NCT Number: NCT02979535

Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially with Cervarix® in Healthy Female Subjects Aged 9 to 14 Years in Mexico

Phase IIIb, randomized, open-label, multicenter study in 480 female subjects aged 9 to 14 years in Mexico.

Clinical Trial Protocol Amendment 1

Health Authority File Number(s):	Not Applicable.
WHO Universal Trial Number (UTN):	U1111-1161-3455
Trial Code:	CYD71
Development Phase:	Phase IIIb
Sponsor:	Sanofi Pasteur 14, Espace Henry Vallée, F-69007 Lyon, France
Investigational Product(s):	CYD Dengue Vaccine
Form / Route:	Powder and solvent for suspension for injection/Subcutaneous
Indication For This Study:	Prevention of dengue fever in 9- to 14-year-old children
Manufacturer:	Same as Sponsor
Coordinating Investigator	This is a multi-center trial with multiple investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Sponsor's Responsible Medical Officer:	[redacted] Sanofi Pasteur Address: [redacted] Tel: [redacted]
Project Manager and Study Leader:	[redacted] Address: 14, Espace Henry Vallée, F-69007 Lyon, France Tel: Fax: [redacted]
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Version and Date of the Protocol: Version 2.0 dated 05 February 2018

This protocol version 2.0 is the first amendment to the initial trial protocol version 1.0, dated 04 January 2016.

Table 1: Previous versions of the protocol

Version*	Date	Comments
1.0	04 January 2016	Original study protocol (first version used in the study)
		Amendment 1

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

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	CYD Dengue Vaccine
Active Substance(s):	Live, attenuated, dengue serotype 1 virus Live, attenuated, dengue serotype 2 virus Live, attenuated, dengue serotype 3 virus Live, attenuated, dengue serotype 4 virus

Title of the Trial:	Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially with Cervarix® in Healthy Female Subjects Aged 9 to 14 Years in Mexico
Development Phase:	Phase IIIb
Coordinating Investigator:	[redacted]
Trial Centers:	This is a multi-center trial conducted in 3 sites in Mexico. Investigators and sites will be listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	Q4 2016 to Q3 2019
Trial Design and Methodology:	Phase IIIb, randomized, open-label, multicenter study in 480 female subjects aged 9 to 14 years in Mexico. Subjects have been randomized in a 1:1 ratio into one of the 2 following groups to receive: • **Group 1 (N=240):** 3 doses of CYD dengue vaccine and 2 doses of Cervarix® (Human Papillomavirus Bivalent [Types 16 and 18] Vaccine, Recombinant; GlaxoSmithKline) concomitantly to the 2 first doses of CYD dengue vaccine • **Group 2 (N=240):** 3 doses of CYD dengue vaccine and 2 doses of Cervarix sequentially (ie, one month before) to the 2 first doses of CYD dengue vaccine For both vaccines, each dose is to be administered 6 months apart. ***New clinical data*** *based on the results of exploratory analyses showed that the efficacy and safety profile of the CYD dengue vaccine was different between subjects previously naturally exposed to the dengue virus prior to vaccination (referred hereafter as "exposed subjects" or seropositive) and subjects never exposed to the dengue virus prior to vaccination (referred hereafter as "unexposed subjects" or seronegative). In light of these results, the Independent Data Monitoring Committee (IDMC) involved in the safety data review of the CYD dengue vaccine clinical development program concluded, in an ad hoc meeting held on 3-4 November 2017,that there is a strong evidence that the CYD dengue vaccine protects exposed subjects from symptomatic, hospitalized and severe dengue while, in unexposed subjects, the vaccine confers limited short term benefit against symptomatic dengue and induces an increased risk of hospitalized or severe dengue in the long term (findings are based on follow-up of dengue unexposed subjects having received 3 CYD dengue vaccine doses).* *Given the IDMC recommendations, Sanofi Pasteur has suspended all vaccinations in the CYD71 study until the baseline dengue serostatus is known for all study*

	participants. To determine the baseline serostatus of the subjects, the PRNT assay will be used on blood samples provided by the subjects before the first vaccination. *As per IDMC recommendations, the following changes will be applied to this trial:* • *All vaccinated subjects will be informed about their baseline dengue serostatus, and what it means, as soon as possible based on blood samples provided by the subjects before the first vaccination.* • *All subjects will be asked about their willingness to continue participating in this study. Subject's consent will be formalized by signing an amended Assent Form (subject's parent[s]/legally acceptable representative[s] will sign an amended Informed Consent Form).* • *Subjects identified as "dengue unexposed" (seronegative) at baseline will not receive further CYD dengue vaccine doses. They will only be able to continue in the study for safety follow-up at 6 months post last dengue vaccine dose, if they consent to, and will have timely access to appropriate care in the event of suspected dengue, for 10 years from the date of last dengue vaccination whether they remains in the study or not.* • *Subjects identified as "dengue exposed" subjects (seropositive) at baseline who are eligible to continue dengue vaccination in the study will be additionally asked to consent for further CYD dengue vaccine injection. Subjects that consent to receive the third and last dose of CYD dengue vaccine will complete the study as it was initially planned. Subjects that consent to remain in the study but prefer not to receive the last injection will be able to continue in the study for safety follow-up at 6 months post last dengue vaccine dose.* Based on these recommendations, the first amendment to the original protocol version 1.0 has been issued. A summary of the schedule of study vaccination and blood samplings for eligible subjects is provided in the table below

Table S 1: Injection and blood sampling schedule by Group (Dengue-exposed subjects)

Period	**Prior to Amendment 1**						**Post Amendment 1**	
Visit (V)	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**
Timing	**D0**	**M1**	**M2**	**M6**	**M7**	**M8†**	**M12 or M13†**	**M13 or M14†**
Group 1*	Cervarix + CYD			Cervarix + CYD			CYD	
	BL	BL			BL			BL
Group 2	Cervarix	CYD		Cervarix	CYD		CYD	
	BL	BL	BL		BL	BL		BL
Subjects not receiving the next CYD‡							Safety follow-up (6 months after the last CYD dengue vaccine injection	

D: day; M: month; BL: blood sample; CYD: CYD dengue vaccine

* When concomitantly administered, the CYD dengue vaccine and Cervarix will be administered in 2 different sites with the CYD dengue vaccine administered in one deltoid and Cervarix in the other deltoid

† In the original protocol v1.0, subjects from Group 1 were expected to attend V07 at M12 and V08 at M13. Likewise, subjects from Group 2 were expect to attend V07 at M13 and V08 at M14.

At the time of Protocol Amendment 1, procedures planned at V07 (most subjects) or V08 (2 subjects from Group 1) were on hold, depending on subjects' progression. Time for the approval of Protocol Amendment 1 by the competent authorities and completion of the associated logistic tasks will result into a delay of study activities (approximately 6 months), and thus to an extension of study duration for dengue exposed subjects.

‡ This includes seronegative subjects that consent to remain in the study and seropositive subjects that consent to stay in the study but prefer not to receive the next dose of CYD dengue vaccine

	For the 2 vaccines, immediate adverse events (AEs) observed to occur within 30 min post-injection will be collected. Solicited reactions will be collected after each injection: between Days 0–7 for injection site reactions and between Days 0–14 for systemic reactions. Unsolicited adverse events (AEs) will be collected between Days 0-28 after each injection. Serious adverse events (SAEs) will be reported throughout the study (from inclusion until 6 months after the last injection). Serious and non-serious adverse events of special interest (AESIs) will be collected in defined time windows according to the type of AESI. In addition, hospitalized suspected dengue cases occurring at any time in the trial will be collected and documented. Subjects will be followed for safety from the first injection up to 6 months after the last injection.
Independent Data Monitoring Committee	An IDMC will be involved in the regular review of hospitalized virologically-confirmed dengue cases (VCD), including assessment of severity. Additionally, any related SAE or death will be promptly reviewed by the IDMC.
Early Safety Data Review:	This trial will not include an early review of safety data. However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), or the governing regulatory authorities

	in Mexico 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 subjects and/or the subjects' parents/legally acceptable representatives and should assure appropriate therapy and follow-up. An internal safety evaluation team (SET) will perform a safety analysis on safety data during the conduct of the trial.
Primary Objectives:	**Immunogenicity** *Cervarix immunogenicity* • To demonstrate that the humoral immune response (in terms of geometric mean titers [GMTs]) to Cervarix after concomitant administration with the CYD dengue vaccine is non-inferior to the humoral immune response (in terms of GMTs) after sequential administration with the CYD dengue vaccine measured 28 days after the last dose of Cervarix* *CYD dengue vaccine immunogenicity* • To demonstrate that the humoral immune response (in terms of GMTs) to the CYD dengue vaccine after concomitant administration with Cervarix is non-inferior to the humoral immune response (in terms of GMTs) to the CYD dengue vaccine after sequential administration with Cervarix measured 28 days after the last dose of the CYD dengue vaccine* **Providing that the number of evaluable seropositive subjects allows a global power of at least 80% (otherwise analyses will be descriptive)*
Primary Endpoints:	**Immunogenicity** *Cervarix immunogenicity* • Antibody (Ab) levels (measured by enzyme-linked immunosorbent assay [ELISA]) against each Cervarix HPV antigen (HPV-16 and HPV-18) 28 days after the last dose of Cervarix in dengue exposed subjects *CYD dengue vaccine immunogenicity* • Neutralizing Ab levels (measured by dengue plaque reduction neutralization test [$PRNT_{50}$]) against each of the four parental dengue virus serotypes of the CYD dengue vaccine (1, 2, 3, 4) 28 days after the last dose of the CYD dengue vaccine in dengue exposed subjects
Secondary Objectives:	**Immunogenicity** *Cervarix immunogenicity* • To demonstrate that the humoral immune response (in terms of seroconversion) to Cervarix after concomitant administration with the CYD dengue vaccine is non-inferior to the humoral immune response (in terms of seroconversion) to Cervarix sequential administration with the CYD dengue vaccine measured 28 days after the last dose of Cervarix* • To describe the humoral immune response to Cervarix at baseline and after each dose of Cervarix in each and any group *CYD dengue vaccine immunogenicity* • To describe the humoral immune response to the CYD dengue vaccine at baseline and after each dose of the CYD dengue vaccine, in each and any group **Providing that the number of evaluable seropositive subjects allows a global power of at least 80% (otherwise analyses will be descriptive)*

	Safety *Cervarix and CYD dengue vaccine safety* • To describe the safety of Cervarix and CYD dengue vaccine after each and any dose in each group
Secondary Endpoints:	**Immunogenicity** *Cervarix immunogenicity* • Ab levels (measured by ELISA) against each Cervarix HPV antigen (HPV-16 and HPV-18) at baseline and after each dose of Cervarix in dengue exposed subjects • Seroconversion against each Cervarix HPV antigen (HPV-16 and HPV-18) 28 days after each dose of Cervarix in dengue exposed subjects Seroconversion is defined as changing serostatus from seronegative at baseline to seropositive (> lower limit of quantitation [LLOQ] of the assay) or ≥ 4-fold rise in Ab titer if seropositive at baseline.
	CYD dengue vaccine immunogenicity • Neutralizing Ab titers against each of the four parental dengue virus serotypes of CYD dengue vaccine as determined by $PRNT_{50}$ at baseline and after each dose of CYD dengue vaccine in dengue exposed subjects • Neutralizing Ab titers ≥ 10 (1/dil) against each of the four and against at least 1, 2, 3, or 4 parental dengue virus serotypes of CYD dengue vaccine as determined by $PRNT_{50}$ at baseline and after each dose of CYD dengue vaccine in dengue exposed subjects • Neutralizing Ab titers ≥ different titer thresholds (1/dil) against each of the four parental dengue virus serotype of CYD dengue vaccine as determined by $PRNT_{50}$ at baseline and after each dose of CYD dengue vaccine in dengue exposed subjects
	Safety *Cervarix and CYD dengue vaccine safety in each group* • Occurrence of immediate AEs reported within 30 minutes after each and any injection • Occurrence of solicited (ie, pre-listed in the subject's diary card [DC] and electronic case report form [eCRF]) injection site reactions (pain, erythema, and swelling) occurring up to 7 days after each and any injection • Occurrence of solicited systemic reactions (fever, headache, malaise, myalgia, and asthenia) occurring up to 14 days after each and any injection • Occurrence of unsolicited AEs occurring up to 28 days after each and any injection • Occurrence of non-serious AESIs* reported within 7 days following each and any injection • Occurrence of SAEs, including serious AESIs (with specific time windows according to the type of AESI*) throughout the trial • Occurrence of hospitalized VCD cases throughout the trial (ie, from D0 through end of the study) *Hypersensitivity/allergic reactions (serious or not) within 7 days after each CYD dengue vaccine injection; serious viscerotropic disease within 30 days after each CYD dengue vaccine injection, serious neurotropic disease within 30 days after each CYD dengue vaccine injection; serious dengue cases requiring

	hospitalization (ie, hospitalized suspected dengue case) will be reported during the entire study. 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 event/reaction led to early termination from the study, seriousness, or outcome. Hospitalized suspected dengue case is defined as an acute febrile illness with diagnosis of dengue requiring hospitalization (with bed attribution). In such cases, 1 unplanned acute blood sample (within the first 5 days after fever onset) will be collected for virological confirmation of dengue disease. A hospitalized suspected dengue case will be considered VCD if there is a detection of wild type (WT) dengue virus by dengue non-structural protein (NS) 1 antigen (Ag) enzyme-linked immunosorbent assay (ELISA) and/or dengue reverse transcriptase-polymerase chain reactions (RT-PCRs) (at the Global Clinical Immunology [GCI] or GCI designated laboratory). **Note:** Acute blood sample for all hospitalized suspected dengue cases should be collected within the pre-specified timeframe as described above. If this cannot be accomplished, this sample should still be obtained as soon as possible thereafter, for IDMC severity assessment.
Planned Sample Size:	A total of 480 subjects are planned to be enrolled, in a 1:1 randomization ratio: • Group 1 (concomitant administration): 240 subjects • Group 2 (sequential administration): 240 subjects ***As per Protocol Amendment 1***, only dengue-exposed subjects prior to the first injection with CYD dengue vaccine will be eligible to complete dengue vaccination schedule. At the time Protocol Amendment 1 is being prepared, the number of dengue exposed subjects per group is not known.

Schedule of Study Procedures:	At the time of Protocol Amendment 1, all subjects have completed V05 (Group 1) or V06 (Group 2). Dengue unexposed subjects will not receive further dengue vaccine injections. If a subject and the subject's parents/ legally acceptable representative consent to continue participating in the study, they will sign the Assent Form (AF) / Informed Consent Form (ICF). All unexposed subjects that consent to continue participating in the study will be contacted by phone for a safety follow-up 6 months after the last injection. They will not attend any further study visits (except the unscheduled visit and/or the next schedule visit planned to sign the ICF/AF). For dengue exposed subjects who consent to continue in the study and to receive the next CYD dengue vaccine injection, study procedures will proceed as planned in the original protocol. ***Visits/phone call :*** Subjects will have 6 (Group 1) or 8 (Group 2) visits. Subjects will be contacted by phone 7 days after each injection and 2 months after blood samples during the 6-month period after each vaccination. The last phone call will be for the 6-month follow-up after the last injection of CYD dengue vaccine. An unscheduled visit or phone call will take place during the study pause in order to communicate the new data on the CYD dengue vaccine to each subject. This visit will be before the next visit initially planned (V07 for most subjects; V08 for 2 subjects). Dengue serostatus at baseline may be communicated to the subjects, if available, at the time of the unscheduled visit. If not available at the time of the unscheduled visit, the dengue serostatus at baseline will be communicated at the next planned visit. ***Vaccination:*** See Table S1. Group 1: Cervarix and CYD dengue vaccine (concomitantly) at D0 and M6, and CYD dengue vaccine (alone) at M12 Group 2: Cervarix (alone) at D0 and M6, and CYD dengue vaccine (alone) at D0+28D (M1), M6+28D (M7), and M12+28D (M13) ***Blood sampling:*** Subjects will provide: • 4 mL, for CYD dengue vaccine immunogenicity assessments by dengue neutralizing Abs (4 mL) before the first vaccination (at D0 in Group 1, and M1 in Group 2) and 28 days after each vaccination with the CYD dengue vaccine • 2 mL, for HPV immunogenicity assessments by cLIA before the first vaccination (at D0) and 28 days after the each vaccination with Cervarix See Table S 1 for details on timings. Additional blood samples that may be collected at any time throughout the study period, regardless of the subject's dengue serostatus: • In the event of a hospitalized suspected dengue case (3 mL approximately), within the first 5 days after fever onset (or as soon as possible if not within the 5 days), for virological confirmation by NS1 Ag ELISA, and/or WT dengue RT-PCR. • In the event of SAEs (including AESIs). • To assess AEs that may be indicative of viscerotropic or neurotropic disease (see Guidelines for Assessing Viscerotropic and Neurotropic AE).

	Urine sampling: All subjects of childbearing potential will provide urine samples for urine pregnancy test before each injection
Duration of Participation in the Trial:	The expected duration of each subject's participation in the trial is approximately 18 months for Group 1 and 19 months for Group 2, including a safety follow-up period of 6 months after the third injection of CYD dengue vaccine. Time for the approval of Protocol Amendment 1 by the competent authorities and completion of the associated logistic tasks will result in a delay of study activities (approximately 6 months), and thus, in an extension of study duration for dengue exposed subjects. The duration of dengue non-exposed subjects' participation will be shorter.
Investigational Product: ***Form:*** ***Composition:*** ***Route:*** ***Batch Number:***	**CYD Dengue Vaccine** (5-dose formulation) Powder and solvent for suspension for injection Each individual 0.5 mL dose of reconstituted vaccine contains: • 4.5 - 6 $\log_{10}$ cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated, recombinant dengue serotype 1, 2, 3, 4 virus • Excipients: essential amino acids, non-essential amino acids, L-arginine hydrochloride, sucrose, D-trehalose dihydrate, D-sorbitol, trometamol, urea, and sodium chloride. • Solvent: NaCl 0.9% Subcutaneous (SC) M5568F01 for the first 2 injections; to be determined for last injection
Other Product: ***Form:*** ***Composition:*** ***Route:*** ***Batch Number:***	**Cervarix** Suspension for injection Each individual 0.5 mL dose contains: • 20 µg of HPV 16 L1 protein* • 20 µg of HPV 18 L1 protein* * adjuvanted by 50 µg of AS04 containing 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), and adsorbed on 0.5 mg of aluminum hydroxide hydrated ($Al(OH)_3$) • Excipients: sodium chloride, sodium dihydrogen phosphate dehydrate, water for injection Intramuscular (IM) Commercial batch
Inclusion Criteria:	An individual must fulfill all of the following criteria in order to be eligible for trial enrollment: 1) Female subject aged 9 to 14 years (ie, from the day of the 9th birthday to the day prior to the 15th birthday) on the day of inclusion 2) ICF or AF has been signed and dated by the subject (based on local regulations), and/or ICF has been signed and dated by the parent(s) or another legally acceptable representative (and by an independent witness if required by local regulations) 3) Subject (or subject and parent[s] or another legally acceptable representative) is (are) able to attend all scheduled visits and to comply with all trial procedures 4) Subject in good health, based on medical history and physical examination

Exclusion Criteria:	An individual fulfilling any of the following criteria is to be excluded from trial enrollment: 1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination and until at least 4 weeks after the last 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) Planned receipt of any vaccine in the 4 weeks following any trial vaccination 4) Previous vaccination against dengue disease with the trial vaccine 5) Previous vaccination against HPV disease with either the trial vaccine or another vaccine 6) Receipt of immune globulins, blood or blood-derived products in the past 3 months 7) Known or suspected congenital or acquired immunodeficiency (including HIV infection with impaired immune function); 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) History of HPV infection, confirmed either clinically, serologically, or microbiologically as reported by subject or parent/legally acceptable representative 9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances 10) Thrombocytopenia, 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) Current alcohol abuse or drug addiction that, based on Investigator's judgment, may interfere with the subject's ability to comply with trial procedures 14) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion 15) Identified as an Investigator or employee of the Investigator with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study 16) Self-reported Hepatitis B, Hepatitis C infection **Temporary Exclusion Criteria:** A prospective subject must not be included in the study until the following conditions and/or symptoms are resolved: 1) Moderate or severe acute illness/infection (according to Investigator judgment) or febrile illness (temperature ≥ 38.0°C) on the day of first

	vaccination. 2) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination
Statistical Methods:	In a general way, non-inferiority testing will be performed on dengue-exposed subjects. The tests will be done only if the number of evaluable subjects provides a global power of at least 80% for the co-primary objectives and secondary objective. In case the global power is insufficient to perform non-inferiority testing, only descriptive analyses will be performed. Only descriptive analyses will be conducted in unexposed subjects and in the overall population. **Non-inferiority on Cervarix** For co-primary endpoints, a non-inferiority testing approach will be used to compare GMTs of the 2 antigens (HPV-16 and HPV-18) 28 days after the last dose of Cervarix, for each antigen "i" based on the following individual hypotheses: $H_0^i: GMT^i_{Group1} / GMT^i_{Group2} \leq \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT^i_{Group1}) - \log_{10}(GMT^i_{Group2}) \leq -\log_{10}(\delta)$ $H_1^i: \frac{1}{\delta} < GMT^i_{Group1} / GMT^i_{Group2} > \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT^i_{Group1}) - \log_{10}(GMT^i_{Group2}) > -\log_{10}(\delta)$ with: i, antigen (HPV-16 and HPV-18) δ non-inferiority limit is set at 2, ie, 0.301 (=$\log_{10}$[2]), for each antigen "i" Non-inferiority for antigen i will be demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) is greater than –δ (α=2.5% one-sided). Additionally, for secondary endpoint, a non-inferiority testing approach will be used to compare seroconversion rates of the 2 antigens (HPV-16 and HPV-18). The individual tested hypotheses for the antigen "i" will be as follows: $H_0^i: P^i_{Group1} - P^i_{Group2} \leq -\delta$ $H_1^i: P^i_{Group1} - P^i_{Group2} > -\delta$ Where the non-inferiority limit δ is set at 5% for each antigen. Non-inferiority for antigen "i" will be demonstrated if the lower bound of the 2-sided 95% CI is greater than -δ. The non-inferiority test will be performed using the 95% 2-sided CI of the difference between Group 1 and Group 2 for seroconversion rates and of the differences of the means of the $\log_{10}$ transformed post-vaccination concentrations/titers for GMTs (α=2.5% one-sided). The 95% CI will be calculated based on the Wilson score method without continuity correction as quoted by Newcombe for seroconversion rates and using the normal approximation of the $\log_{10}$ transformed post-vaccination titers for GMTs. <u>Global hypotheses for non-inferiority on Cervarix response</u> For both primary and secondary objectives, the global hypotheses are: H_{0G}: Non inferiority of Cervarix co-administered with CYD dengue vaccine versus Cervarix administered alone is not demonstrated for at least one antigen. H_{1G}: Non-inferiority of Cervarix co-administered with CYD dengue vaccine versus Cervarix administered alone is demonstrated for all the antigens. H_0^G : at least one H_0^i *not rejected* H_1^G : all H_0^i *are rejected*

Non-inferiority on CYD dengue vaccine

For co-primary endpoints, a non-inferiority testing approach will be used to compare GMTs 28 days after the third injection of CYD dengue vaccine, between Group 1 and Group 2 for each serotypes "i" based on the following individual hypotheses:

$$H_0^i : GMT^i_{Group1} / GMT^i_{Group2} \leq \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT^i_{Group1}) - \log_{10}(GMT^i_{Group2}) \leq -\log_{10}(\delta)$$

$$H_1^i : \frac{1}{\delta} < GMT^i_{Group1} / GMT^i_{Group2} > \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT^i_{Group1}) - \log_{10}(GMT^i_{Group2}) > -\log_{10}(\delta)$$

with:

i, serotypes in {1, 2, 3, 4}

δ non-inferiority limit is set at 2, ie, 0.301 (=$\log_{10}$[2]), for each serotype "i"

Non-inferiority for serotype i will be demonstrated if the lower bound of the 2-sided 95% CI is greater than -δ.

The statistical methodology will be based on the use of the 2-sided 95% CI of the differences of the means of the $\log_{10}$ transformed post-vaccination titers between Group 1 and Group 2. The CI for differences will be calculated using normal approximation of log-transformed titers.

Global hypotheses for non-inferiority on CYD response

$$H_0^G : \text{at least one } H_0^i \textit{ not rejected}$$

$$H_1^G : \text{all } H_0^i \textit{ are rejected}$$

Overall, non-inferiority among the groups will be demonstrated if, for each antigen of Cervarix and each serotype of CYD dengue vaccine, the two-sided 95% CIs lie above -δ.

The per-protocol analysis set will be used for the main analysis and is to be confirmed using the FAS.

Calculation of Sample Size:

A total of 480 subjects will be enrolled: 240 subjects in each group.

The reference standard deviations (SD) considered for Cervarix are 0.4 for both HPV-16 and HPV-18.

The reference seroconversion rates for Cervarix were set to 99% for both antigens.

The reference SD considered are the following for CYD dengue vaccine: 0.9 for serotype 1, 0.7 for serotypes 2 and 3 and 0.5 for serotype 4 (based on CYD13 and CYD15 efficacy studies conducted in subjects aged 9 to 16 years in Latin American countries).

Considering a potential attrition rate of 15%, it was initially planned that such sample size would provide 204 evaluable subjects in the per protocol population per group. This will give, for the co-primary objectives, a global power of 90.2% and for secondary objectives (in terms of Cervarix seroconversion) a power of 91.8%.

This sample size will also provide a 95% probability of observing an AE that has a true incidence of 1.2% in each group.

Following Protocol Amendment 1, the number of evaluable subjects may be difficult to achieve (considering only exposed/seropositive subjects at baseline to be included in the Per-Protocol populations). Thus the non-inferiority testing will be done only if the number of evaluable subjects provides a global power of at least 80% for the co-primary objectives and secondary objective ie, if the number of evaluable subjects per group is at least 163 per group for the co-primary

	objectives and 168 per group for the secondary objective. **Interim analysis:** Two planned statistical analyses will be performed: An interim statistical analysis of the data obtained up to Day 28 post third CYD dengue vaccination might be performed once data are available and a database lock has been conducted. A final analysis will be performed once the 6 month safety data have been collected and the final database lock has occurred. No statistical adjustment is necessary because there will be no repeated analyses of the primary objective (as the test will be performed at the time of the first analysis).

Table of Study Procedures

Phase IIIb Trial; 5 Injections; **Group 1**: 6 Visits and a 6-month follow-up Phone Call, 4 Blood Samples, 18 Months duration per subject, 6 interim phone calls; **Group 2**: 8 Visits and a 6-month follow-up Phone Call, 6 Blood Samples, 19 Months duration per subject, 8 interim phone calls. Interim phone calls will be given 7 days after each injection (PC1, PC2, PC4, PC5, and PC7) and 2 months after blood samples (PC3, PC6, and PC8) during the 6-month period after each vaccination. As per Protocol Amendment 1, only dengue-exposed subjects before the first dengue vaccine injection will be eligible to continue study vaccinations with the CYD dengue vaccine.

	Time period prior to Protocol Amendment 1						**Time period post Protocol Amendment 1***		
Visit (V) Number	**V01**	**V02**	**V03 (Group 2)**	**V04**	**V05**	**V06†‡ (Group 2)**	**V07†**	**V08†**	**Phone Call§**
Trial Timelines	**D0**	**M1 (V01+28D)**	**M2 (V02+28D)**	**M6 (V01 + 6M)**	**M7 (V04+28D) (Group 1)** **(V02+6M) (Group 2)**	**M8 (V05+28D)**	**M12 (V01 + 12M)** (Group 1) **M13 (V02+ 12M)** (Group 2)	**M13 (V07+28D)** (Group 1) **M14 (V07+28D)** (Group 2)	**M18 (V07+6M)** (Group 1) **M19 (V07+6M)** (Group 2)
Time Windows (days)		**+14**	**+14**	**±20**	**+14**	**+14**	**±20**	**+14**	**+30**
Informed Consent and assent form (if applicable) signed	X								
Amendment 1to AF and ICF						X (Amdt 1) (as applicable)	X (Amdt 1) (as applicable)		
Inclusion/Exclusion Criteria	X								
Significant Medical History	X								
History of Dengue Infection/Vaccination	X								
Demography/Body Stature	X								
Physical/Clinical Examination and Temperature**	X	X (Group 2)	X (Group 2)	X	X	X (Group 2)	X	X	
Concomitant Therapy††	X	X	X (Group 2)	X	X	X (Group 2)	X	X	
Urine Pregnancy Test‡‡	X	X (Group 2)		X	X (Group 2)		X		
Randomization	X								
Contraindications		X (Group 2)		X	X (Group 2)	X	X		
Blood Sampling§§									
Dengue neutralizing Abs	X (Group 1)	X	X (Group 2)		X (Group 1)	X (Group 2)		X	
HPV Abs	X	X			X				
Virological confirmation of dengue***	**All acute febrile illness with diagnosis of dengue requiring hospitalization within the first 5 days after fever onset, occurring anytime throughout the trial period**								

	Time period prior to Protocol Amendment 1						**Time period post Protocol Amendment 1***		
Visit (V) Number	**V01**	**V02**	**V03 (Group 2)**	**V04**	**V05**	**V06†‡ (Group 2)**	**V07†**	**V08†**	**Phone Call§**
Trial Timelines	**D0**	**M1 (V01+28D)**	**M2 (V02+28D)**	**M6 (V01 + 6M)**	**M7 (V04+28D) (Group 1)** **(V02+6M) (Group 2)**	**M8 (V05+28D)**	**M12 (V01 + 12M)** (Group 1) **M13 (V02+ 12M)** (Group 2)	**M13 (V07+28D)** (Group 1) **M14 (V07+28D)** (Group 2)	**M18 (V07+6M)** (Group 1) **M19 (V07+6M)** (Group 2)
Vaccine injection	**Cervarix Dose 1** (Groups 1 and 2) **CYD Dose 1** (Group 1)	**CYD Dose 1** (Group 2)		**Cervarix Dose 2** (Groups 1 and 2) **CYD Dose 2** (Group 1)	**CYD Dose 2** (Group 2)		**CYD Dose 3** (Groups 1 and 2)		
Post-injection phone call†††	**Interim phone calls will be given 7 days after each injection and 2 months after blood samples during the 6-month period after each vaccination.**								
Diary Card (DC)									
Provided	X	X (Group 1 for SAE only and Group 2)	X (Group 2 for SAE only)	X	X (Group 1 for SAE only and Group 2)	X (Group2 for SAE only)	X		
Checked		X	X (Group 2)	X	X	X (Group 2)	X	X	
Collected		X	X (Group 2)	X	X	X (Group 2)	X	X	
Memory Aid (MA)									
Provided‡‡‡						X	X	X	
Checked									X
30-Min. Observation Period	X	X (Group 2)		X	X (Group 2)		X		
Injection Site Reactions & Systemic Events Assessment§§§	X	X	X (Group 2)	X	X	X (Group 2)	X	X	
Collection of SAEs, and serious AESIs§§§	**Throughout the trial period (for SAEs) or in defined time windows according to the type of AESI**								
Termination Record****								X	

Abs: antibodies; AE: Adverse event; AESI: AE of special interest; BL: blood sample; CYD: CYD dengue vaccine; D: Day; M: Month; SAE: Serious adverse event; V: Visit;

* Visits to be performed by dengue exposed subjects only, if they consent to receive the next CYD vaccine injection

† Vaccinations and associated or subsequent procedures may be out of the defined time-windows in dengue-immune subjects continuing the study due to study pause

‡	All subjects will either attend an unscheduled visit (V00) or have an unscheduled phone call (PC00) during the study pause and **before** the next scheduled visit (V07 for most subjects; V08 for 2 subjects). During the unscheduled visit or phone call, the subject will be informed about the new safety data thanks to a "dear participant letter" and on their baseline serostatus result. The signature of the ICF/AF by the parents/subjects and the check of contraindications to continue in the study will be performed at the next visit planned, as applicable.
§	The 6-month phone call will be given to all subjects who consented to continue in the study whether they were identified as "dengue-exposed" or "dengue unexposed"
**	A full physical and clinical examination will be performed and documented on each vaccination visit (mandatory before vaccination) and at the Investigator's discretion if necessary based on the health status of the subject for the other visits.
††	Concomitant therapy will be collected for Days 0–28 after each injection only
‡‡	In female subjects of childbearing potential. Result of urine pregnancy test should be confirmed as negative before vaccination.
§§	Blood samples planned during vaccination visits will be taken before vaccination
***	In such case, 1 unplanned acute blood sample (approximately 3 mL) will be collected for virological confirmation of dengue disease, by NS1 (nonstructural protein 1) antigen test (ELISA), and/or WT dengue RT-PCR
†††	Interim phone calls will be given 7 days (+8 days of time window) after each injection (PC1: V01 + 7 days, PC2: V02 + 7 days, PC4: V04 + 7 days, PC5: V05 + 7 days, and PC7: V07 + 7 days) and approximately 2 months after blood samples (PC3: M3 or M4, PC6: M9 or M10, and PC8: M15 or M16) during the 6-month period after each vaccination.
‡‡‡	MA will be delivered to subjects who will not receive further CYD dengue vaccine injection but consent to continue their participation in the study.
§§§	Solicited injection site reactions will be collected for Days 0–7 after each injection. Solicited systemic reactions will be collected for Days 0–14 after each injection. Unsolicited events will be collected for Days 0-28 after each injection. SAEs will be reported throughout the study and AESIs will be collected in defined time windows according to the type of AESI (hypersensitivity/allergic reactions [serious or not] within 7 days after each CYD dengue vaccine injection, serious viscerotropic disease within 30 days after each CYD dengue vaccine injection, serious neurotropic disease within 30 days after each CYD dengue vaccine injection; serious dengue cases requiring hospitalization [ie, hospitalized suspected dengue case] will be reported during the entire study).
****	Termination record will be checked either during a planned study visit or a phone call

List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AF	assent form
Ag	antigen
AR	adverse reactions
BL	blood sample
$CCID_{50}$	cell-culture infectious dose 50%
CDM	clinical data management
CI	confidence interval
CIN	cervical intraepithelial neoplasia
C&MQO	Clinical and Medical Quality Operations department
CRA	clinical research associate
CRF	case report form
CTA	clinical trial agreement
D	day
DC	diary card
dil	dilution
DHF	dengue hemorrhagic fever
DSS	dengue shock syndrome
EDC	Electronic Data Capture
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FASE	full analysis set for exposed subjects
FV	flavivirus
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	geometric mean of titer
GMTR	Geometric mean of the titer ratio
GPV	Global PharmacoVigilance
HPV	human papillomavirus
ICF	informed consent form
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	Institutional Review Board
LCLS	last contact last subject
LLOQ	lower limit of quantitation
LLT	lowest level term
M	month
MAbs	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NS1	non-structural protein 1
OD	optical density
Pap	Papanicolaou
PC	Phone call
PD	post-dose
PFU	plaque-forming unit
PPAS	per-protocol analysis set
PPC	per-protocol analysis set for CYD dengue vaccine
PPX	per-protocol analysis set for Cervarix
$PRNT_{50}$	50% plaque reduction neutralization test
PSO	Product Safety Officer
RCTM	Regional Clinical Trial Manager
RMO	Responsible Medical Officer
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SAP	Statistical Analysis Plan
SafAS	safety analysis set
SC	subcutaneous
SD	standard deviations
SMT	safety management team
TMF	trial master file
RT-PCR	reverse transcriptase-polymerase chain reaction
UAR	unexpected adverse reaction
V	visit
VCD	virologically-confirmed dengue
VE	vaccine efficacy

YF	yellow fever
WHO	World Health Organization
WT	wild type

1 Introduction

1.1 Background

The study will assess the safety and immunogenicity of the CYD dengue vaccine when administered concomitantly or sequentially with Cervarix® (Human Papillomavirus Bivalent [Types 16 and 18] Vaccine, Recombinant; GlaxoSmithKline)

Dengue Disease

Dengue is the most common mosquito-borne viral disease in humans, found in tropical and sub-tropical regions around the world. In recent years, transmission has increased predominantly in urban and semi urban areas and has become a major international public health concern. Dengue virus is essentially transmitted by mosquitoe bites primarily by the female *Aedes aegypti*, but the global spread of dengue due to *A albopictus* is increasing. There are four closely related, but antigenically distinct, dengue virus serotypes (1, 2, 3, 4) of the genus Flavivirus (FV) that cause dengue. All four serotypes can cause the full spectrum of disease from subclinical infection to a mild self-limiting disease, dengue fever and severe disease that may be fatal, due to dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) (1).

The clinical presentation of acute dengue is non-specific and is characterized by biphasic fever, headache, pain in various parts of the body, prostration, rash, and lymphadenopathy for which recovery is usually complete in 7 to 10 days. However, 5-10% of patients progress to DHF/DSS which is characterized by abnormalities of homeostasis and increased vascular permeability that can lead to hypovolemia and hypotension (DSS), often complicated by severe internal bleeding. The case fatality rate of DHF can be as high as 10% without therapy, but is below 1% in most centers with modern intensive supportive therapy.

Routine laboratory diagnosis of dengue infections is based on the detection of dengue virus-specific antibodies (Abs) (immunoglobulin M [IgM]) and/or isolation of the virus or detection of viral ribonucleic acid (RNA) by reverse transcription-polymerase chain reaction (RT-PCR) or viral non-structural protein 1 (NS1) antigen (Ag) by enzyme-linked immunosorbent assay (ELISA) (2) (3) (4). The diagnosis of dengue falls into 2 stages: Stage I, the acute fever period lasting a few days when viremia and NS1 Ag may be detected; and Stage II, the early post-febrile period lasting a few weeks when IgM and immunoglobulin G (IgG) are increased.

According to the World Health Organization (WHO), an estimated 3.9 billion people are at risk living in dengue endemic countries in Africa, the Americas, the Eastern Mediterranean, South East Asia, and the Western Pacific. The American, South East Asian and the Western Pacific regions are the most seriously affected. The WHO currently estimates there may be 390 million dengue virus infections worldwide every year, of which 96 million are associated with clinical manifestations of dengue. An estimated 500,000 people with severe dengue require hospitalization each year of which 2.5% of those die (1). The populations most affected by dengue are pre-adolescents, adolescents and adults living in dengue endemic areas. All 4 dengue virus serotypes vary unpredictably over time, causing a continuous risk of infection in populations living in dengue-endemic regions. No currently available preventative measures have significantly

impacted dengue disease, thus as recognized by the WHO, the need for a safe and effective vaccine against all 4 serotypes of dengue virus to protect people in endemic countries (5).

Human Papillomavirus Disease (HPV) (6)

HPV is a common DNA virus the papillomavirus family that can infect different parts of the body. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. There are over 170 types of HPV and more than 40 types of HPV are primarily sexually transmitted and can cause anal and genital warts. Other types may lead to more serious consequences such as cervical, penile and anal cancers as well as certain cancers of the head and neck. Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are carcinogenic "high-risk" sexually transmitted HPVs and may lead to the development of precancerous disease and cancer including cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia, penile intraepithelial neoplasia, and/or anal intraepithelial neoplasia.

Most HPV infections are subclinical, rapidly cleared by the immune system and go away without treatment over the course of a few years. However, in some people subclinical infections can become clinical through persistence of HPV infections. 70% of clinical HPV infections, in young men and women, may regress to subclinical in one year and 90% in two years. In 5% to 10% of infected women, persistent HPV infection may cause benign papillomas (such as warts [verrucae] or squamous cell papilloma), or cancers of the cervix, vulva, vagina, oropharynx and anus. In particular, persistent infection with “high-risk” HPV types may progress to precancerous lesions and invasive cancer. High-risk HPV infection with HPV16 and HPV18 are known to cause around 70% of cervical cancer cases.

In more developed countries, cervical screening using a Papanicolaou (Pap) test or liquid-based cytology is used to detect abnormal cells that may develop into cancer. If abnormal cells are found, women are invited to have a colposcopy. During a colposcopic inspection, biopsies can be taken and abnormal areas can be removed with a simple procedure, typically with a cauterizing loop or, more commonly in the developing world—by freezing (cryotherapy). Treating abnormal cells in this way can prevent them from developing into cervical cancer. Pap smears have reduced the incidence and fatalities of cervical cancer in the developed world.

Worldwide in 2002, an estimated 561,200 new cancer cases (5.2% of all new cancers) were attributable to HPV, making HPV one of the most important infectious causes of cancer 84% of new cervical cancers were in the developing world, compared with about 50% of all new cancers.

HPV infection is the most frequently sexually transmitted disease in the world. Methods of reducing the chances of infection include sexual abstinence, condoms, vaccination and microbicides.

1.2 Background of the Investigational Product

Sanofi Pasteur’s tetravalent CYD dengue vaccine, using recombinant technology to obtain a live-attenuated vaccine, is currently indicated for the prevention of dengue disease caused by all 4 serotypes (1, 2, 3, and 4) in individuals 9-60 years of age living in endemic regions. Immunization against dengue is based on a 3-dose immunization schedule, 6 months apart (0, 6, and 12 months) administered subcutaneously with CYD dengue vaccine. The indicated population

has been defined based on a Benefit / Risk evaluation of the overall population included in the clinical development plan.

In support of this product profile, an extensive clinical development program, compliant with WHO and European Medicines Agency guidelines has been conducted (7), for which the CYD dengue vaccine efficacy, immunogenicity and safety has been assessed in various formulations, schedules and populations.

- In Phase I trials, a total of 396 subjects aged 2-49 years of age were evaluated for safety. Subjects were evaluated in both non-endemic and endemic areas and were received at least one dose of Phase I lots of CYD dengue vaccine containing either 4 $\log_{10}$ or 5 ± 1 $\log_{10}$ cell-culture infectious dose 50% ($CCID_{50}$) per serotype.
- In Phase II trials, approximately 4900 subjects aged 12 months-45 years of age to further evaluate safety and immunogenicity in non-endemic and endemic areas including Asia Pacific and Latin America which supported the selection of the final formulation of 3 doses of CYD dengue vaccine of 5 $\log_{10}$ $CCID_{50}$ per serotype as 3 injections administered 6 months apart. A proof of concept efficacy study (CYD23) in Thailand in 4-11 years old has been completed in 2012 (8). Subjects from CYD23 are being followed for safety in a long-term follow-up study (CYD57) for a total of 5 years post-dose 3 (PD3).
- In Phase III trials, approximately 23,140 subjects aged 9 months to 60 years of age have received at least 1 dose of Phase III lots of CYD dengue vaccine (4.5 – 6.0 $\log_{10}$ $CCID_{50}$ per serotype). Two pivotal large-scale efficacy studies (CYD14 (9) and CYD15 (10) conducted in Asia Pacific (10,275 subjects aged 2 to 14 years old) and Latin America (20,869 subjects aged 9 to 16 years old) respectively, have completed the 25 months of the Active Phase and the first year of the Hospital Phase (long-term follow-up). These efficacy studies were powered to independently demonstrate significant vaccine efficacy (VE) of the CYD dengue vaccine and they met their primary endpoints. To include the totality of efficacy studies (CYD14, CYD15) analyzed over the 25 months of Active Phase, and the availability of further safety data for an additional one year of long term follow-up in the Hospital Phase, post-hoc meta-analyses were performed with improved point estimate precision for descriptive outcomes (11). Consistent VE was demonstrated during the 25 months of Active Phase for virologically-confirmed dengue (VCD): 65% (95% CI: 60.7-69.9) for any severity of dengue disease, caused by any and each of the 4 dengue serotypes, severe dengue 93.2 % (95% CI: 77.3-96.0) and dengue leading to hospitalization 80.8% (95% CI: 70.1-87.7). VE was also demonstrated for dengue-seropositive 81.9% (95% CI: 67.2-90) and dengue-seronegative 52.5% (95% CI: 5.9-76.1) vaccinees. No safety issues have been identified in subjects 9-16 years of age during the 25 months of active period or during the first year of long term follow-up in the Hospital Phase (9) (10) (11). This included no observed increase in dengue disease severity compared to the placebo group.

In interim results of the long term follow-up, for the first 3 years of the Hospitalized Phase pooled efficacy results demonstrated a continued benefit in subjects who were 9 years and above with lower risk of hospitalized VCD (relative risk [RR] of 0.535 [95% CI: 0.38; 0.75] in the vaccine compared to the placebo group, after at least 1 dose of CYD dengue vaccine). All subjects who were hospitalized due to dengue fully recovered after receiving appropriate supportive treatment (12). However, in CYD14, during the first year of the Hospital Phase, the RR suggests an overall

trend to increased risk of hospitalized VCD in the vaccine compared to the placebo group among subjects <9 years of age (RR of 1.146 [95% CI: 0.83; 1.59] after at least 1 dose of CYD dengue vaccine), in particular in the 2 to 5 years old age group.

As of September 2016, a total of 25 completed or ongoing clinical studies in 15 endemic and non-endemic countries including Latin America and Asia Pacific have been conducted, comprising more than 41,500 subjects from 9 months through 60 years of age. Of these subjects, 21,215 were aged 9 through 60 years of age and received at least 1 dose of CYD dengue vaccine formulation. Furthermore, the CYD dengue vaccine has demonstrated a consistent and acceptable safety profile within 6 months post any injection, comparable with placebo, across many populations (age groups, gender, region, and dengue immune status) in subjects 9 to 60 years of age. The high post-injection neutralizing antibody titers observed in adults living in endemic areas, allows the extrapolation of vaccine efficacy through immunological bridging to adult populations living in endemic areas.

As of December 2017, 6 additional clinical studies including CYD71 are being conducted with the CYD dengue vaccine in Asia Pacific and Latin America since the first license was obtained (CYD63, CYD64, CYD65, CYD66 and CYD67). These studies are either investigating the safety and immunogenicity of the CYD dengue vaccine when co-administered with other vaccines (CYD66/67/71) or the need and timing of a booster dose (CYD63/64/65). All these studies are being amended in accordance with the Independent Data Monitoring Committee (IDMC) recommendation to vaccinate only dengue exposed subjects.

CYD dengue vaccine is indicated for the prevention of dengue disease caused by any of the DENV serotypes 1, 2, 3, and 4, in individuals aged 9 years and above living in dengue-endemic countries. Currently in Mexico, CYD dengue vaccine also known as Dengvaxia®, is indicated for the prevention of disease caused by all four dengue virus serotypes in preadolescents, adolescents and adults, 9 to 45/60 years of age.

Sanofi has recently proposed that national regulatory agencies update the prescribing information, known as the label in many countries, adding a “Warning” to the intention of individuals who have not been previously infected by dengue virus and for whom vaccination is not recommended.

1.3 Potential Benefits and Risks

Detailed risk/benefit analysis is presented in the Investigator’s Brochure.

1.3.1 Potential Benefits to Subjects

In terms of benefit, the subjects participating in the present clinical trial may develop immunity and protection against dengue disease after vaccination with CYD dengue vaccine.

The subjects participating in this trial who receive the 2-dose series of Cervarix (HPV vaccine) will likely gain immunological protection against HPV Types 16 and 18.

A number of supplemental exploratory analyses (see Section 1.4, Rationale for Amendment 1) have provided evidences that, for subjects that were naturally dengue exposed prior to the first CYD dengue vaccine injection, the vaccine protects against symptomatic dengue, and provides

persistent protective benefit against hospitalized dengue, and severe dengue disease up to 5 years after the first injection.

As with any vaccine, immunological protection may not be elicited in all individuals against the disease they are designed to prevent.

1.3.2 Potential Risks to Subjects

CYD Dengue Vaccine

During the clinical development of dengue vaccine as well as during the Active Phase of the Phase III efficacy studies, no safety concerns after administration of the CYD dengue vaccine emerged from the pooled safety analysis, providing sufficient evidence that the safety profile of the CYD dengue vaccine is acceptable and similar to the safety profile of licensed vaccines in similar population.

Potential unwanted effects include injection site reactions such as erythema, swelling, induration, and pain. General disorders may also be observed such as fever, malaise, asthenia, myalgia and headache. As for any drugs, a risk of allergic reaction cannot be excluded. Vasovagal malaise linked to the injection procedure may be observed in susceptible individuals. Full list of expected adverse events (AEs) can be found in the Investigator's Brochure.

As CYD dengue vaccine has a yellow fever (YF) vaccine backbone, and YF vaccination has been rarely associated with viscerotropic and neurotropic AEs, this risk has to be considered. This theoretical risk linked to viscerotropism and neurotropism is further addressed in the "Guidelines for assessing viscerotropic and neurotropic AE" document. In the previous studies conducted with the CYD dengue vaccine, no confirmed viscerotropic or neurotropic AEs have been observed.

Although an unexplained higher incidence of hospitalization for dengue in year 1 of follow-up among children younger than 9 years was observed in CYD14 efficacy trial, in particular in children from 2 to 5 years old, the combined analysis of efficacy trials up to year 5 post-injection 1 showed a lower risk of hospitalization for dengue among participants who were 9 years of age or older in the vaccine group than among those in the control group. All subjects who were hospitalized due to dengue fully recovered after receiving appropriate supportive treatment (11).

Following a number of supplemental exploratory analyses (see Section 1.4, Rationale for Amendment 1), it was shown that subjects that were never dengue exposed prior to the first CYD dengue vaccine injection have an increased risk of hospitalized or severe disease, as compared to subjects who received the placebo.

Cervarix

Potential risks for subjects receiving Cervarix include fatigue, myalgia, gastrointestinal symptoms, and arthralgia.

All subjects

The potential risks associated with blood drawing include local injection site reactions such as erythema, swelling, induration, and pain, bruising and, rarely infection.

General disorders may also be observed such as fever, malaise, asthenia, myalgia and headache.

The potential risk for vasovagal syncope (fainting) can occur following, or even before, any vaccination in this age group (CYD dengue vaccine or Cervarix), as a psychogenic response to the needle injection. This is sometimes associated by other neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic movements on resolution of syncope.

The potential risks listed here are not exhaustive; refer to the package inserts of Cervarix for additional information regarding potential risks. Full list of expected AEs for the CYD dengue vaccine can be found in the Investigator's Brochure.

1.4 Rationale for the Trial

Previous preventive measures presently relied on mosquito control and personal protection. These measures are limited in efficacy, difficult to enforce, and expensive. The best method of prevention lies with the development of a safe and effective vaccine directed at the 4 serotypes of dengue virus responsible for the disease. Currently licensed in Mexico and in the Philippines, CYD dengue vaccine also known as Dengvaxia, is indicated for the prevention of disease caused by all four dengue virus serotypes in preadolescents, adolescents and adults, 9 to 45/60 years of age.

This post-licensure study will assess the immunogenicity and safety of CYD dengue vaccine when administered concomitantly or sequentially with Cervarix.

Cervarix is a suspension for injection of HPV bivalent (types 16 and 18) vaccine (recombinant, adjuvanted, adsorbed) indicated for the prevention of cervical cancer, CIN grade 2 or worse and adenocarcinoma in situ, and CIN grade 1 caused by oncogenic HPV types 16 and 18, in females aged 9 through 26 years of age (13). Cervarix is currently recommended by WHO for female subjects 9 through 14 years of age in a 2 dose schedule (0, 6 months), and 15 years to 26 years in a 3 dose schedule (0, 1, 6 months) (14). Since 2006, HPV vaccines have been licensed in over 100 countries (15).

There is currently no data on concomitant administration of CYD dengue vaccine with other vaccines in the indicated population in subjects 9 years and above. Co-administration of CYD dengue vaccine with other vaccines has been assessed in clinical studies outside the age indication, in toddlers 9 to 15 months of age at inclusion in dengue endemic countries. A Phase II study was conducted to evaluate the co-administration of CYD dengue vaccine together with Measles, Mumps and Rubella (MMR, Trimovax®, Live attenuated virus vaccine against Measles [Schwartz strain], Mumps [Urabe AM-9 strain] and Rubella [Wistar RA 27/3M strain; Sanofi Pasteur) vaccine (CYD08) (16), and 2 Phase III studies (CYD29 and CYD33) were conducted to evaluate the co-administration of CYD dengue vaccine together with the YF vaccine (Stamaril®, Yellow fever vaccine [live]; Sanofi Pasteur) and the DTaP-IPV-PRP-T (Hib) vaccine (Pentaxim®, Diphtheria, Tetanus, Pertussis [acellular, component], Poliomyelitis [inactivated] vaccine [adsorbed] and *Haemophilus Influenza* Type b Conjugate Vaccine; Sanofi Pasteur). These trials demonstrated that the CYD dengue vaccine could be administered concomitantly with these pediatric vaccines and no safety concerns or impact on the immune response was observed.

Based on the current age indication of the dengue vaccine, and to facilitate implementation of school-based dengue vaccination programs, co-administration with Cervarix, currently used in

public sector school-based vaccination programs in several dengue-endemic countries in subjects aged 9 years and above, is needed.

The main purpose of this study is to demonstrate that CYD dengue vaccine can be safely co-administered with Cervarix without impacting the immune responses to either vaccine. The present Phase IIIb randomized, open-label trial (CYD71) will investigate the immunogenicity and safety of the CYD dengue vaccine when it is administered concomitantly or sequentially with Cervarix at least 28 days apart in 480 subjects aged 9 to 14 years.

Rationale for Protocol Amendment 1

This amended protocol introduces one important change to the original protocol of the ongoing CYD71 clinical study.

In July 2016, the WHO issued a position paper on Sanofi Pasteur's CYD dengue vaccine based on the "Strategic Advisory Group of Experts" (SAGE) assessment that recognized its potential public health value when introduced in highly endemic countries. In addition, the SAGE also underlined the importance of addressing the question of the potential risk, over time, of hospitalized/severe dengue in individuals with no prior exposure to dengue before vaccination (17) (18). Other scientific, public health, and regulatory leaders have expressed similar interest in obtaining more information on the long-term safety and efficacy of the CYD vaccine in seronegative individuals.

Sanofi Pasteur recognized this knowledge gap and remained committed to further evaluate the performance of the CYD vaccine.

Analyzing long-term safety according to dengue serostatus at baseline presented an important challenge as serostatus had only been assessed in a subset of subjects (the so-called immunogenicity subset) in each of the 3 efficacy studies (CYD14, CYD15 and CYD23/57). As a consequence of this, and in order to address the question of vaccine performance in seronegative individuals, Sanofi Pasteur decided to conduct an Exploratory Case-Cohort study using a time point for which a blood sample was collected in all study participants: approximately 1 month after the third injection of CYD dengue vaccine or placebo (month [M] 13). The rationale behind this approach was that the classification of study participants according to dengue serostatus at this time point (as a surrogate of prior natural dengue exposure) could be used as a baseline for the evaluation of outcomes that occur later. However, the PRNT assay routinely used to quantify neutralizing Ab titers cannot discriminate between neutralizing Abs against wild-type dengue virus and chimeric dengue virus. Said otherwise, a positive PRNT assay at M13 can be the result of either prior dengue exposure or CYD dengue vaccination.

To overcome this challenge, Sanofi Pasteur leveraged an assay originally developed at University of Pittsburg (Pittsburg, PA, USA) and optimized by Sanofi Pasteur's Global Clinical Immunology (GCI) Department. This assay measures total immunoglobulin G (IgG) antibodies against the non-structural protein 1 (NS1) of the dengue virus by Enzyme-Linked Immunosorbent Assay (ELISA). Because the NS1 protein is not conserved between the dengue virus and the yellow-fever virus, previous exposure to CYD dengue vaccine is not expected to induce meaningful levels of antibody against the dengue NS1 protein. The application of the Dengue anti-NS1 IgG ELISA assay to M13 samples was therefore considered useful for expanding the existing data on both VE and potential risk of dengue hospitalization and/or severe dengue according to baseline serostatus in the CYD dengue vaccine efficacy trials. Thus, dengue serostatus was used in a

supplemental case-cohort study as a covariate to assess the effects of CYD dengue vaccine for outcomes that occur after M13. In addition, the Dengue anti-NS1 IgG ELISA values were used in conjunction with multiple additional variables in imputation models to predict the D0 PRNT50 serostatus, to evaluate outcomes occurring after M0 and M13 by measured (where available), or imputed PRNT50 serostatus.

Sanofi Pasteur presented the full data of this supplemental analysis to the IDMC in an *ad hoc* meeting held on 3-4 November 2017. During this meeting, the IDMC reviewed the data from these extended safety and efficacy analyses. It concluded that, in the case of subjects exposed to dengue prior to vaccination (henceforth, "exposed subjects" or seropositive subjects), there is strong evidence that the vaccine protects them from symptomatic dengue, hospitalized dengue and severe dengue. In the case of subjects unexposed to dengue before vaccination (henceforth, "unexposed" subjects or seronegative subjects), the conclusion was that although vaccination may confer limited short-term benefit against symptomatic dengue, it also induces an increased risk of severe disease in the longer term. The IDMC stated that these findings are based on follow-up of dengue unexposed subjects having received 3 CYD dengue vaccine doses and no data exist to conclude if the risk in partially vaccinated dengue unexposed subjects is different from that in fully vaccinated dengue unexposed subjects.

Given these conclusions, the IDMC recommended that no further vaccination occurs in unexposed subjects in ongoing or future trials, and on precautionary basis, including partially vaccinated subjects in ongoing trials. In addition, they recommended making available information on baseline serostatus for all vaccinated subjects whenever possible. Finally, for unexposed subjects that were vaccinated during a study, the IDMC recommended instituting mechanisms to provide timely access to appropriate care in the event of suspected dengue, for 10 years from the date of last vaccination.

Given the IDMC recommendations, Sanofi Pasteur decided to put this study on hold and to amend its study protocol. As a general rule, only subjects assessed as dengue exposed at baseline (ie, before receiving the first CYD dengue vaccine injection) will be eligible to receive any further dose of CYD dengue vaccine in an ongoing study. In CYD71, all subjects will be informed about their serostatus at baseline and what it means. Moreover, all subjects will be asked about their willingness to continue participating in this study by signing an updated Informed Consent Form (ICF) and/or Assent Form (AF), as applicable. To determine the basal serostatus of the subjects already included in the study, the PRNT assay will be used.

At the time CYD71 was paused, all subjects had received 2 injections of Cervarix and 2 injections of CYD dengue vaccine. Further information is provided in Section 5.1.3.

Subjects identified as dengue unexposed (seronegative) at baseline, will only be able to continue in the study for safety follow-up but will receive no further injections of CYD dengue vaccine. Subjects assessed as dengue-exposed at baseline will be eligible to receive the third injection of CYD dengue vaccine to complete the 3-dose schedule. Dengue-exposed subjects that remain in the study but decide against receiving the last injection will continue in the study for safety follow-up (see Section 5.1.4).

2 Trial Objectives

2.1 Primary Objectives

Immunogenicity

Cervarix immunogenicity

- To demonstrate that the humoral immune response (in terms of geometric mean titers [GMTs]) to Cervarix after concomitant administration with the CYD dengue vaccine is non-inferior to the humoral immune response (in terms of GMTs) after sequential administration with the CYD dengue vaccine measured 28 days after the last dose of Cervarix*

CYD dengue vaccine immunogenicity

- To demonstrate that the humoral immune response (in terms of GMTs) to the CYD dengue vaccine after concomitant administration with Cervarix is non-inferior to the humoral immune response (in terms of GMTs) to the CYD dengue vaccine after sequential administration with Cervarix measured 28 days after the last dose of the CYD dengue vaccine*

* Providing that the number of evaluable seropositive subjects allows a global power of at least 80% (otherwise analyses will be descriptive). The endpoints for the primary objectives are presented in Section 9.1.

2.2 Secondary Objectives

Immunogenicity

Cervarix immunogenicity

- To demonstrate that the humoral immune response (in terms of seroconversion) to Cervarix after concomitant administration with the CYD dengue vaccine is non-inferior to the humoral immune response (in terms of seroconversion) to Cervarix sequential administration with the CYD dengue vaccine measured 28 days after the last dose of Cervarix*
- To describe the humoral immune response to Cervarix at baseline and after each dose of Cervarix in each and any group

CYD dengue vaccine immunogenicity

- To describe the humoral immune response to the CYD dengue vaccine at baseline and after each dose of the CYD dengue vaccine, in each and any group

* Providing that the number of evaluable seropositive subjects allows a global power of at least 80% (otherwise analyses will be descriptive).

Safety

Cervarix and CYD dengue vaccine safety

- To describe the safety of Cervarix and CYD dengue vaccine after each and any dose in each group

The endpoints for the secondary objectives are presented in Section 9.2.1.1 and Section 9.2.2.2.

3 Investigators and Trial Organization

This trial will be conducted in approximately 3 centers in Mexico. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by one Coordinating Investigator. Details of the trial centers, the Investigators at each center, and the Coordinating Investigator(s) are provided in the "List of Investigators and Centers Involved in the Trial" document.

Independent Data Monitoring Committee

An IDMC will be involved in the regular review of hospitalized VCD cases, including assessment of severity. Additionally, any related serious adverse event (SAE) or death will be promptly reviewed by the IDMC.

Safety Management Team

An internal safety management team (SMT) will perform a safety analysis on safety data during the conduct of the trial.

Laboratories

Immunogenicity assessments will be performed by Sanofi Pasteur GCI (Swiftwater, Pennsylvania, USA) or outsourced laboratory under the management of GCI.

Sponsor's Responsible Medical Officer

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

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the ICF and 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 will submit written summaries of the status of the trial to the IEC/IRB annually, or more frequently if requested. All SAEs occurring during the trial that are related to vaccination

will be reported by the Investigator to the IEC/IRB, according to the IEC/IRB policy. The submission to Ministry of Health will be completed by the Sponsor.

5 Investigational Plan

5.1 Description of the Overall Trial Design and Plan

5.1.1 Trial Design

This is a Phase IIIb, randomized, open-label, multicenter study in 480 female subjects aged 9 to 14 years in Mexico.

Subjects have been randomized in a 1:1 ratio into one of the 2 following groups to receive:

- Group 1 (N=240): 3 doses of CYD dengue vaccine and 2 doses of Cervarix (Human Papillomavirus Bivalent [Types 16 and 18] Vaccine, Recombinant; GlaxoSmithKline) concomitantly to the 2 first doses of CYD dengue vaccine
- Group 2 (N=240): 3 doses of CYD dengue vaccine and 2 doses of Cervarix sequentially to the 2 first doses of CYD dengue vaccine

For both vaccines, each dose is to be administered 6 months apart.

As per Protocol Amendment 1, only subjects identified as dengue-exposed (seropositive) before administration of the first CYD dengue injection and who consented to receive the remaining injection of dengue vaccine will continue in the study as per initial study procedures. Subjects identified as unexposed (seronegative) at baseline, will only be able to continue in the study for a 6-month safety follow-up. They will not receive the third and last injection of CYD dengue vaccine.

5.1.2 Justification of the Trial Design

There is currently no data on concomitant administration of CYD dengue vaccine with other vaccines in the indicated population aged 9-45/60 years of age. Based on the current age indication of the CYD dengue vaccine, co-administration data with Cervarix, currently used in public sector school-based vaccination programs in females aged 9 years and above, could support implementation of school-based vaccination programs for CYD vaccine. Therefore, the present CYD71 study will investigate the immunogenicity and safety of the CYD dengue vaccine candidate when it is administered concomitantly or sequentially with Cervarix at least 28 days apart in female subjects aged 9 to 14 years.

5.1.3 Trial Plan

A summary of the schedule of study vaccination and blood samplings for eligible subjects is provided in Table 5.1.

Table 5.1: Injection and blood sampling schedule by Group

Period	**Prior to Amendment 1**						**Post Amendment 1**	
Visit (V)	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**
Timing	**D0**	**M1**	**M2**	**M6**	**M7**	**M8***	**M12 or M13***	**M13 or M14***
Group 1†	Cervarix + CYD			Cervarix + CYD			CYD	
	BL	BL			BL			BL
Group 2	Cervarix	CYD		Cervarix	CYD		CYD	
	BL	BL	BL		BL	BL		BL
Subjects not receiving the next CYD‡							Safety follow-up (6 months after the last CYD dengue vaccine injection	

D: day; M: month; BL: blood sample; CYD: CYD dengue vaccine

* In the original protocol v1.0, subjects from Group 1 were expected to attend V07 at M12 and V08 at M13. Likewise, subjects from Group 2 were expected to attend V07 at M13 and V08 at M14.

At the time of Protocol Amendment 1, procedures planned at V07 (most subjects) or V08 (2 subjects from Group 1) were on hold, depending on subjects' progression. Time for the approval of Protocol Amendment 1 by the competent authorities and completion of the associated logistic tasks will result into a delay of study activities (approximately 6 months), and thus to an extension of study duration for dengue exposed subjects.

† When concomitantly administered, the CYD dengue vaccine and Cervarix will be administered in 2 different sites with the CYD dengue vaccine administered in one deltoid and Cervarix in the other deltoid

‡ This includes seronegative subjects that consent to remain in the study and seropositive subjects that consent to stay in the study but prefer not to receive the next dose of CYD dengue vaccine

At the time of Protocol Amendment 1 writing, all subjects from both groups have received the second injection of CYD dengue vaccine and completed the vaccination schedule for Cervarix. Only 2 subjects from Group 1 had completed the 3-dose schedule for the CYD dengue vaccine. Visits on hold were:

- *For Group 1, Visit 7 (M12) was on hold for most of the subjects and Visit 8 (M13) was on hold for the 2 subjects who had received the third dose of CYD dengue vaccine.*
- *For Group 2, Visit 7 (M13).*

Dengue unexposed subjects will not receive further dengue vaccine injection. If they consent to continue their participation in the study, they will be contacted by phone call for a safety follow-up 6 months after the last injection. They will not attend any further study visits (except the unscheduled visit and/or the next schedule visit planned to sign the ICF) and will no longer provide blood samples.

Dengue exposed subjects who consent to continue in the study but decided against receiving the last CYD dengue vaccine injection will be contacted by phone call for a safety follow-up 6 months after the last injection. They will not attend any further study visits (except the unscheduled visit and/or the next schedule visit planned to sign the ICF) and will no longer provide blood samples.

For dengue exposed subjects who consent to continue in the study and to receive the next CYD dengue vaccine injection, procedures will be as followed:

Vaccinations

Subjects will receive 5 injections, 3 doses of CYD dengue vaccine and 2 doses of Cervarix administered either concomitantly (Group 1) or sequentially (Group 2):

- Group 1: Cervarix and CYD dengue vaccine (concomitantly) at Day (D)0 and Month (M)6, and CYD dengue vaccine (alone) at M12
- Group 2: Cervarix (alone) at D0 and M6, and CYD dengue vaccine (alone) at D0+28D (M1), M6+28D (M7), and M12+28D (M13)

Study Visits

Subjects will have to attend 6 (Group 1) or 8 (Group 2) visits and will have 1 phone call for the 6-month follow-up after the last injection of CYD dengue vaccine. Interim phone calls will be given 7 days (+8 days of time windows) after each injection and approximately 2 months after blood samples during the 6-month period between each vaccination.

An unscheduled visit or phone call will take place during the study pause in order to communicate the new data on the CYD dengue vaccine to each subject (delivering or reading of a "Dear ParticipantLetter"). This visit will be before the next visit initially planned (V07 for most subjects; V08 for 2 subjects). Dengue serostatus at baseline may be communicated to the subjects, if available, at the time of the unscheduled visit.

Subject's participation in the study was expected to be of 18 or 19 months. Time for the approval of Protocol Amendment 1 by the competent authorities and completion of the associated logistic tasks will result in a hold of study activities (approximately 6 months), and thus, in an extension of study duration for dengue exposed subjects.

Blood Samples

Subjects will provide blood samples:

- for CYD dengue vaccine immunogenicity assessments by dengue neutralizing Abs (4 mL) before the first vaccination (at D0 in Group 1, and M1 in Group 2), and 28 days after each vaccination with CYD dengue vaccine (M1, M7 and M13 in Group 1, and M2, M8 and M14 in Group 2)
- for HPV immunogenicity assessments by ELISA (2 mL) before the first vaccination at D0, and 28 days after each vaccination with Cervarix (M1 and M7)

Additional biological samples that may be collected at any time throughout the study period, regardless of the subject's dengue serostatus:

- for virological confirmation of hospitalized suspected dengue case within the first 5 days after fever onset (or as soon as possible if not within the 5 days) (approximately 3 mL) by NS1 Ag ELISA, and/or wild type (WT) dengue RT-PCR
- in the event of SAEs (including serious AEs of special interest [AESIs])
- to assess AEs that may be indicative of viscerotropic or neurotropic disease (see Guidelines for Assessing Viscerotropic and Neurotropic AE).

Urine samples

All subjects of childbearing potential will provide urine samples for urine pregnancy test before each injection.

A schedule of assessments and study vaccinations is provided in the table of study procedures.

5.1.4 Visit Procedures

All information collected during the study visits must be reported into the source documents. Some of the following information will also be recorded in the case report form (CRF).

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

The Investigator or designated study personnel will:

1) Give the subject's parent/legally acceptable representative information about the trial, obtain written informed consent (ICF and AF when applicable), and give him/her a signed copy.
2) Obtain significant medical history about the subject and history of dengue infection.
3) Collect demographic data.
4) Check concomitant medications and record every reportable medication ongoing at the time of vaccination.
5) Check inclusion and exclusion criteria for eligibility.
6) Perform a physical examination and record the subject's axillary temperature.
7) For subjects of childbearing potential[a], perform a urine pregnancy test.
8) Allocate a subject number to the subject.
9) Scratch-off the randomization list to obtain the group allocation, and sign it.
10) Obtain the first blood sample[b] (see Section 7.1 for detailed instructions regarding the handling of blood samples). Blood is to be taken from the limb opposite to the one that will

[a] To be considered of non-child-bearing potential, a female must be pre-menarche, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at least 3 weeks after vaccination.

[b] It is important to note that, if the attempt(s) to collect blood is (are) unsuccessful, the subject should be given the opportunity for another attempt, even on another day. If ultimately a blood sample cannot be obtained, the reason will be recorded in the CRF. In that case, and if the subject wants to participate in the trial, she will be vaccinated.

be used for vaccination for sequential injection (Group 2), or from the limb opposite to the one that will be used for CYD dengue vaccine injection for concomitant injection (Group 1).

11) Inject the first dose of Cervarix to all subjects (from Groups 1 and 2) and the first dose of CYD dengue vaccine to subjects randomized into Group 1 (for concomitant vaccination, the injections are made in opposite deltoid
12) Keep the subject under observation for 30 minutes, and record any immediate AE in the source document.
13) Record the date of injection(s), the site and side of injection(s) and the route of administration(s), as well as the dose number of the vaccine(s).
14) Give the parent/legally acceptable representative a diary card (DC), a thermometer, and a ruler, and go over the instructions for their use.
15) Remind the parent/legally acceptable representative to bring back the DC when they return for Visit 2 at a specified date and time.
16) Remind the parent/legally acceptable representative to call the study center if a serious medical event occurs.
17) Complete the relevant case report form (CRF) pages for this visit.

Phone Call 1 (PC1) (7 days [+8 days] after Visit 1)

All subjects, who received study vaccination(s), will be contacted 7 days after vaccination (+8 days time windows). During this contact, the Investigator or designated study personnel will ask the subject or parent/legally acceptable representative if the subject has experienced any SAE, including hospitalized suspected dengue case, in the time since vaccination. If it did occur, follow the instructions for reporting it. The Investigator or designated study personnel will also remind the instructions to the parent/legally acceptable representative and to complete regularly the DC. A follow-up visit can be arranged depending on the info recorded during the phone call.

Visit 2 (Month 1; 28 [+14] days after Visit 1)

The Investigator or designated study personnel will:

1) Check the information entered into the DC by interviewing the subject / subject's parent(s) / legally acceptable representative(s) and request information concerning any medical event, serious or not, that may have occurred since Visit 1.
2) Perform a physical examination (Group 2 only) and record the subject's axillary temperature (if necessary).
3) Collect information regarding the subject's medication status since the previous visit.
4) For subjects of childbearing potential, perform a urine pregnancy test before injection (subjects in Group 2 only).
5) Obtain the second blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
6) Review temporary and definitive contraindications to vaccination (Group 2 only).

7) Inject the first dose of CYD dengue vaccine to subjects randomized into Group 2.
8) Keep the subject under observation for 30 minutes, and record any immediate AE in the source document (Group 2).
9) Record the date of injection, the site and side of injection and the route of administration, as well as the dose number of the vaccine.
10) Give the parent(s)/legally acceptable representative(s) a DC for Group 2 and Group 1 (for Group 1 DC for SAE collection only).
11) Remind the parent(s)/legally acceptable representative(s) of subjects in Group 2 to bring back the DC when they return for Visit 3 at a specified date and time.
12) Remind the parent(s)/legally acceptable representative(s) of subjects in Group 1 to bring back the DC when they return for Visit 4 at a specified date and time.
13) Complete the relevant CRF pages for this visit.

Phone Call 2 (PC2) (7 days [+8 days] after Visit 2)

The same procedures as those descried for PC1 will be followed.

Visit 3 (Month 2; 28 [+14] days after Visit 2)

This visit is applicable only for subjects in Group 2. These subjects will receive their first dose of CYD dengue vaccine at Visit 2 and will come to Visit 3 for blood sampling. The Investigator or designated study personnel will:

1) Check the information entered into the DC by interviewing the subject / subject's parent(s) / legally acceptable representative(s) and request information concerning any medical event, serious or not, that may have occurred since Visit 2.
2) Perform a physical examination and record the subject's axillary temperature.
3) Check concomitant medications and record every reportable medication ongoing at the time of vaccination.
4) Obtain the blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) Give the parent(s)/legally acceptable representative(s) a DC for SAE collection only.
6) Remind the parent(s)/legally acceptable representative(s) to bring back the DC when they return for Visit 4 at a specified date and time.
7) Complete the relevant CRF pages for this visit.

Phone Call 3(PC3) (approximately 2 months after Visit 2 for Group1 and 2 months after Visit 3 for Group 2)

The same procedures as those described for PC1 will be followed.

Visit 4 (Month 6; 6 months [± 20 days] after Visit 1)

The Investigator or designated study personnel will:

1) Review the pages of the DC with the parent(s)/legally acceptable representative(s)
2) Perform a physical examination and record the subject's axillary temperature
3) Collect information regarding the subject's medication status since the previous visit.
4) Perform a urine pregnancy test before injection (for woman of childbearing potential only).
5) Review temporary and definitive contraindications to vaccination
6) Inject the second dose of Cervarix to all subjects (Groups 1 and 2) and the second dose of CYD dengue vaccine to subjects in Group 1 (6 months post-dose 1).
7) Keep the subject under observation for 30 minutes, and record any immediate AE in the source document.
8) Record the date of injection(s), the site and side of injection(s) and the route of administration(s), as well as the dose number of the vaccine(s).
9) Give the parent(s)/legally acceptable representative(s) a DC.
10) Remind the parent(s)/legally acceptable representative(s) to bring back the DC when they return for Visit 5 at a specified date and time.
11) Complete the relevant CRF pages for this visit.

Phone Call 4 (PC4) (7 [+8 days] days after Visit 4)

The same procedures as those descried for PC1 will be followed.

Visit 5 (Month 7; 6 months [± 20 days] after Visit 2)

The Investigator or designated study personnel will:

1) Review the pages of the DC with the parent(s)/legally acceptable representative(s), including any AEs, medications, or therapy that occurred since vaccination.
2) Perform a physical examination and record the subject's axillary temperature
3) Check concomitant medications and record every reportable medication ongoing at the time of vaccination.
4) Obtain the blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) For female subjects of childbearing potential, perform a urine pregnancy test before injection (subjects in Group 2 only).
6) Review temporary and definitive contraindications to vaccination
7) Inject the second dose of CYD dengue vaccine to subjects in Group 2 (6 months post dose 1).
8) Keep the subject under observation for 30 minutes, and record any immediate AE in the source document (Group 2).
9) Record the date of injection, the site and side of injection and the route of administration, as well as the dose number of the vaccine (Group 2).

10) Give the parent(s)/legally acceptable representative(s) a DC for Group 2 and Group 1 (for Group 1 DC for SAE collection only).
11) Remind the parent(s)/legally acceptable representative(s) of subjects in Group 2 to bring back the DC when they return for Visit 6 at a specified date and time.
12) Remind the parent(s)/legally acceptable representative(s) of subjects in Group 1 to bring back the DC when they return for Visit 7 at a specified date and time.
13) Complete the relevant CRF pages for this visit.

Phone Call 5 (PC5) (7 days [+8 days] after Visit 5)

The same procedures as those descried for PC1 will be followed.

Visit 6 (Month 8; 28 [+14] days after Visit 5)

This visit is applicable only for subjects in Group 2 and the same procedures as those described for Visit 3 will be followed.

Phone Call 6 (PC6) (2 months after Visit 5 and 2 months after Visit 6)

The same procedures as those described for PC1 will be followed.

Additional Unscheduled Visit (V00)/Phone Call (PC00)- As per Protocol Amendment 1

This unscheduled visit/phone call is to take place between Visit 5 (subjects from Group 1) or Visit 6 (subjects from Group 2) and Visit 7. During this visit/phone call, subjects will be informed by the mean of the "Dear Participant Letter" about the results of the exploratory analyses, ie, 1° the increased risk of hospitalized or severe dengue for those unexposed to dengue infection prior to the first injection with the CYD dengue vaccine; and 2° the confirmed and sustained benefit of vaccination in dengue exposed subjects. Subjects will be informed about their dengue serostatus at baseline if available.

At the latest, this visit will take place at the same time as the next subject's scheduled visit.

Visit 7 (initially planned at Month 12 [± 20 days] after Visit 1 (Group 1) or Month 12 [± 20 days] after Visit 2 (Group 2)

For subjects who will return at V07 after the suspension of vaccination

1) Present the changes brought to the study design to the subject and the subject's parent(s)/legally acceptable representative(s) in more detail, answer any of their questions, and ensure that they have been informed of all aspects that are relevant to their decision to continue participating in the study
2) Have the subject and the subject's parent(s) /legally acceptable representative(s), date and sign the new AF and/or ICF version, as applicable
3) Depending on subject's serostatus at baseline:

- **Subjects identified as dengue exposed, choosing to receive the last CYD dengue vaccine injection.** The procedures described for Visit 4 will be followed, except that no dose of Cervarix will be injected and CYD dengue vaccine will be injected to all eligible subjects (third and last dose, given 12 months post-injection 1, depending on the duration of the study pause).
- **Subjects identified as dengue exposed, choosing not to receive the last CYD dengue vaccine injection AND subjects identified as dengue unexposed:**
  a) Give the parent(s)/legally acceptable representative(s) a memory aid (MA).
  b) Remind the parent(s)/legally acceptable representative(s) to keep the MA available when they will be called for Safety Follow-up Telephone Call at a specified date and time.
  c) Complete the relevant CRF pages for this visit.
  d) Complete the termination record of the CRF.

The following visit procedures will only apply to Subjects identified as dengue exposed, choosing to receive the last CYD dengue vaccine injection

Phone Call 7 (PC5) (7 days [+8 days] after Visit 7)

The same procedures as those described for PC1 will be followed.

Visit 8 (Month 13 (Group 1) or Month 14 (Group 2); 28 [+14] days after Visit 7)

The Investigator or designated study personnel will:

1) Review the pages of the DC with the parent(s)/legally acceptable representative(s), including any AEs, medications, or therapy that occurred since vaccination.
2) Perform a physical examination and record the subject's axillary temperature.
3) Check concomitant medications and record every reportable medication ongoing at the time of vaccination.
4) Obtain a blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) Give the parent(s)/legally acceptable representative(s) a memory aid (MA).
6) Remind the parent(s)/legally acceptable representative(s) to keep the MA available when they will be called for Safety Follow-up Telephone Call at a specified date and time.
7) Complete the relevant CRF pages for this visit.
8) Complete the termination record of the CRF.

Phone Call 8 (PC8) (approximately 2 months after Visit 8)

The same procedures as those described for PC1 will be followed.

Safety Follow-up (6-month period after last vaccination) for all subjects, exposed and unexposed, having accepted to continue participation in the trial post-amendment 1

During the 6-month safety follow-up after the last vaccination, subjects will be highly invited to contact the sponsor in case of SAE. In case of hospitalized suspected dengue case, one unplanned acute blood sample will have to be collected within the first 5 days after fever onset for virological confirmation of dengue disease. If this cannot be accomplished within the first 5 days after fever onset, this sample should still be obtained as soon as possible thereafter, for IDMC severity assessment.

Safety Follow-up Telephone Call (6 months after last vaccination): Collection of SAEs for all subjects, exposed and unexposed, having accepted to continue participation in the trial post-amendment 1

The last contact is planned to be held 6 months after the last injection with the CYD dengue vaccine, regardless of the number of doses received by the subject. The Investigator or designated study personnel will:

1) Ask the parent(s)/legally acceptable representative(s) if the subject has experienced any SAE in the time since vaccination. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Complete the relevant CRF pages for this contact.

A follow-up visit can be arranged depending on the information recorded during the phone call.

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.

Planned trial period (FVFS to LCLS[a]): Q4 2016 to Q3 2019

Planned vaccination period: Q4 2016 to Q4 2018

[a] FVFS: first visit of first subject; LCLS: last contact of last subject.

Planned end of trial[a]: Q3 2019

Planned date of final clinical study report: Q1 2020

Initially, the expected duration of each subject's participation in the trial was approximately 18 months for Group 1 and 19 months for Group 2, including a safety follow-up period of 6 months after the third injection of CYD dengue vaccine. However, the time for the approval of Protocol Amendment 1 by the competent authorities and completion of the associated logistic tasks will result in a hold of study activities (approximately 6 months), and thus, in an extension of study duration for dengue exposed subjects.

5.1.6 Early Safety Data Review

This trial will not include an early review of safety data. However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in Mexico 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 subjects and/or the subjects' parents/legally acceptable representatives and should assure appropriate therapy and follow-up.

An internal Safety Evaluation Team (SET) performed a safety analysis on safety data during the conduct of the trial.

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 site will ensure that any advertisements or materials they plan to use to recruit subjects (e.g., letters, pamphlets, posters, etc.) are submitted to Sanofi Pasteur for review prior to submission to the IEC/IRB for approval.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject and 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

[a] End of trial is defined as the date of the last contact with a trial subject within the scope of the trial.

documented by means of a written, signed, and dated ICF. Depending on age, the subject may be required to sign and date the AF, which varies according to local or regional regulations. The AF is in addition to, not in place of, an ICF that is signed by the parent(s)/legally acceptable representative(s).

Following Protocol Amendment 1 to the original protocol Version 1.0 dated 04 January 2016, subject/subject's parent(s)/legally acceptable representative(s) is to sign the Amendment 1 to AF/ICF, as per local regulations.

In accordance with GCP, prior to signing and dating the consent form, the subject and 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 the appropriate and legally acceptable representative are 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 and AF 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 or 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 and AF.

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 or the subject's 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) Female subjects aged 9 to 14 years (ie, from the day of the 9th birthday to the day prior to the 15th birthday) on the day of inclusion
2) Informed consent form (ICF) or Assent form (AF) has been signed and dated by the subject (based on local regulations), and/or ICF has been signed and dated by the parent(s) or another legally acceptable representative (and by an independent witness if required by local regulations)

3) Subject (or subject and parent[s] or another legally acceptable representative[s]) is (are) able to attend all scheduled visits and to comply with all trial procedures
4) Subject in good health, based on medical history, and physical examination

5.2.5 Exclusion Criteria

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

1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche[a], surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination and until at least 4 weeks after the last 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) Planned receipt of any vaccine in the 4 weeks following any trial vaccination
4) Previous vaccination against dengue disease with the trial vaccine
5) Previous vaccination against HPV disease with either the trial vaccine or another vaccine
6) Receipt of immune globulins, blood or blood-derived products in the past 3 months
7) Known or suspected congenital or acquired immunodeficiency (including HIV infection with impaired immune function); 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) History of HPV infection, confirmed either clinically, serologically, or microbiologically as reported by subject or parent/legally acceptable representative
9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[b]
10) Thrombocytopenia, contraindicating intramuscular vaccination
11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination

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[a] For pre-menarche females, the young female patients will declare by themselves (and/or their parent(s) or other legally acceptable representative(s) if they have not yet started menstruation. If a young female patient reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward. Examples of effective methods of contraception include oral contraception (pill), intrauterine device, diaphragm or condoms, contraceptive foam or cream, hormonal implants, transdermal patch, or parenteral contraception

[b] The components of CYD dengue vaccine and Cervarix are listed in Section 6.1 and in the Investigator's Brochure

12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
13) Current alcohol abuse or drug addiction that, based on Investigator's judgment, may interfere with the subject's ability to comply with trial procedures.
14) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion
15) Identified as an Investigator or employee of the Investigator with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
16) Self-reported Hepatitis B, Hepatitis C infection

Temporary Exclusion Criteria:

A prospective subject must not be included in the study until the following conditions and/or symptoms are resolved:

1) Moderate or severe acute illness/infection (according to Investigator judgment) or febrile illness (temperature ≥ 38.0°C) on the day of first vaccination.
2) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination

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 that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

The reporting of signs and symptoms 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

5.2.7.1 Temporary Contraindications

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

- Febrile illness (temperature ≥ 38.0°C) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment
- Receipt of any vaccine (other than trial vaccine) in the 4 weeks preceding the trial vaccination

5.2.7.2 Definitive Contraindications

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

1) Pregnancy, as indicated by a positive urine test, or lactation
2) An anaphylactic or other significant allergic reaction to the previous dose of vaccine
3) Individual with acquired immunodeficiency (including HIV infection with impaired immune function); or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy, radiation therapy or systemic corticosteroid therapy (prednisone or equivalent)
4) Ongoing clinical AE related to the previous trial vaccination, and in the Investigator's opinion, contraindicating further vaccination
5) SAE related to the study vaccine following the previous trial vaccination

The following definitive contraindication has been added in Protocol Amendment 1 and is applicable for the third injection of the CYD dengue vaccine:

6) Subjects identified as "dengue unexposed" (seronegative) before the first CYD dengue vaccine injection

Subjects will not be withdrawn due to contraindication but will be followed up for safety and possibly immunogenicity assessment. If a subject has been identified as "dengue unexposed", she will have the possibility to continue participating to the study and will be follow-up for safety.

5.2.8 Conditions for Withdrawal

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

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission
- At the request of the subject/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.

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the 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 are listed below from the most significant to the least significant (refer to the CRF completion guidelines for additional details and examples):

- **Serious adverse event:** 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 9.2.2.1.
- **Other adverse event:** 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 9.2.2.1.
- **Non-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow the protocol, including when 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 (ie, return of unsigned certified letter receipt).
- **Voluntary withdrawal not due to an adverse event:** To be used when a subject drops out of the study for any reason other than those listed above.

As per Protocol Amendment 1, every effort will be made to contact dengue unexposed subjects lost to follow-up or who discontinued after having received at least 1 dengue vaccine injection to inform them about their dengue status and their rights to access medical care in case of fever consistent with dengue illness for 10 years after the last dengue vaccine injection.

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the trial because of an 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 for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

As per Protocol Amendment 1, unexposed subjects before vaccination who discontinued or withdrew their consent after having received at least 1 dengue vaccine injection will be contacted and informed about their dengue status and their rights to access medical care in case of fever consistent with dengue illness for 10 years after the last dengue vaccine injection.

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). However, no additional vaccination will be administered.

All pregnancy cases should be reported if they occurred during the study and during the 6 month follow-up period. To report the pregnancy case, the Investigator must fill out an Electronic Pregnancy Reporting Form in the Electronic Data Capture (EDC) system and inform the Sponsor within a month after identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome—ie, 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. Additional follow-up visits may be performed according to the local regulations.

Pregnancy itself is not considered as 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).

Also for all pregnancy cases the Study staff must keep in touch with the subject, in order to follow the pregnancy during the 9 months of gestation and for the first 6 next months of life of the new born baby and also during the child's breast feeding period because the dengue vaccine may be excreted in breast milk and the monitoring has to be done during the breast feeding period and 3 months after this period has finished. This monitoring of pregnancy and breastfeeding is in

compliance with the Mexico sanitary regulations, but is not part of the study procedures and the principal investigator should check subject´s health and the baby after these time periods.

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.

An administrative amendment to a protocol is one that modifies some administrative or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. The IECs/IRBs and regulatory authorities must be notified of administrative changes and will provide approval according to local regulations.

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

5.4 Interruption of the Trial

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

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

6 Vaccines Administered

All subjects will be administered 2 doses of Cervarix 6 months apart, and 3 doses of CYD dengue vaccine 6 months apart. This trial will be using the 5-dose presentation of the CYD dengue vaccine as per Sponsor's Operating Guidelines.

6.1 Identity of the Investigational Products

6.1.1 Identity of Trial Product 1: CYD Dengue Vaccine

CYD dengue vaccine:	Live, attenuated, tetravalent dengue virus vaccine
Presentation:	multi-dose (5 doses vial)
Form:	Powder and solvent for suspension for injection

Dose:	0.5 milliliters (mL) of the reconstituted vaccine
Route:	Subcutaneous (SC) injection
Batch number:	M5568F01 for the first 2 injections; to be determined for last injection

6.1.1.1 Composition

Each 0.5 mL dose of reconstituted vaccine contains the following components:

- 4.5 – 6 $\log_{10}$ cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated, recombinant dengue virus serotype 1, 2, 3, 4
- Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, sucrose, D-trehalose dihydrate, D-sorbitol, Trometamol, urea, and sodium chloride
- Solvent: NaCl 0.9%

6.1.1.2 Preparation and Administration

Sanofi Pasteur's CYD dengue vaccine consists of a powder and solvent for suspension for injection and must be stored between +2°C and +8°C.

The vaccine must be removed from the refrigerator, reconstituted with the solvent supplied for this purpose, and used immediately after reconstitution.

The vaccine is to be administered subcutaneously in the deltoid region of the upper arm in a volume of 0.5 mL according to Operating Guidelines.

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.

After reconstitution with the solvent provided, the vaccine must be used as soon as possible and, for the multidose, discarded at the end of the immunization session or within 6 hours after reconstitution, whichever comes first. During this period, the vaccine must be kept between 2°C and 8°C, ie, in a refrigerator, and protected from light.

For the multidose, before each injection, the reconstituted suspension should be gently swirled once again and a partially used multidose vial must be discarded immediately if:

- Sterile dose withdrawal has not been fully observed.
- A new sterile syringe and needle was not used for reconstitution or withdrawal of each of the previous doses.
- There is any suspicion that the partially used vial has been contaminated.

There is visible evidence of contamination, such as a change in appearance.

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.

If a vial or syringe is accidentally broken and the product spilled out, appropriate disinfection procedures must be used (please refer to the Operating Guidelines and/or trial center's procedures).

6.1.1.3 Dose Selection and Timing

Tetravalent vaccine:

CYD01 assessed safety and immunogenicity of a single dose of monovalent DENV-2 chimeric vaccine which demonstrated a satisfactory immune response to serotype 2 but low seropositivity rates to other serotypes thus confirming the need for a tetravalent vaccine. In CYD04, CYD05, and CYD06 the choice of a tetravalent vaccine against all 4 serotypes was confirmed as assessed by immunogenicity responses in several populations across different age groups and with different FV background (FV naïve or immune). Furthermore this was supported by CYD11, whereby several bivalent formulations did not improve the immune response compared to tetravalent formulations.

5 log_{10} $CCID_{50}$ per serotype (5555) Formulation:

The results of an early Phase I study (CYD02) showed that a tetravalent formulation with 4 log_{10} $CCID_{50}$ per serotype (2 doses given at 5 to 9 month interval) induced moderate but unbalanced Ab levels against the four serotypes (19). Based on these results, it was decided to evaluate a formulation with a higher virus concentration 5 log_{10} $CCID_{50}$ per serotype (5555) and to introduce a third injection. The safety and immunogenicity of the 5555 formulation of CYD dengue vaccine (5 log_{10} $CCID_{50}$ per serotype) was thus evaluated in additional Phase I trials (CYD04, CYD05, CYD06, CYD12). The 5555 formulation reliably induced an immune response against all 4 serotypes after 3 injections in various populations.

Vaccination schedule:

The schedule was selected based on the results from phase I studies (CYD02, CYD04, CYD05, and CYD06) in groups receiving tetravalent vaccine at a 3-injection regimen 0,3/4,12 months in different age groups (children, adolescents, adults), different regions (non-endemic USA and Latin America, and endemic Asia Pacific) and different baseline FV status at baseline. The data from initial Phase I studies demonstrated that increasing the interval between injections was beneficial. Furthermore, the benefit of the third injection in terms of seropositivity rate was more marked in younger children and/or subjects who were FV non-immune at baseline. A potential priming effect was also observed following administration of YF vaccine (CYD06) (20).

The choice of the final 3 dose schedule at 6 month intervals apart of the 5555 formulation was based on data from phase II studies, especially CYD12. The 3-dose schedule (0, 3–4, and 12 months) and 2-dose schedule (0 and 8–9 months) were adapted to adjust for the higher immunogenicity that occurred when Dose 2 was delayed, balanced by providing protection as soon as possible. CYD12 was the first phase II study testing the final 5555 formulation with the 3 dose schedule 0, 6, and 12 months demonstrating a satisfactory immune response to all 4

serotypes in FV non-immune subjects. Overall, 3 injections at 0, 6 and 12 months of 5555 formulation led to consistent immune response against all serotypes in all age groups, regardless of baseline FV status (21).

6.1.2 Identity of Trial Product 2: Cervarix

Form:	Suspension for injection
Dose:	0.5 mL
Route:	Intramuscular (IM) injection
Batch number:	Commercial batch

6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

- 20 µg of HPV 16 L1 protein*
- 20 µg of HPV 18 L1 protein*

  * adjuvanted by 50 µg of AS04 containing 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), and adsorbed on 0.5 mg of aluminum hydroxide hydrated ($Al(OH)_3$)
- Excipients: sodium chloride, sodium dihydrogen phosphate dehydrate, water for injection

6.1.2.2 Preparation and Administration

The product must be stored between +2°C and +8°C and will be administered intramuscularly in the deltoid region of the upper arm (the one who did not receive the CYD dengue vaccine) in a volume of 0.5 mL.

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.

6.1.2.3 Dose Selection and Timing

The recommended dose will be administered (this should follow the leaflet).

6.1.3 Identity of Control Product(s)

Not applicable

6.2 Identity of Other Product(s)

Not applicable

6.3 Product Logistics

6.3.1 Labeling and Packaging

CYD dengue vaccine will be supplied in vials/syringes and will be labeled and packaged according to national regulations. The information on the label will include:

- Study code
- Name of product
- Route of injection (SC)
- Investigational use only statement
- Storage conditions
- Batch number
- Dose number (ie, vial number for CYD dengue vaccine)
- Name of Sponsor
- Expiry date

For Cervarix, a commercial batch will be used, and the manufacturer's packaging will be used and labelled with specific clinical mention according to national regulation.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

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

6.3.2.2 Product Storage

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

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the 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 CRFs.

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

6.3.3 Replacement Doses

If a replacement dose is required (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

Unused or wasted products will be either disposed of 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

The study CYD71 will be an open-labeled study, no blinding is required.

6.5 Randomization and Allocation Procedures

Subjects will be randomized in a 1:1 ratio into Group 1 or Group 2.

The full detailed procedures for randomization are described in the Operating Guidelines.

Subject numbers will be 8 digits long, with a 3-digit center identifier and a 5-digit subject identifier. For example, [redacted]

Subject numbers should not be reassigned for any reason.

The Statistical Platform of the Sponsor will provide scratchable randomization lists (one per site). These lists will mention the randomization number of the subject and the corresponding study group covered by a silver-colored patch. After subject number allocation to a subject, the Investigator will scratch off the list to know the study group. Once scratched, each randomization line will be dated and signed by the Investigator or the sub-investigator in charge of administering the study vaccine(s).

Each subject will be vaccinated with the product(s) corresponding to the group mentioned on the randomization list. If the dose initially taken for the vaccination is broken or cannot be used, the Investigator will take another dose of the same vaccine.

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

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

Documentation in the 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 (e.g., 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.

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

- Category 1 (Restricted therapies): antipyretics, analgesics, non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immune modulators.

Note: inhaled and topical steroids should not be captured.

- Category 2 (Prohibited therapies for the PP):

- Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy or long-term systemic corticosteroids (for more than 2 consecutive weeks) in the 4 weeks after each trial vaccination
- Immune globulins, blood or blood-derived products in the 4 weeks before and after each trial vaccination
- Vaccines (other than the trial vaccines) in the 4 weeks before and after each trial vaccination

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

- Trade name
- Given as treatment or as prophylaxis
- 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.

The fact that a medication was 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 Visits 1, 2, 3, 5, 6, and 8. See the Table of Study Procedures and Section 5.1.4 for details of the sampling schedule.

7.1 Sample Collection

7.1.1 Serum Samples for Neutralizing Ab Assessment

As per Protocol Amendment 1, dengue exposed subjects who will continue in the study and consent to receive the remaining CYD vaccine injection will provide all blood samples as initially planned. All other subjects will not provide the blood samples initially planned. At Visits 1, 2, 3, 5, 6, and 8, 4 to 6 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity; will write the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination for sequential injection (Group 2), or from the limb opposite to the one that will be used for CYD dengue vaccine injection for concomitant injection (Group 1).

Table 7.1: Blood sampling volume (mL) per visit

Visit Number Trial Timelines (Days/Months) Time Windows (Days)	V01 D0	V02 M1 (V01+28D) +14	V03 M2 (V02+28D) +14	V05 M7 (V04+28D) +14	V06 M8 (V05+28D) +14	V08† M13 (V07+28D) (Group 1) M14 (V07+28D) (Group 2) +14
Dengue Neutralizing Abs	4 (Group 1)	4 (Both groups)	4 (Group 2)	4 (Group 1)	4 (Group 2)	4 (Both groups)
HPV Abs	2 (Both groups)	2 (Both groups)		2 (Both groups)		
TOTAL (mL)	**6 (Group 1)** **2 (Group 2)**	**6 (Group 1)** **6 (Group 2)**	**0 (Group 1)** **4 (Group 2)**	**6 (Group 1)** **2 (Group 2)**	**0 (Group 1)** **4 (Group 2)**	**4 (Group 1)** **4 (Group 2)**

† BL post Protocol Amendment 1 (dengue exposed subjects who consent to continue in the study and receive the next injection(s) of CYD dengue vaccine)

7.1.2 Blood Sample for Virological Confirmation of Hospitalized Suspected Dengue Case and Assessment of Disease Severity

In the event of hospitalized suspected dengue case, one 3 mL acute blood sample will be collected (within the 5 days after the fever onset) as presented in Table 7.2. The acute blood sample for all hospitalized suspected dengue cases should be collected within the pre-specified timeframe as described above. If this cannot be accomplished, this sample should still be obtained as soon as possible thereafter, for IDMC severity assessment. This blood sample will be used to confirm whether a hospitalized suspected dengue case is dengue disease or not, and upon confirmation of infection, to identify dengue virus serotype.

For all hospitalized suspected dengue cases, the Investigator must ensure that key biological parameters (aspartate aminotransferase [AST], alanine transaminase [ALT], hematocrit and platelet count) have been checked or are planned to be checked as part of local standard of care at the hospital (ideally within the 5 days after the fever onset). If these parameters have not been measured, additional blood specimens will be taken. The aim of these tests is the assessment of severity according to the WHO/IDMC classification (see Section 9.2.3 for more details).

Table 7.2 presents the additional serum aliquots to be taken from subject with hospitalized suspected dengue case at any time during the trial. Additional details are found in the Operating Guidelines.

Table 7.2: Blood sampling volume (mL) for hospitalized suspected dengue case

		In case of hospitalized suspected dengue case
		Blood volume (mL)
	GCI (USA) or GCI outsourced laboratory	
	Dengue Screen RT-PCR & Simplexa dengue RT-PCR	1
	Serum bank	1
	Dengue NS1 Ag ELISA	1
	Local laboratory (if needed)	*x*
	TOTAL	**3 + *x***

More detailed instructions are provided in the Operating Guidelines.

7.1.3 Additional Blood Samples

Additional blood samples may be taken to assess AEs that may be indicative of viscerotropic or neurotropic disease (see Guidelines for Assessing Viscerotropic and Neurotropic AE, (22) (23) (24).

7.1.4 Urine Samples

Urine samples for pregnancy tests at the vaccination visits (V01, V02 [Group 2], V04, V05 [Group 2], and V07) will be taken and analyzed at the trial center only for women of childbearing potential.

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 sampling tube should be stored at room temperature for a minimum of 60 minutes and a maximum of 2 hours to allow the blood to clot before centrifugation. The tube must be stored vertically and will not be shaken.

Beyond 2 hours, the sampling tube must be refrigerated at a temperature of +2°C to +8°C and must be centrifuged within a maximum of 24 hours.

After clotting and centrifugation, the serum will be harvested and divided into appropriate number of aliquots. Samples will then be handled one subject at a time to avoid a mix-up of subjects' blood tubes. Serum will be transferred to the appropriate number of tubes, pre-labeled with adhesive labels that clearly identify the subject's number and sampling stage or visit number.

The subject's identification number and code, the date of sampling, the number of aliquots obtained, and the date and time of preparation are to be specified on a sample identification list. Space is provided on this list for comments on the quality of samples.

Serum will be aliquoted in tubes which are specified in the Operating Guidelines. Aliquots will be frozen immediately at -20°C or below until testing.

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 GCI at Sanofi Pasteur. The address is provided in the Operating Guidelines.

7.4 Future Use of Stored Serum Samples for Research

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

Subjects or subjects' parents/legally representatives will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission (anonymity of samples will be ensured). The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve laboratory methods. Genetic tests will never be performed on these samples without individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the trial sites with protocols, ICFs, AF, CRFs, DCs, memory aids, and other trial documents, as well as with the following trial materials: all study vaccines and injection materials, 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 approximately 1 week for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity endpoints

The primary endpoint(s) for the evaluation of immunogenicity are:

Cervarix immunogenicity

- Ab levels (measured by ELISA) against each Cervarix HPV antigen (HPV-16 and HPV-18) 28 days after the last dose of Cervarix in dengue exposed subjects

CYD dengue vaccine immunogenicity

- Neutralizing Ab levels (measured by dengue plaque reduction neutralization test [$PRNT_{50}$]) against each of the four parental dengue virus serotypes of CYD dengue vaccine (1, 2, 3, 4) 28 days after the last dose of CYD dengue vaccine in dengue exposed subjects

Definition of dengue serostatus

The dengue serostatus at baseline is defined as the presence of Abs against at least one dengue serotype in the baseline sample (by dengue 50% plaque reduction neutralization test [PRNT50) in the blood sample collected at V01 (BL1) from all subjects. The baseline dengue status variable will be calculated for each subject as follows:

- Dengue immune subjects (dengue exposed) at baseline are defined as those subjects with titers ≥10 (1/dil) for at least one serotype with the parental dengue virus strain
- Dengue non-immune subjects (dengue unexposed) at baseline are defined as those subjects with titers <10 (1/dil) (not quantified) for all serotypes with parental dengue virus strains with available "valid" results (i.e. different from missing or "NR")

The baseline dengue status will be set to missing when the titer for any serotypes with parental dengue virus is either missing or not quantified. If the titer for all serotypes with parental dengue virus is either missing or not quantified, the dengue status is non-immune.

In case of limited serum volume, the priority will be given to the testing of the dengue serostatus at baseline testing over the other testing (HPV immunogenicity post Cervarix may be not performed if not enough blood volume).

9.1.1.2 Immunogenicity Assessment Methods

HPV Abs

The Ab response to HPV will be performed at Sanofi Pasteur GCI, Swiftwater, USA, or GCI outsourced laboratory. The HPV16/18 virus-like particle-based enzyme linked immunosorbent assay (VLP-ELISA) is performed using serial dilutions of serum samples and standards added to HPV VLP-coated ELISA microtiter plates. A peroxidase-conjugated anti-human IgG polyclonal antibody, enzyme substrate, and chromogen are added; reactions are then stopped. Optical density (OD) at 620 nm (background) is read and subtracted from OD at 450 nm. Antibody levels in ELISA units (EU)/mL are calculated by interpolating OD values from the standard curve.

This assay will be performed on blood samples taken from V01, V02 and V05.

Dengue Neutralizing Abs

Dengue neutralizing Ab levels will be measured by $PRNT_{50}$ (using parental dengue virus strains of CYD dengue vaccine constructs) by Sanofi Pasteur GCI, Swiftwater, USA (or outsourced with a GCI selected external laboratory).

Serial, two-fold dilutions of serum to be tested (previously heat-inactivated) are mixed with a constant challenge-dose of each dengue virus serotype 1, 2, 3 or 4 (expressed as plaque-forming unit [PFU]/mL). The mixtures are inoculated into wells of a microplate with confluent Vero cell monolayers. After adsorption, cell monolayers are incubated for a few days. The presence of dengue virus infected cells is indicated by formation of plaques. A reduction in virus infectivity due to neutralization by Ab present in serum samples is detected. The reported value (end point neutralization titer) represents the highest dilution of serum at which ≥ 50% of dengue challenge virus (in plaque counts) is neutralized when compared to the mean viral plaque count in the negative control wells which represents the 100% virus load. The end point neutralization titers are presented as continuous values. The lower limit of quantitation (LLOQ) of the assay is 10 (1/dilution [dil]).

This assay will be performed on each blood samples taken at V01 (Group 1 only), V02, V03 (Group 2 only), V05 (Group 1 only), V06 (Group 2 only), and V08.

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

There are no primary objectives for efficacy.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

Cervarix immunogenicity:

- Ab levels (measured by ELISA) against each Cervarix HPV antigen (HPV-16 and HPV-18) at baseline and after each dose of Cervarix in dengue exposed subjects
- Seroconversion against each Cervarix HPV antigen (HPV-16 and HPV-18) 28 days after each dose of Cervarix in dengue exposed subjects

Seroconversion is defined as changing serostatus from seronegative at baseline to seropositive (> LLOQ of the assay) or ≥ 4-fold rise in Ab titer if seropositive at baseline.

CYD dengue vaccine immunogenicity:

- Neutralizing Ab titers against each of the four parental dengue virus serotypes of CYD dengue vaccine as determined by $PRNT_{50}$ at baseline and after each dose of CYD dengue vaccine in dengue exposed subjects
- Neutralizing Ab titers ≥ 10 (1/dil) against each of the four and against at least 1, 2, 3, or 4 parental dengue virus serotypes of CYD dengue vaccine as determined by $PRNT_{50}$ at baseline and after each dose of CYD dengue vaccine in dengue exposed subjects
- Neutralizing Ab titers ≥ different titer thresholds (1/dil) against each parental dengue virus serotype of CYD dengue vaccine as determined by $PRNT_{50}$ at baseline and after each dose of CYD dengue vaccine in dengue exposed subjects

9.2.1.2 Immunogenicity Assessment Methods

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

9.2.2 Safety

9.2.2.1 Safety Definitions

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

Adverse Event (AE):

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

associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

- A new illness
- The worsening of a 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

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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.

- Is an important medical event[a]

Additionally, the following important medical events are to be considered as SAEs and reported to the Sponsor according to the procedure described in Section 10:

Adverse Reaction (AR):

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

(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 (UAR):

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

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the 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 pain between D0 and D7 post-vaccination, or headache between D0 and D14.

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

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, ie, excluding solicited reactions, e.g., if headache between D0 and D14 is a solicited reaction (ie, prelisted in the CRF), then a headache starting on D14 is a solicited reaction, whereas headache starting on D15 post-vaccination is an unsolicited AE.

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

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[a] 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.

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):

AEs of special interest are AEs that are considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine.

9.2.2.2 Safety Endpoints

Cervarix and CYD dengue vaccine safety in each group:

- Occurrence of immediate AEs reported within 30 minutes after each and any injection
- Occurrence of solicited (ie, pre-listed in the subject's DC and CRF) injection site reactions (pain, erythema, and swelling) occurring up to 7 days after each and any injection
- Occurrence of solicited systemic reactions (fever, headache, malaise, myalgia, and asthenia) occurring up to 14 days after each and any injection
- Occurrence of unsolicited AEs occurring up to 28 days after each and any injection
- Occurrence of non-serious AESIs* reported within 7 days following each and any injection
- Occurrence of SAEs, including serious AESIs (with specific time windows according to the type of AESI*) throughout the trial
- Occurrence of hospitalized VCD cases throughout the trial (ie, from D0 through end of the study)

*Hypersensitivity/allergic reactions (serious or not) within 7 days after each CYD dengue vaccine injection, serious viscerotropic disease within 30 days after each CYD dengue vaccine injection, serious neurotropic disease within 30 days after each CYD dengue vaccine injection; serious dengue cases requiring hospitalization will be reported during the entire study.

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

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

severity, relationship to vaccine, action taken, whether the event/reaction led to early termination from the study, seriousness, or outcome.

Hospitalized suspected dengue case is defined as an acute febrile illness with diagnosis of dengue requiring hospitalization (with bed attribution). In such cases, 1 unplanned acute blood sample (within the first 5 days after fever onset) will be collected for virological confirmation of hospitalized suspected dengue case. A suspected case will be considered VCD if there is a detection of WT dengue virus by dengue NS1 Ag ELISA and/or dengue RT-PCRs (at the GCI or GCI designated laboratory).

Note: Acute blood sample for all hospitalized suspected dengue cases should be collected within the pre-specified timeframe as described above. If this cannot be accomplished, this sample should still be obtained as soon as possible thereafter, for IDMC severity assessment.

9.2.2.3 Safety Assessment Methods

At each visit, the Investigator or a delegate will perform a clinical or medically-driven physical examination, and will ask the subject or legally acceptable representative about any solicited reactions and unsolicited AEs recorded in the DC or MA, 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.

9.2.2.3.1 Immediate Post-vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the 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 occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10

9.2.2.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 (Injection Site Reactions) or Day 14 (Systemic Reactions) After Each Vaccination

After each vaccination, subjects or 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 (ie, D0 to D7) for the solicited injection site reactions and for the next 14 days (ie, D0 to D14) for the solicited systemic reactions, 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 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 to Table 9.3 present the injection site reactions and systemic reactions that are prelisted in the DCs and CRF, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales for Subjects aged 9 to 11 Years

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: 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 or 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 ≥ 12 Years

CRF term (MedDRA lowest level term [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*	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 9.3: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA [LLT])	Fever	Headache	Malaise	Myalgia	Asthenia
DC term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Weakness
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Generalized weakness
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, subjects or 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 or 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/MA, and the highest temperature will be recorded by the site in the CRF. The preferred route for this trial is axillary. Pre-vaccination temperature is also systematically collected by the Investigator in the CRF for subjects aged between 0 and 11 years old, and on the source document for other subjects. Tympanic thermometers must not be used.

9.2.2.3.3 Unsolicited Non-serious Adverse Events From Day 0 to Day 28 After Each Vaccination

In addition to recording solicited reactions, subjects or legally acceptable representatives will be instructed to record any other medical events that may occur during the 28-day period after each vaccination to be taken as per the trial design. Space will be provided in the DC for this purpose.

For each unsolicited non-serious 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 9.3)
  - 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 subject or legally acceptable representative 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 vaccination (for unsolicited systemic AEs)

9.2.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 6 months after the last vaccination.

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.

9.2.2.3.5 Adverse Events of Special Interest

The following AESIs will be considered:

Non-Serious AESIs

- Non-serious hypersensitivity/allergic reactions occurring in all subjects within 7 days after vaccination.

Serious AESIs

- Serious hypersensitivity/allergic reactions occurring in all subjects within 7 days after CYD dengue vaccine injection
- Serious viscerotropic[a] disease occurring in all subjects within 30 days after vaccination CYD dengue vaccine injection
- Serious neurotropic[a] disease occurring in all subjects within 30 days after vaccination CYD dengue vaccine injection
- Serious dengue cases requiring hospitalization[b], occurring in all subjects at any time during the study

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[a] Specific guidelines will be provided to the Investigator to help in the assessment of AEs that may be indicative of viscerotropic or neurotropic disease (see Guidelines for Assessing Viscerotropic and Neurotropic AE).

[b] Meaning hospitalized suspected dengue cases.

9.2.2.3.6 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 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

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, whether serious or not, that persist at the end of the trial will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event.

9.2.3 Methods for Assessing Virological Confirmation of Hospitalized Suspected Dengue Case and Assessment of Disease Severity

In the event of a hospitalized suspected dengue case, the following tests will be performed on the acute blood sample based on the process described below.

Dengue Screen RT-PCR

Dengue screen RT-PCR test will be performed by Sanofi Pasteur GCI, Swiftwater, USA or GCI designated laboratory.

Assessment and quantitation of dengue viremia is determined by testing serum samples with a nucleic-acid based assay. RNA is extracted from the serum to discard potential Taq polymerase inhibitors or interfering factors, using a commercial kit. Then, a RT-PCR is carried out with primers from a gene sequence conserved among dengue viruses. Due to a virus standard included in each run, results can be expressed as a concentration of $\log_{10}$ PFU/mL

Dengue NS1 Ag ELISA

The NS1 Ag ELISA will be performed using a commercially available kit: "Platelia™ Dengue NS1 Ag" from Bio-Rad (Marnes-la-Coquette, France). The manufacturer's instructions are followed. The Dengue NS1 Ag test is a one-step sandwich-ELISA based assay that enables detection of NS1 Ag in serum. The test uses murine monoclonal antibodies (MAbs) for capture and revelation. Samples and controls are directly and simultaneously incubated with the conjugate

[a] ICH Guidelines, Clinical Safety Data Management E2A

within the microplate wells coated with MAb. If NS1 Ag is present in the sample, an immune-complex MAb-NS1-MAb/peroxidase will be formed. The presence of immune-complex is demonstrated by addition of a chromogenic solution that initiates a color development reaction. After 30 minutes of incubation at room temperature, the enzymatic reaction is stopped by addition of an acid solution. The optical density (OD) reading obtained with a spectrophotometer set at 450/620 nm is proportional to the amount of NS1 Ag present in the sample. The presence of NS1 Ag in an individual sample is determined by comparing the OD reading of the sample to the OD of the cutoff control serum.

Sample ratios of < 0.5, ≥ 0.5 to ≤ 1.0, and > 1.0 will be indicative of negative, equivocal, and positive results, respectively.

Simplexa™ Dengue RT-PCR

Serotype identification of post-infectious dengue viremia is determined by testing serum samples with a nucleic-acid based assay. Briefly, RNA is extracted from the serum to discard potential polymerase inhibitors or interfering factors, using a commercial kit. Then the Simplexa dengue RT-PCR assay is carried out which incorporates serotype-specific primers from dengue sequences. The results are expressed qualitatively and reported for each dengue serotype as detected or not detected.

This assay will be used on all DS RT-PCR positive or Dengue NS1 Ag ELISA positive samples for serotype identification. In addition sequencing analysis may be attempted on isolates from the serotyped samples.

Interpretation of Results

If a sample is positive for the dengue screen RT-PCR (ie, $\geq$ LLOQ) and/or the NS1 assay is positive and/or the Simplexa™ dengue RT-PCR is positive, this will be classified as a virologically-confirmed dengue infection (ie, the associated AE will be considered as a hospitalized VCD case).

Hematology – Biochemistry

Hematology and biochemistry parameters (AST, ALT, creatinine, blood cell count, total bilirubin, and hematocrit count) will be measured by local laboratories using standard methods as per routine standard of care in Mexico. However, the measurement of any of these biological parameters may be undertaken (or repeated), based on the Investigator's judgment, to ensure the adequate evaluation of hospitalized VCD case severity. It is noteworthy that hematocrit and platelet counts are required parameters in the WHO/IDMC severity assessment protocol. The results will be collected in the CRF.

The assessment of biological parameters will be: within normal range or outside normal range. Normal ranges for each biological parameter will be provided by the local laboratory and collected in the CRF.

Severity of hospitalized VCD cases

Each hospitalized VCD case will be assessed for severity by an IDMC.

The following potential manifestations of severity in all hospitalized VCD cases will be considered:

1) Platelet count ≤ 100,000 µL *and* bleeding (tourniquet, petechiae or any bleeding) *plus* plasma leakage (effusion on chest x-ray or clinically apparent ascites including imaging procedures or hematocrit ≥ 20% above baseline recovery level or standard for age if only one reading)
2) Shock (pulse pressure ≤ 20 mmHg in a child, or hypotension [≤ 90 mmHg] with tachycardia, weak pulse and poor perfusion)
3) Bleeding requiring blood transfusion
4) Encephalopathy ie, unconsciousness or poor conscious state or fitting not attributable to simple febrile convulsion or focal neurological signs. Poor conscious state or unconsciousness must be supported by Glasgow Coma Scale or Blantyre Coma score
5) Liver impairment (AST > 1000 U/L or prothrombin time International normalized ratio > 1.5)
6) Impaired kidney function (Serum creatinine ≥ 1.5 mg/dL)
7) Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X-ray, echocardiography, electrocardiogram or cardiac enzymes where these are available
8) Every effort must be made to identify and document any existing chronic co-morbidity, such as uncontrolled epilepsy, chronic liver disease, of existing cardiac disease or acute co-morbidity, such as acute hepatitis.

The designation of such cases as severe or otherwise will be made on a case by case basis by the IDMC.

9.2.4 Efficacy

No clinical efficacy data will be obtained in the trial.

9.3 Observational Endpoints and Assessment Methods

There are no observational objectives in this study.

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) and/or the Regional Clinical Trial Manager (RCTM) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA and/or the RCTM 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 SAE Reporting 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, the Global Medical Expert. 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, 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]
- By express mail, to the following address:
    - Sanofi Pasteur
      Global PharmacoVigilance Department
      14, Espace Henry Vallée
      69007 Lyon France

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 "Investigators and Other Important Study Participants" 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 and to the CRA and/or the RCTM. 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.

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 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 may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

The Sponsor's Responsible Medical Officer (RMO) will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators/Sponsor will be responsible for informing the IECs or IRBs that reviewed the trial protocol.

11 Data Collection and Management

11.1 Data Collection and 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 9.2.2.3. These DCs will include prelisted terms and intensity scales (see Table 9.1 to

Table 9.3) as well as areas for free text to capture additional safety information or other relevant details. Subjects or legally acceptable representatives 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 or legally acceptable representatives on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects either during a visit or over the telephone using a questionnaire to capture SAEs and AEs of particular interest, if applicable. A memory aid will be provided to the subjects at the preceding trial visit to help them record information on events occurring between this visit and the 6-month follow-up.

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

The clinical team may decide to replace the memory aid by a DC if a follow-up visit is planned for the subjects.

At specified intervals, the Investigator or an authorized designee will interview the subjects or legally acceptable representatives 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 and pregnancies, which are reported by the Investigator respectively on the eSAE Forms or SAE Reporting Forms and e-Pregnancy 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.

Data Management of SAEs and Pregnancies

During the trial, data pertaining to SAEs reported on eSAE Forms and data pertaining to pregnancies reported in e-Pregnancy form 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. Each SAE case will be assigned a case identification number. Each case will be entered in the GPV database and assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. Assessment of related cases will be done in collaboration with the PSO and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information 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 each database lock.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, at least Version 9.4 (SAS Institute, Cary, NC, USA).

A detailed Statistical Analysis Plan (SAP) will be written before the database lock. In accordance with the protocol, the SAP will describe all analyses to be performed, statistical tables, and listings including descriptions of the analysis conventions used.

In a general way, non-inferiority testing will be performed on dengue-exposed subjects. The tests will be done only if the number of evaluable subjects provides a global power of at least 80% for the co-primary objectives and secondary objective. In case the global power is insufficient to perform non-inferiority testing, only descriptive analyses will be performed.

Only descriptive analyses will be conducted in unexposed subjects and in the overall population.

12.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

12.1.1.1 Hypotheses

Non-inferiority on Cervarix

The objective is to demonstrate that the humoral immune response to the Cervarix administered concomitantly with CYD dengue vaccine is non-inferior to the immune response to Cervarix administered sequentially with CYD dengue vaccine.

Individual hypotheses on Cervarix response for each antigen:

A non-inferiority testing approach will be used to compare geometric mean of titer (GMTs) for the 2 antigens (HPV-16 and HPV-18) 28 days after the last dose of Cervarix, based on the following individual hypotheses:

$$H_0^i : GMT_{Group1}^i / GMT_{Group2}^i \leq \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT_{Group1}^i) - \log_{10}(GMT_{Group2}^i) \leq -\log_{10}(\delta)$$

$$H_1^i : \frac{1}{\delta} < GMT_{Group1}^i / GMT_{Group2}^i > \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT_{Group1}^i) - \log_{10}(GMT_{Group2}^i) > -\log_{10}(\delta)$$

with:

i, antigen (HPV-16 and HPV-18)

δ non-inferiority limit is set at 2, ie, 0.301 (=$\log_{10}$[2]), for each antigen "i"

Non-inferiority for antigen i will be demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) is greater than -δ (α=2.5% one-sided).

Global hypotheses for non-inferiority on Cervarix response

The global hypotheses are:

H_{0G}: Non inferiority of Cervarix co-administered with CYD dengue vaccine versus Cervarix administered sequentially with CYD dengue vaccine is not demonstrated for at least one antigen.

H_{1G}: Non-inferiority of Cervarix co-administered with CYD dengue vaccine versus Cervarix administered sequentially with CYD dengue vaccine is demonstrated for all the antigens.

$$H_0^G : \text{at least one } H_0^i \text{ not rejected}$$

$$H_1^G : \text{all } H_0^i \text{ are rejected}$$

Non-inferiority on CYD Dengue Vaccine

The objective is to demonstrate that the humoral immune response to the CYD dengue vaccine administered concomitantly with Cervarix is non-inferior to the immune response to CYD dengue vaccine administered sequentially with Cervarix.

Individual hypotheses on CYD response for each antigen:

A non-inferiority testing approach will be used to compare GMTs 28 days after the third injection of CYD dengue vaccine between groups for each serotype "i" based on the following individual hypotheses:

$$H_0^i : GMT^i_{Group1} / GMT^i_{Group2} \leq \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT^i_{Group1}) - \log_{10}(GMT^i_{Group2}) \leq -\log_{10}(\delta)$$

$$H_1^i : \frac{1}{\delta} < GMT^i_{Group1} / GMT^i_{Group2} > \frac{1}{\delta} \Leftrightarrow \log_{10}(GMT^i_{Group1}) - \log_{10}(GMT^i_{Group2}) > -\log_{10}(\delta)$$

with:

i, serotypes in {1, 2, 3, 4}

δ non-inferiority limit is set at 2 ie, 0.301 (=$\log_{10}$[2]), for each serotype "i"

Non-inferiority for serotype i will be demonstrated if the lower bound of the 2-sided 95% CI is greater than -δ.

Global hypotheses for non-inferiority on CYD response

$$H_0^G : \text{at least one } H_0^i \text{ not rejected}$$

$$H_1^G : \text{all } H_0^i \text{ are rejected}$$

Overall, non-inferiority among the groups will be demonstrated if, for each antigen of Cervarix and each serotype of CYD dengue vaccine, the 2-sided 95% CIs lie above -δ.

12.1.1.2 Statistical Methods

The non-inferiority test will be performed using the 95% 2-sided CI of the difference of the means of the $\log_{10}$ transformed post- vaccination titers between Group 1 and Group 2 (α=2.5% one-sided). The CI for differences will be calculated using normal approximation of log-transformed titers.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses

Non-inferiority on Cervarix

The objective is to demonstrate that the humoral immune response (in terms of seroconversion) to Cervarix after concomitant administration is non-inferior to sequential administration with CYD dengue vaccine measured 28 days after the last of dose of Cervarix.

A non-inferiority testing approach will be used to compare seroconversion rates for the 2 antigens (HPV-16 and HPV-18) 28 days after the last dose of Cervarix.

The individual tested hypotheses for the antigen "i" will be as follows:

$$H_0^i : P_{Group1}^i - P_{Group2}^i \leq -\delta$$

$$H_1^i : P_{Group1}^i - P_{Group2}^i > -\delta$$

where the non-inferiority limit δ is set at 5% for each antigen "i".

Non-inferiority on CYD dengue vaccine

No statistical hypothesis will be tested on CYD dengue vaccine for secondary objectives.

12.1.2.2 Statistical Methods

Non-inferiority on Cervarix

Non-inferiority for antigen "i" will be demonstrated if the lower bound of the 2-sided 95% CI is greater than -δ.

The non-inferiority test will be performed using the 95% 2-sided CI of the difference between groups (α=2.5% one-sided). The 95% CI will be calculated based on the Wilson score method without continuity correction as quoted by Newcombe for seroconversion rates.

Descriptive analysis on Cervarix and CYD dengue vaccine immunogenicity

No hypotheses will be tested. Immunogenicity point estimates and their 95% CI will be presented for each and any group, at baseline and after each dose of Cervarix and CYD dengue vaccine.

A complementary analysis on CYD dengue vaccine immunogenicity after each dose will be conducted for each and any group according to the dengue status at baseline (dengue immune, dengue non-immune, and all subjects).

The 95% CIs will be calculated using:

- The normal approximate method for GMTs and GMTRs

  Assuming that Log_{10} transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log_{10} (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 geometric means (GMs) and their 95% CI.

- The exact binomial distribution for single proportions (Clopper-Pearson's method, quoted by Newcombe)

Safety

All analyses will be descriptive; no hypotheses will be tested. Safety will be assessed for all after each and any dose of Cervarix and CYD Dengue vaccine. Moreover, a complementary analysis will be performed for each dose of CYD dengue vaccine, for each and any group, according to the dengue status at baseline.

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, quoted by Newcombe) for single proportions.

12.2 Analysis Sets

Three analysis sets will be used: the Per-Protocol Set (PPAS), the Full Analysis Set (FAS), and the Safety Analysis Set (SafAS).

12.2.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as the subset of subjects who received at least one dose of the study vaccine.

The FASE (full analysis set for exposed subjects) is defined as the subset of subjects who were seropositive at baseline and received at least one dose of the study vaccine.

Subjects will be analyzed by the vaccine treatment group to which they were randomized.

12.2.2 Per-Protocol Analysis Set

Two per-protocol analysis sets will be defined: one for Cervarix (PPX) and one for CYD dengue vaccine (PPC). The per-protocol analysis sets are subsets of the FAS.

PPX

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPX:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subjects identified as dengue unexposed (seronegative) at baseline
- Subject is seropositive at baseline for Cervarix (ie, at least one Ab levels against Cervarix HPV antigens > LLOQ at baseline)
- Subject did not complete the vaccination schedule (until V05 for Group 1, V06 for Group 2)
- Subject received a vaccine other than the one that she was randomized to receive (until V05 for Group 1, V06 for Group 2)
- Administration of vaccine was not done as per-protocol (site and route of administration)

- Subject did not receive vaccine in the proper time window (until V05 for Group 1, V06 for Group 2)
- Subject did not provide after the 2nd dose of Cervarix a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn (V05 for Group 1, V06 for Group 2)
- Subject received a protocol-prohibited medication (prohibited therapies/medications/vaccines are indicated in Section 6.7) (until V05 for Group 1, V06 for Group 2)
- Subject's serology sample did not produce a valid test result, ie, no Cervarix antigen titer available

PPC

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPC:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subjects identified as dengue unexposed (seronegative) at baseline
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that she was randomized to receive
- Administration of vaccines was not done as per-protocol (site and route of administration)
- Subject did not receive vaccines in the proper time window
- Subject did not provide after the 3rd dose of CYD dengue vaccine a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn (V08, M13 for Group 1 and M14 for Group 2)
- Subject received a protocol-prohibited medication (prohibited therapies/medications/vaccines are indicated in Section 6.7) (until V07)
- Subject's serology sample did not produce a valid test result, ie, no Neutralizing Ab titers against any of the four parental dengue virus serotypes of CYD dengue vaccine available (at V08, M13 for Group 1 and M14 for Group 2)

12.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccines. All subjects will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at first dose. The safety data will also be presented separately for dengue-exposed and dengue unexposed subjects.

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

Note: Subjects will be included in the "any dose" analysis according to the 1st dose received that correspond to a protocol group.

12.2.4 Other Analysis Set(s)

Randomized subjects

A randomized subject is a subject for whom an injection group has been allocated.

12.2.5 Populations Used in Analyses

The main immunogenicity analyses (non-inferiority tests) will be performed on the PPASs, and will be confirmed on the FASE. In the FASE, subjects will be analyzed by the vaccine group to which they were randomized.

All other immunogenicity analyses will be performed on the FASE and on the FAS. For the complementary analyses, subjects will be analyzed by the vaccine group to which they were randomized.

The safety analyses will be performed on the SafAS. Subjects will be analyzed according to the vaccine they actually received.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

For the computation of GMTs, any titer reported as < LLOQ will be converted to a value of 1/2 LLOQ.

While a single approach was used for GMTs, two different approaches for GMT ratios were applied:

- For Cervarix, < LLOQ will be converted to 1/2 LLOQ
- For CYD dengue vaccine, < LLOQ will be converted to 1/2 LLOQ for a numerator and < LLOQ will be converted to LLOQ for a denominator

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

12.3.3 Efficacy

Not applicable.

12.4 Interim / Preliminary Analysis

Two planned statistical analyses will be performed (after the third CYD dengue vaccine injection, and after the end of the follow-up period).

An interim statistical analysis of the data obtained up to Day 28 post third vaccination (V08) might be performed once data are available and an interim database lock has been conducted. A final analysis will be performed once the 6 month safety data have been collected and the final database lock has occurred.

No statistical adjustment is necessary because there will be no repeated analyses of the primary objective (as the test will be performed at the time of the first analysis).

12.5 Determination of Sample Size and Power Calculation

A total of 480 subjects will be enrolled: 240 subjects in each group.

The reference standard deviations (SD) considered for Cervarix are 0.4 for both HPV-16 and HPV-18 (25) (26).

The reference seroconversion rates for Cervarix were set to 99% for both antigens (25) (26).

The reference SD considered are the following for CYD dengue vaccine: 0.9 for serotype 1, 0.7 for serotypes 2 and 3 and 0.5 for serotype 4 (based on CYD13 and CYD15 efficacy studies conducted in subjects aged 9 to 16 years in Latin American countries).

Considering a potential attrition rate of 15%, such sample size would provide 204 evaluable subjects in the per protocol (PP) population per group. This will give, for the co-primary objectives, a global power of 90.2% and for secondary objectives (in terms of Cervarix seroconversion) a power of 91.8%.

Following Protocol Amendment 1, the number of evaluable subjects may be difficult to achieve (considering only exposed/seropositive subjects at baseline to be included in the Per-Protocol populations). Thus the non-inferiority testing will be done only if the number of evaluable subjects provides a global power of at least 80% for the co-primary objectives and secondary objective ie, if the number of evaluable subjects per group is at least 163 per group for the co-primary objectives and 168 per group for the secondary objective. The power for non-inferiority in terms of GMTs per antigen and serotype is detailed in Table 12.1 and Table 12.2.

This sample size will also provide a 95% probability of observing an AE that has a true incidence of 1.2% in each group.

Table 12.1: Powers for Non-inferiority between GMT for each antigen and serotype

Antigen/Serotype	Alpha	δ	References SD(s)	Power (%) for 204 evaluable subjects per group	Power (%) for 163 evaluable subjects per group
HPV-16	0.025	0.301	0.4	>99.9%	>99.9%
HPV-18	0.025	0.301	0.4	>99.9%	>99.9%
Dengue serotype 1	0.025	0.301	0.9	92.1%	85.3%
Dengue serotype 2	0.025	0.301	0.7	99.1%	97.2%
Dengue serotype 3	0.025	0.301	0.7	99.1%	97.2%
Dengue serotype 4	0.025	0.301	0.5	>99.9%	>99.9%
Power global				90.2%	80.3%

Table 12.2: Powers for Cervarix seroconversion for each antigen

Antigen	Alpha	Δ	Power (%) for 204 evaluable subjects per group	Power (%) for 168 evaluable subjects per group
HPV-16	0.025	5%	95.8%	89.6%
HPV-18	0.025	5%	95.8%	89.6%
Power global				80.4%

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 / assent forms, telephone contact logs, and worksheets. The purpose of trial source documents is to document the existence of subjects and to substantiate the integrity of the trial data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

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

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

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

13.3 Confidentiality of Data and Access to Subject Records

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

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

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

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

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

[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.

After the start of the trial, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject medical files and CRFs. During these visits, the Sponsor/delegate 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 deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the 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 either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

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

13.4.3 Archiving

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

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

Specifically for the subjects identified as unexposed/seronegative at baseline, Sanofi Pasteur will also cover reasonable expenses related to healthcare for dengue illness for 10 years after the last dengue vaccine injection received. Details will be communicated to IEC/IRB, to the Investigator, and to study participants.

13.6 Stipends for Participation

Expenses that are directly related to the subject's participation in the trial (for example cost of transportation for attending visits) will be compensated. Subjects/parents/legally acceptable representatives 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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15 Signature Pages

Sponsor's Signature

I have read the protocol version 2.0 for the study CYD71 and confirm that, to the best of my knowledge, it accurately describes the conduct of the study.

[redacted]

8/Feb/2018
Date

[redacted]

8 Feb 2018
Date