) of QIV.

9.1.1 Immunogenicity Endpoints

Immunogenicity will be evaluated before and 28 days after the final vaccination[a] using the HAI technique. For each vaccine strain, serum HA antibody titers will be expressed as geometric mean (GM) of HAI titers obtained in duplicates for pre- (D0) and post-vaccination (28 days after the final vaccination[a]).

[a] D56 for subjects aged 6 months to 8 years, and D28 for subjects aged 9 years and older

The derived endpoints will be:

- Individual geometric mean of duplicate titers (GM of titers) pre- and post-vaccination
- Detectable HAI: titer ≥10 (1/dilution [1/dil]) pre- and post-vaccination
- Individual titer ratio post-vaccination/pre-vaccination
- Seroprotection status: titer ≥ 40 (1/dil) pre- and post-vaccination
- Seroconversion or significant increase status:
  - Seroconversion status: pre-vaccination titer < 10 (1/dil) and post-vaccination titer ≥ 40 (1/dil)
  - Significant increase status: pre-vaccination titer ≥ 10 (1/dil) and ≥ 4-fold increase of post-vaccination titer

9.1.2 Immunogenicity Assessment Methods

Anti-HA antibody titers will be measured using the HAI method from the sera obtained on D0 and D28 after the last vaccination[a], according to a reference technique. For each vaccine strain, samples obtained pre- and post-vaccination from a same subject will be tested simultaneously in duplicates. The titer assigned at the time of the statistical analysis to each sample will be the GM of 2 independent determinations.

Additional analyses may be performed on the blood samples if required by the Sponsor to obtain further influenza antibody titration. In such a case, these analyses will not require additional blood samplings.

Anti-Influenza Virus Antibody Titration by Inhibition of Hemagglutination

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

Test serum samples and quality control sera are incubated with NA to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins is then performed by incubating the serum samples and quality control sera with a red blood cell (RBC) suspension. The mixtures are then centrifuged and the supernatants containing the treated sera are collected for testing.

Ten two-fold dilutions of the initial 1/10 dilution of the treated serum samples and quality control sera are incubated with previously titrated HA antigen (4 hemagglutination units [HAU]/25 µL). HA antigen is not added to 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 serum titer against each influenza strain tested is determined as the reciprocal of the highest dilution that exhibits complete inhibition of hemagglutination. Each serum sample is titrated in independent duplicates and the two values, which cannot differ by more than a two-fold dilution, are reported. The lower limit of quantitation (LLOQ) is set at the reciprocal of the lowest dilution used in the assay, i.e., 10 (1/dil). Titers below this level are reported as <10 (1/dil). The upper limit of quantitation (ULOQ) is 10240 (1/dil). Titers above this level are reported as ≥ 10240 (1/dil).

9.2 Safety

The safety objective is to describe in each age group the safety profile of QIV.

9.2.1 Safety Definitions

The following definitions are taken from the International Conference on Harmonisation (ICH) E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

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

Therefore an AE may be:

- A new illness
- The worsening of a concomitant illness
- An effect of the vaccination, including the comparator
- A combination of the above
- All AEs include serious and non-serious AEs.
- Surgical procedures are not AEs; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the trial period).

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose:

- Results in death

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

Additionally, AESIs listed in Section 9.2.3.3.3 are to be considered as SAEs and reported to the Sponsor according to the procedure described in Section 10.

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)

Unexpected Adverse Reaction:

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

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

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

- Symptom and
- Onset post-vaccination

e.g., injection site swelling between D0 and D7 post-vaccination, or fever between D0 and D7.

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

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

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

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

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

Unsolicited AE / AR:

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

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction[a] is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

Systemic AE:

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

Adverse Events of Special Interest (AESIs):

AESIs are AEs that are considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine (see Section 9.2.3.3.3).

9.2.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence of unsolicited AEs reported in the 30 minutes after each / any injection
- Occurrence of solicited (prelisted in the subject DC and CRF) injection site reactions and systemic reactions within 7 days following each / any injection
- Occurrence of unsolicited (spontaneously reported) AEs within 28 days following each / any injection
- Occurrence of SAEs (including AESIs) throughout the trial (i.e., from D0 through end of the study)

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

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

9.2.3 Safety Assessment Methods

At Visit 2 (subjects aged 9 or older) or at Visit 2 and Visit 3 (subjects aged 6 months to 8 years), the Investigator or a delegate will perform a clinical or medically-driven physical examination, and will ask the subjects / parents / legally acceptable representatives about any solicited reactions and unsolicited AEs recorded in the DC, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRF according to the instructions provided by the Sponsor.

9.2.3.1 Immediate Post-vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. Any AE that occurs during this period will be noted on the source document and identified as an immediate event / reaction; and will additionally be recorded in the CRF, as follows:

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

9.2.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After the Vaccination)

After vaccination, subjects / parents / legally acceptable representatives will be provided with a safety DC, 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 DC on the day of vaccination and for the next 7 days (i.e., D0 to D7) until resolution:

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

The action taken by the subjects / parents or legally acceptable representatives to treat any **solicited reactions** will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

4: Hospitalization (inpatient)

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 DCs and CRF for the different age group, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales for subjects aged 6 to 23 months

CRF term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition		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
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 moved, or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

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

Table 9.2: Solicited injection site reactions: terminology, definitions, and intensity scales for subjects aged 2 to 11 years

CRF term (MedDRA LLT)	Injection site pain	Injection site erythema	Injection site swelling
DC term	Pain	Redness	Swelling
Definition		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
Intensity scale* for subjects aged 2 to 11 years	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

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

Table 9.3: Solicited injection site reactions: terminology, definitions, and intensity scales for subjects aged 12 years or older

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition		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
Intensity scale*	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	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 / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 9.4: Solicited systemic reactions: terminology, definitions, and intensity scales for subjects aged 6 to 23 months

CRF term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C	Vomiting does not include spitting up	Inconsolable crying without a 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	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	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	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 / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the DC. 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.

Table 9.5: Solicited systemic reactions: terminology, definitions, and intensity scales for subjects aged 2 years or older

CRF term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia	Shivering
DC term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Shivering
Definition	Elevation of temperature to ≥°38.0°C	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling
Intensity scale*	Grade 1: ≥38.0°C to ≤38.4°C Grade 2: ≥38.5°C to ≤38.9°C Grade 3: ≥39.0°C	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

* For all reactions but fever, parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the DC. 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.

Important notes for the accurate assessment of temperature:

Subjects / Parents / legally acceptable representatives 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 DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for this trial is axillary for all subjects. Pre-vaccination axillary temperature is also systematically collected by the investigator in the CRF for subjects aged between 6 months and 11 years old, and on the source document for other subjects. Tympanic thermometers must not be used.

9.2.3.3 Unsolicited Adverse Events From Day 0 to Day 28 After the Vaccination

9.2.3.3.1 Unsolicited Non-Serious Adverse Events

In addition to recording solicited reactions, subjects / parents / legally acceptable representatives 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 DC for this purpose. For each AE, the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:
  - For measurable unsolicited non-serious 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 to Table 9.5).
  - Other unsolicited non-serious AEs will be classified according to the following intensity scale:

  Grade 1: No interference with activity

  Grade 2: Some interference with activity

  Grade 3: Significant; prevents daily activity

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

The action taken by the subjects / parents or legally acceptable representatives to treat any unsolicited AEs will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

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

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to discontinuation
- Whether the AE was related to the investigational product (see Section 9.2.3.4)

9.2.3.3.2 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, i.e. up to Visit 2 after vaccination for subjects aged 9 years or older and up to Visit 3 after vaccination for subjects aged 6 months to 8 years.

Any SAE occurring at any time during the trial will be reported by the Investigator through the EDC system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship between the SAE and the investigational product as either "Not related" or "Related", as described in Section 10.4.

See Section 10 for further details on SAE reporting.

9.2.3.3.3 Adverse Events of Special Interest

AESIs will be collected from Visit 1 to Visit 2 for subjects aged 9 years or older and from Visit 1 to Visit 3 for subjects aged 6 months to 8 years. AESIs are to be reported as SAEs (according to the procedure described in Section 10) and are considered by the Sponsor to be relevant for the monitoring of the safety profile of investigational products.

AESIs will be captured as SAEs. These include new onset of GBS, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and febrile seizures.

9.2.3.4 Assessment of Causality

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

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

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

[a] ICH Guidelines, Clinical Safety Data Management E2A

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

AEs likely to be related to the product that persist at the end of the trial will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event.

10 Reporting of Serious Adverse Events

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

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's 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 SAE form must be signed by a licensed physician (M.D. or D.O) for whom the task is listed on the Study Task Delegation and Signature List after each update to the Form.

The Investigator must complete the "eSAE Form" in the EDC application. After validation, an e-mail alert will automatically be sent to the GPV mailbox, the CRA, and the GME. This message will include the country, the study code, the subject number, whether the report is initial or a follow-up, the diagnosis and / or symptoms, the seriousness criteria, the relationship and the outcome if fatal.

If the EDC system is unavailable, the site must notify the Sponsor using the paper version of the SAE Reporting Form, as follows:

The Investigator must complete the SAE Reporting Form, check off the "Initial Reporting Form" box, and send it to the Sponsor by one of the following means:

- By fax, to the following number: [redacted]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted] A copy should also be sent to the local PV department [redacted])
- By express mail, to the following address:
  [redacted]

When the system becomes available, the Investigator must transcribe the information from the paper version of the eSAE Form into the EDC system.

If there is need for urgent consultation, the Investigator is to contact a designated Sponsor representative. The contact information is provided in the "List of Investigators and Centers Involved in the Trial" document.

10.2 Follow-up Reporting by the Investigator

The eSAE Form completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). After validation, an e-mail alert will be sent automatically to the GPV Department, GME, and to the CRA. All relevant information must be included directly in the eSAE form. Copies of documents (e.g., 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 product 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, using the paper version of the SAE Reporting Form.

10.4 Assessment of Causality

The causal relationship between the SAE and the product will first be evaluated by the Investigator, using the following definitions:

> **0 - 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 SAE is incompatible with a causal relationship; or the SAE started before the first vaccination (screening phase, if applicable).
>
> **1 - Related**: There is a "reasonable possibility" that the SAE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.
>
> *(ICH Guidelines, Clinical Safety Data Management E2A)*

Following this, the Sponsor's Product safety officer (PSO) will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The decision to modify or discontinue the trial, or to break individual or all trial codes, may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Investigator will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements, i.e.,

- initial reporting within 24hours from SAE occurrence to the Chairman of the Ethics Committee and the licensing Authority (DCGI) in required regulatory format (Appendix XI)
- submission of the analyzed report within 14 calendar days from SAE occurrence to the Licensing Authority, Chairman of the Ethics Committee, and the head of the institution where the trial has been conducted

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.

11 Data Collection and Management

11.1 Data Collection and CRF Completion

Individual safety DCs, specifically designed for this trial by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.2.3. These DCs will include prelisted terms and intensity scales (see Table 9.1 to Table 9.5) as well as areas for free text to capture additional safety information or other relevant details. Subject / parent(s) / legally acceptable representative(s) 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 / legally acceptable representatives on how to correctly use these tools.

At Visit 2 for subjects aged 9 years or older and at Visit 2 and Visit 3 for subjects aged 6 months to 8 years, the Investigator or an authorized designee will interview the subject / parent(s) / legally acceptable representative(s) to collect the information recorded in the DC, and will attempt to clarify anything that is incomplete or unclear. All clinical trial information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. (Any information that was not documented in the DC will first be captured in the source document and then reported electronically.) The CRF has been designed specifically for this trial under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRFs, 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 guidelines will be provided to assist with data entry during the course of the trial.

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

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

11.2 Data Management

Management of Clinical Data

Data generated during the trial will be managed following two different processes:

- Clinical data, defined as all data reported in the CRF, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.
- Data pertaining to SAEs, which are reported by the Investigator on the eSAE Forms or SAE Reporting Forms, will be handled by the Sponsor's GPV Department.

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

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

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.

Management of SAE Data

During the trial, data pertaining to SAEs reported on eSAE Forms will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an eSAE Form, the data will be entered into the GPV database after a duplicate check. Related, fatal, and AESI cases will be reviewed and assessed by the PSO, and the other cases will be reviewed and assessed by the CRO medical reviewer. Each case is reviewed, locked, and approved in the GPV database before being reported to the relevant authorities as necessary. If clarification is required, PV Queries will be sent to the Investigator. Follow-up information concerning a locked and approved case will be entered into the GPV database, and a new version of the case will be created.

The information pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

11.3 Data Review

A 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

Data will be analyzed under the responsibility of the Sponsor's Biostatistics platform with the SAS® software, at least Version 9.2 (SAS Institute, Cary, North Carolina, USA).

The SAP, covering all the analyses to be performed on all data, will be written before database lock.

12.1 Statistical Methods

For descriptive purposes, the following statistics will be presented:

Table 12.1: Descriptive statistics produced

Baseline characteristics	**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% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cut-off)**	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 GM, 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 (37), i.e., 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 GM of titers and GM of titer ratios (GMTRs) and their 95% CI.

12.1.1 Hypotheses and Statistical Methods for the Immunogenicity Objective

12.1.1.1 Hypotheses

No statistical hypotheses will be tested.

12.1.1.2 Statistical Methods

The following parameters will be presented:

- GM of titers on pre-vaccination (D0) and post-vaccination (D28/D56[a])
- GMTR D28/D0 or D56/D0
- Rate of subjects with titer ≥ 10 (1/dil) on D0 and D28 or D56
- Seroprotection rate (titer ≥ 40 [1/dil]) on D0 and D28 or D56
- Seroconversion or significant increase rate from D0 to D28 or D56

12.1.2 Hypotheses and Statistical Methods for Safety Objective

12.1.2.1 Hypotheses

No statistical hypotheses will be tested.

12.1.2.2 Statistical Methods

The analysis of safety will address the number and percentage of subjects experiencing injection site or systemic ARs or events until 28 days after each injection (solicited reactions from 0 to 7 days and unsolicited AEs/reactions from 0 to 28 days).

The number and percentage of subjects experiencing the following items will be described:

- solicited reactions (from 0 to 7 days) after each injection according to intensity, time of onset, and number of days of occurrence
- immediate and delayed unsolicited non-serious AEs (MedDRA System Organ Class and Preferred Term) (from 0 to 28 days) after each injection according to relationship, intensity, time of onset, and duration
- SAE (MedDRA Preferred Term) throughout the study, related or not, according to seriousness and outcome.
- AESI (MedDRA Preferred Term) throughout the study

Safety analyses, at least on solicited reactions, will be performed according to the following age sub-groups following the schedule and the reactogenicity scales applied:

- 6 to 23 months
- 24 to 35 months

[a] D56 for subjects aged 6 months to 8 years and D28 for subjects aged 9 years or older

- 3 to 17 years: analyses will be also performed in the 3 to 8 years, 9 to 11 years, and 12 to 17 years
- 18 to 64 years
- 65 years or older

12.2 Analysis Sets

Three main analysis sets will be used: the full analysis set (FAS), the per protocol analysis set (PPAS) and the safety analysis set (SafAS).

12.2.1 Full Analysis Set

The FAS will include all subjects who provided at least some data that will be used in the analysis of the secondary endpoints of the study. In this trial, the FAS will consist of all subjects who received at least one dose of vaccine and had at least one valid post-vaccination serology result.

12.2.2 Per Protocol Analysis Set

For each strain, subjects will be excluded from the PPAS for the following reasons:

- Subject did not meet all protocol-specified inclusion/exclusion criteria
- Subject received a vaccine other than the one that he/she was supposed to receive at Visit 1
- Preparation and/or administration of vaccine was not done as per protocol at Visit 1
- Subject did not provide a post-vaccination serology sample in the proper time window at Visit 2 for subjects aged 9 years or older or at Visit 3 for subjects aged 6 months to 8 years
- Subject received a protocol-restricted therapy (as defined in Section 6.7)
- Subject's serology sample at Visit 1 and after vaccination (on Visit 2 or Visit 3) did not produce a valid test result
- For subjects from 6 months to 8 years old, the following deviations will also conduct to the exclusion of subjects:
- Subject received a vaccine other than the one that he/she was supposed to receive at Visit 2
- Preparation and/or administration of vaccine was not done as per protocol at Visit 2
- Subject did not receive vaccine in the proper time window at Visit 2

In the event of national immunization days for OPV, subjects who receive one or more doses of OPV at any time during the trial will not be withdrawn from the trial.

A subject will also be excluded if a deviation was assessed as having interfered with the vaccine response was reported. Such deviations will be identified through the data review process and be confirmed based on the clinical team decision.

12.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccine.

12.2.4 Populations Used in Analyses

All subjects with data in the CRF will be taken into account in the description of the population. The immunogenicity analysis will be done on the FAS and confirmed on the PPAS. Finally, the SafAS will be used for the analysis of safety.

12.3 Handling of Missing Data and Outliers

12.3.1 Immunogenicity

For the calculation of GMTs and seroprotection, any pre-vaccination or post-vaccination titer reported as < LLOQ (lower limit of quantitation) will be converted to a value of 0.5 LLOQ. For the calculation of 4-fold rise and GMTR, any pre-vaccination value reported as < LLOQ will be converted to LLOQ, and any post-vaccination titer reported as < LLOQ will be converted to a titer of 0.5 LLOQ when only either the numerator or the denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way so that the 4-fold rise is defined as 1. Any titer reported as > ULOQ (upper limit of quantitation) will be converted to ULOQ.

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

12.3.2 Safety

Missing safety data will not be replaced.

No search for outliers will be performed.

12.4 Interim / Preliminary Analysis

Preliminary data line listings on subjects aged 18 years or older, 9 to 17 years, and 3 to 8 years will be prepared in the scope of the 3 early safety reviews.

No formal interim analyses are planned. However, the statistical analysis may be performed in 2 steps:

- A first analysis of the immunogenicity and safety data from the 100 adult subjects may be performed once data are available and after first data base lock.
- A final analysis at the end of the study when immunogenicity and safety data from all subjects are available and the final database lock.

12.5 Determination of Sample Size and Power Calculation

The sample size was set to 100 subjects per age group.

A 5% drop-out rate can be anticipated; therefore, 95 subjects per age group are expected to be evaluable for immunogenicity. With this sample size, the immunogenicity assessment in terms of percentages of subjects will have 95% CI widths of less than 21% (see Table 12.2).

Table 12.2: 95% Confidence intervals for proportions (Exact method)

n/N	% subjects observed	95% CI
45/95	47.40%	(37.0;57.9)
50/95	52.60%	(42.1;63.0)
55/95	57.90%	(47.3;68.0)
70/95	73.70%	(63.6;82.2)
90/95	94.70%	(88.1;98.3)
95/95	100.00%	(96.2;100.0)

For the safety assessment, a sample size of 100 subjects vaccinated will allow detecting with 0.95 probability an AE with a frequency of 3%.

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Trial / Good Clinical Practice

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

13.2 Source Data and Source Documents

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

For missing or discrepant data on a DC, the Investigator or designee will obtain verbal clarification from the subjects / parents / legally acceptable representatives, enter the response into the source document, and transfer the information to the CRF.

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

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

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

13.3 Confidentiality of Data and Access to Subject Records

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

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the trial (i.e., before the inclusion of the first subject in the first center), the Investigators and the Sponsor's monitoring staff or a representative will meet at the site-initiation visit to discuss the trial protocol and the detailed trial procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRF completion, and the handling of samples and products.

The Sponsor's monitoring staff or a representative will ensure and document that all material to be used during the trial has been received at the site; and that the study investigator team and local monitoring staff have been properly informed about the trial, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

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

After the start of the trial, the Sponsor's monitoring 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 monitoring staff direct access to subject medical files and CRFs. During these visits, the monitoring staff will:

- Evaluate the quality of the trial progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRFs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol violations, 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 CRF, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

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

- The center has all the documents necessary for archiving

- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been 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 and Medical Quality Operations or by independent auditors to verify that the trial has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to trial documents during these inspections and audits.

13.4.3 Archiving

The Investigator must keep all trial documents at a minimum for the duration indicated on the Clinical Trial Agreement (CTA), or longer if required by local regulation, after the completion or discontinuation of the trial, whatever the nature of the investigational center (private practice, hospital, institution). The Investigator will inform Sanofi Pasteur SA of any address change or if they will no longer be able to house the trial documents.

The Sponsor, or subsequent owner, will retain all documentation pertaining to the trial for the lifetime of the product or at a minimum for a retention period of 30 years. Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the trial, including certificates attesting that satisfactory audit and inspection procedures have been carried out, will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

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

Payment for medical management and compensation will be provided as per local regulations.

13.6 Stipends for Participation

Subject, subject's parent(s)/legally acceptable representative(s) will not receive any remuneration for participation in the trial.

13.7 Publication Policy

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

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

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

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