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Version and Date of the Protocol: Version 2.0 dated 04 January 2018

Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially with Adacel® in Healthy Subjects Aged 9 to 60 Years in the Philippines

A phase IIIb, randomized, multicenter, open-label study in 688 subjects aged from 9 to 60 years in the Philippines

Clinical Trial Protocol Amendment 1

WHO Universal Trial Number (UTN):	U1111-1161-3294
Trial Code:	CYD66
Development Phase:	Phase IIIb
Sponsor:	Sanofi Pasteur 14, Espace Henry Vallée, 69007 Lyon, France
Investigational Products:	CYD Dengue Vaccine
Form/Route:	Powder and solvent for suspension for injection/Subcutaneous
Indication For This Study:	Prevention of dengue fever in 9- to 60-year-old subjects
Manufacturer:	Same as Sponsor
Coordinating Investigators:	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.
Principal Investigator:	[redacted]
Project Manager and Study Leader:	
Sponsor's Responsible Medical Officer (Sponsor's Signatory):	

Regional Director of Medical Affairs	[redacted]
Global Safety Officer:	
Clinical Trial Manager:	

Version and Date of the Protocol: Version 2.0 dated 04 January 2018

This protocol version 2.0 is the first amendment to the initial trial protocol version 1.0, dated 17 March 2016.

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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 Adacel® in Healthy Subjects Aged 9 to 60 Years in the Philippines
Development Phase:	Phase IIIb
Principal Investigator:	[redacted]
Trial Centers:	This will be a multi-center trial with approximately 4 trial centers. Investigators and sites will be listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	4Q 2016 to 1Q 2019
Trial Design and Methodology:	Phase IIIb, randomized, open label, multicenter study in 688 healthy subjects aged 9 to 60 years in the Philippines. As per Protocol version 1.0 dated 17 March 2016, subjects were to receive 3 doses of CYD dengue vaccine given 6 months apart, with the first dose administered concomitantly or sequentially with Adacel. Subjects received the first dose of the CYD dengue vaccine either concomitantly or sequentially (i.e., 28 days prior to the first dose of CYD dengue vaccine) with a booster dose of the tetanus (T), reduced-dose diphtheria (D), and 5-component acellular pertussis vaccine (ap), consisting of pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM2+3); Tdap vaccine, known by preferred product trade name Adacel®. Subjects were randomized at the first visit (V01; day 0 [D0]) according to a 1:1 ratio into the 2 groups with stratification on age (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years): • Group 1 (concomitant administration): subjects were administered 28 days later (at the second visit [V02; Month 1 [M1]) with the first dose of CYD dengue vaccine given concomitantly to the dose of Tdap vaccine • Group 2 (sequential administration): subjects were administered with the Tdap vaccine at the first Visit (V01; D0) and the first dose of CYD dengue vaccine was administered 28 days later, at the second visit (V02; M1) Since the CYD dengue is administered according to a 3-dose schedule, given 6 months apart, initial trial design included administration of the second and third doses of CYD dengue vaccine at V04 (Month 7 [M7] and at V06 (M13) in all subjects. All but 19 subjects (from both, Group1 and Group 2) did receive dose 2 of the CYD dengue vaccine as planned. However, changes in the conduct of the study (reason for this Protocol Amendment 1) were triggered following the recommendations issued from an Independent Data Monitoring Committee (IDMC).

	Indeed, new supportive clinical data based on the results of supplemental exploratory analyses confirmed 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") and subjects never exposed to the dengue virus prior to vaccination (referred hereafter as "unexposed subjects"). In light of this results, the IDMC involved in the safety data review of the CYD dengue vaccine clinical development program concluded, in and 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 starting on the third year after the first injection (findings based on follow-up of dengue unexposed subjects having received 3 CYD dengue vaccine doses). The IDMC recommended that no further vaccination occurred in unexposed subjects in ongoing or future trials, and on precautionary basis, including partially vaccinated subjects in ongoing trials. Given the IDMC recommendations, Sanofi Pasteur paused all vaccinations in this study (CYD66) and amended this study protocol. To determine the basal serostatus of the subjects already included in the study, 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 • All subjects will be asked about their willingness to continue participating in this study, and consent will be formalized by signing an ICF and/or AF addendum, as applicable. • Subjects seropositive at baseline will additionally be asked for consent to receive remaining CYD dengue doses. • Subjects seronegative at baseline will be able to continue in the study for safety follow-up if they consent to, but will not receive further injections of CYD dengue vaccine. • Subjects seronegative at baseline who were vaccinated during this study will have timely access to appropriate care in the event of suspected dengue, for 10 years from the date of last dengue vaccination. Time between communication of the results from the exploratory analyses and approval of Protocol Amendment 1 by the competent authorities and for the associated logistic tasks will result into a hold of study activities of several months (approximately 4-6 months). Study-hold intervenes after V03, V04 or V05, depending on each subject's visit-calendar at the time of study-hold (see table below). In order to communicate to each subject his/her dengue serostatus at baseline, there will be either 1 unscheduled visit or phone call during the study-hold before the next visit initially planned (V06 at the latest): The subject will consent to continue participation in the study by signing an ICF/AF addendum 1 at subject's next planned visit (either V04, V05 or V06). Thus, dose 2 and 3, or dose 3 only (provided that dose 2 was received, as planned) will be administered selectively to those subjects dengue seropositive at baseline who consent continue participation in the study and consent receiving the remaining CYD dengue doses planned.

For all subjects who received at least 1 dose and who consent to continue participation in the study, a 6 month safety follow up is planned. This period will start after the last CYD dose the subject received (whether 1, 2 or 3 doses).

At the time vaccinations were paused, subjects already provided 2 or 3 blood samples (BL), depending on their allocation group. Only dengue-exposed subjects who will continue in the study and choose to receive remaining CYD dengue doses will provide 1 subsequent BL, as initially planned in Protocol version 1.0.

The following table summarizes those study procedures (visits, vaccine injections and blood sampling) that were carried out as per protocol version 1.0 before Protocol amendment 1 and those paused (study hold) and planned during the study.

Visit Number	**V01**	**V02**	**V03**	**V04‡**	**V05‡**	**V06‡**	**V07‡**
				Unscheduled visit / phone call† study-hold			
Timelines	**D0**	**M1**	**M2**	**M7**	**M8**	**M 13**	**M14**
Status at study-hold	**Finished**	**Finished**	**Finished**	**Paused (finished for some subjects)**	**Paused (finished for some subjects)**	**Planned**	**Planned**
Group 1		Blood sample Adacel® + CYD dengue vaccine dose 1	Blood sample Safety data collection	CYD dengue vaccine dose 2	Safety data collection	CYD dengue vaccine dose 3	Blood sample Safety data collection
Group 2	Blood sample Adacel®	Blood sample CYD dengue vaccine dose 1	Blood sample Safety data collection	CYD dengue vaccine dose 2	Safety data collection	CYD dengue vaccine dose 3	Blood sample Safety data collection

BL: blood sample
CYD and Tdap were be administered at 2 different sites, with the CYD dengue vaccine administered in one deltoid and Tdap in the other deltoid

†All subjects will attend an unscheduled visit or have an unscheduled phone call after the hold of activities and before their next scheduled visit to be informed about their dengue serostatus at baseline.

‡ V04 and/or V05 (if they were not carried out) and V06 and V07 will take place, for those subjects dengue seropositive at baseline who consent continue participation in the study and consent administration of remaining CYD dengue doses. All other subjects will not attend their next scheduled visit unless it is to provide consent to study continuation.

Additional BL may be drawn for virological confirmation of hospitalized suspected dengue case during the duration of the trial.

For the 2 vaccines, 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 AEs (SAEs) will be reported throughout the study (from inclusion until 6 months after the last injection). Serious and non-serious AEs 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 Independent Data Monitoring Committee (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 Ethic Committees (IECs)/Institutional Review Boards (IRBs), or the governing regulatory authorities in the Philippines 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:	***Tdap immunogenicity*** • To demonstrate the non-inferiority of the humoral immune response to the Tdap booster dose concomitantly administered with the first dose of CYD dengue vaccine as compared to sequential administration, measured 28 days after Tdap booster dose* ***CYD dengue vaccine immunogenicity*** • To demonstrate the non-inferiority of the humoral immune response to the first dose of CYD dengue vaccine concomitantly administered with Tdap as compared to sequential administration, measured 28 days after the first dose of 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:	***Tdap immunogenicity*** • Antibody (Ab) concentrations against pertussis antigens (PT, FHA, PRN, FIM2+3) as measured by enzyme-linked immunosorbent assay (ELISA), 28 days after the dose of Tdap vaccine • Seroprotection against D and T, defined as anti-D and anti-T Ab concentrations ≥ 0.1 international units (IU)/mL, as measured by ELISA for T and by Diphtheria Micrometabolic Inhibition Test - Toxin Neutralization assay (MIT-TNA) for D, 28 days after the dose of Tdap vaccine ***CYD dengue vaccine immunogenicity*** • Neutralizing Ab titers against each of the 4 dengue serotypes, as measured

	by dengue 50% plaque reduction neutralization test ($PRNT_{50}$), 28 days after the first dose of CYD dengue vaccine
Secondary Objectives:	***CYD dengue vaccine Immunogenicity:*** • To demonstrate the non-inferiority of the humoral immune response of 3 doses of CYD dengue vaccine with the first dose concomitantly administered with Tdap as compared to sequential administration, measured 28 days after the third dose of CYD dengue vaccine* • To describe the humoral immune response at baseline and 28 days after the first and third doses of CYD dengue vaccine, in each and any group ***Tdap Immunogenicity:*** • To describe the humoral immune response of Tdap vaccine at baseline and 28 days after concomitant administration with the first dose of CYD dengue vaccine as compared to the sequential administration, in each and any group ***Safety*** • To describe the safety of the CYD dengue vaccine and of the Tdap booster dose after each and any injection in each group ** Providing that the number of evaluable seropositive subjects allows a global power of at least 80% (otherwise analyses will be descriptive)*
Secondary Endpoints:	***CYD dengue vaccine immunogenicity*** • Neutralizing Ab titers against each of the 4 dengue serotypes, as measured by dengue $PRNT_{50,}$ at baseline (M1) and 28 days after the first and third doses of CYD dengue vaccine • Neutralizing Ab titers ≥ 10 1/dil against each of the 4 dengue serotypes and against at least 1, 2, 3, or 4 dengue serotypes, as measured by dengue $PRNT_{50,}$ at baseline (M1) and 28 days after the first and third doses of CYD dengue vaccine • Neutralizing Ab titers ≥ different thresholds (1/dil) against each of the 4 dengue serotypes, as measured by dengue $PRNT_{50,}$ at baseline (M1) and 28 days after the first and third doses of CYD dengue vaccine ***Tdap immunogenicity*** • Ab concentrations against PT, FHA, PRN, and FIM2+3, as measured by ELISA, at baseline (D0 for Group 2, M1 for Group 1) and 28 days after the dose of Tdap vaccine • Anti-T and anti-D Ab concentrations ≥ 0.1 IU/mL, as measured by ELISA for T and by MIT-TNA for D, at baseline (D0 for Group 2, M1 for Group 1) and 28 days after the dose of Tdap vaccine ***Safety*** *Tdap and CYD dengue vaccine safety in each group* • Occurrence of immediate AEs reported in the 30 minutes after each/any injection • Occurrence of solicited (i.e., pre-listed in the subject's diary card [DC] and electronic case report form [eCRF]) injection site reactions (pain, erythema, and swelling) within 7 days following each/any injection • Occurrence of solicited systemic reactions (fever, headache, malaise, myalgia, and asthenia) occurring up to 14 days following each/any injection • Occurrence of unsolicited (spontaneously reported) AEs within 28 days following each/any injection

	• Occurrence of non-serious AESIs* occurring within 7 days following each and any vaccination • 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 (i.e., from D0 through the 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 (i.e., hospitalized suspected dengue case) occurring in all subjects at any time during the study ** Subjects from Group 1 will not be vaccinated at V01 but will receive the first vaccinations at V02. However, SAEs will be recorded from inclusion and subjects from Group 1 will receive a SAE-specific DC at V01 that will be collected at V02. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome. 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 hospitalized suspected case will be considered VCD if there is a detection of wild type (WT) dengue virus by dengue non-structural protein 1 (NS1) antigen (Ag) 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:	As per Protocol version 1.0 , a total of 688 subjects were planned to be enrolled: Group 1: n = 344 (86 subjects per age group) Group 2: n = 344 (86 subjects per age group) ***As per Protocol Amendment 1***, only dengue-exposed subjects prior to vaccination will be eligible to continue and complete dengue study vaccination schedules.

Schedule of Study Procedures:	The study procedures (Visits, vaccinations and BLs) are summarized in the Table presented in the Trial Design and Methodology section. ***Visits/phone call:*** As per Protocol version 1.0, all subjects attended 3 visits (V01 to V03), and some subjects attended 4 or 5 visits (V01 to V04, or V01 to V05, respectively). All subjects had 1 interim phone call approximately 3 months after the first dose of the CYD dengue vaccine. *Upon implementation of Protocol Amendment1:* • All subjects will attend an unscheduled visit or have an unscheduled phone call after the hold of activities and before their next scheduled visit to be informed about their serostatus at baseline. • All subjects who consent to continue in the study will attend their next scheduled visit to sign the ICF/AF addendum1. • All subjects who consent continue participation in the study will receive a 6 months follow up "safety phone call" 6 months after their last vaccine dose received. • Seropositive subjects who consent to continue participation in the study and consent to receive remaining CYD dengue doses will attend their next planned visits and have interim phone calls as initially planned (per protocol version 1.0); ie, 7 planned visits overall; V01 to V07, and 2 more interim phone calls during the 6-month period after dose 2 and dose 3 of the CYD dengue vaccine (approximately 3 months after each vaccine injection). ***Vaccination:*** As per Protocol version 1.0, all subjects, depending on the group they were randomized to, received the first dose of the CYD dengue vaccine and the booster dose of Tdap as follows: • Group 1: subjects were administered the first dose of CYD dengue vaccine concomitantly with the booster dose of Tdap vaccine at the second visit (V02; M1) • Group 2: subjects received Tdap vaccine at the first visit (V01; D0), and then CYD dengue vaccine 28 days later at the second visit (V02; M1) All but 19 subjects (both, from Group 1 and from Group 2) received the dose 2 of the CYD vaccine at V04 (M7), as planned. *Upon implementation of Protocol Amendment1:* Only seropositive subjects who provide consent to continue participation in the study and to receive remaining CYD doses will be administered dose 2 (applicable to subjects who did not receive dose 2 yet), and dose 3 of the CYD dengue vaccine, as initially planned. All other subjects will not receive remaining CYD dengue doses. ***Blood Sampling:*** As per Protocol version 1.0, all subjects provided 2 (Group 1) or 3 (Group 2) BLs before the study hold. Note that in Group 2 the BL 28 days after Tdap vaccination corresponds to the BL prior to the first dose for CYD dengue vaccine. *Upon implementation of Protocol Amendment1:* Only seropositive subjects who consent to continue participation in the study and to receive further CYD dengue doses will provide 1 more BL, as initially planned.

	Individual samples will not exceed 6 mL: • for Tdap immunogenicity assessments (2 mL) before the first vaccination (D0 for Group 2 and M1 for Group 1) and 28 days after vaccination with Tdap vaccine (M1 for Group 2 and M2 for Group 1) • for CYD dengue vaccine immunogenicity assessments (4 mL) before the first vaccination (M1 for both groups) and 28 days after the first and third vaccinations with CYD dengue vaccine (M2 and M14 for both groups) Additional blood samples might be collected: • In case of hospitalized suspected dengue case, one unplanned BL (=acute BL, of approximately 3 mL) will have to be collected within the first 5 days after fever onset for virological confirmation of dengue disease. • In case of SAEs (including AESI). • To assess AEs that may be indicative of viscerotropic or neurotropic disease (see Guidelines for Assessing Viscerotropic and Neurotropic AE). ***Urine sampling:*** All female subjects of childbearing potential will provide urine samples for urine pregnancy test before each injection.
Duration of Participation in the Trial:	For seropositive subjects who consent continue participation in the study and administration of remaining CYD dengue doses, due to period of study-hold, the duration of each subject's participation in the trial will be approximately 23-25 months, since it will be extended by 4-6 months with respect to the initial plan (ie, as per protocol version1.0: approximately 19 months, including a vaccination phase of 12 months for subjects in Group 1 and 13 months for subjects in Group 2, followed by a safety follow-up period of 6 months after the third injection of CYD dengue vaccine). For seropositive subjects who consent continue participation in the study but refuse to receive remaining CYD dengue doses and seronegative subjects who provide their consent to continue participation in the study, their participation in the trial will be less than 19 months as initially planned. (i. e., taking into account the study-hold and the 6 months safety follow up Subjects declining continue participation in the study will end the study on the date this decision is communicated to the Sponsor.
Investigational Product:	**CYD Dengue Vaccine**
Form:	Powder and solvent for suspension for injection.
Composition:	Each 0.5 mL dose of reconstituted vaccine contains: ***Active Ingredients:*** 4.5 – 6 $\log_{10}$ cell-culture infectious dose 50% (CCID50) of each live, attenuated, recombinant dengue virus serotype 1, 2, 3, 4 ***Excipients:*** Essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminomethane, and urea. ***Solvent:*** NaCl 0.4%.
Route:	Subcutaneous (SC)
Batch Number:	TBD

Other Product:	**Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Adacel®, referred to in this protocol as Tdap)**
Form:	Vial presentation
Composition:	Each 0.5 mL dose is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain the following active ingredients: ***Active Ingredients:*** 5 Lf tetanus toxoid 2 Lf diphtheria toxoid 2.5 µg pertussis toxoid 5 µg filamentous hemagglutinin 3 µg pertactin 5 µg fimbriae types 2 and 3 ***Excipients:*** 1.5 mg aluminum phosphate (adjuvant) 0.6% v/v 2-phenoxyethanol
Route:	Intramuscular (IM)
Batch Number:	Commercial Batch
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Subject aged 9 to 60 years (i.e., from the day of the 9th birthday to the day prior to the 61th birthday) on the day of inclusion 2) Subject in good health, based on medical history and physical examination 3) 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) 4) For subject aged 9 to 11 years: known (documented) receipt of at least 4 previous doses of diphtheria toxoid, tetanus toxoid and acellular pertussis-containing (DTaP) vaccines, with the last dose not within the last 5 years prior to enrolment OR For subject aged at least 12 years: known (documented or self-reported) receipt of at least 3 previous doses of diphtheria toxoid, tetanus toxoid, and whole cell pertussis-containing (DTwP) vaccines, with the last dose not within the last 5 years prior to enrolment 5) Subject (or subject and parent[s]/legally acceptable representatives) able to attend all scheduled visits and to comply with all trial procedures
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination 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 CYD dengue vaccine 5) Receipt of immune globulins, blood or blood-derived products in the past 3 months, which might interfere with assessment of the immune response 6) 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 corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months) 7) A previous severe reaction to pertussis, diphtheria or tetanus vaccine including immediate anaphylaxis, encephalopathy within 7 days or seizure within 3 days of receiving the vaccine 8) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances 9) Thrombocytopenia, contraindicating intramuscular vaccination 10) Bleeding disorder or receipt of anticoagulants within 3 weeks preceding inclusion, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator 11) Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily 12) Current alcohol abuse or drug addiction that, based on Investigator's judgment, may interfere with the subject's ability to comply with trial procedures 13) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion 14) Identified as an Investigator or employee of the Investigator with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study 15) Self-reported Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection 16) Personal history of Guillain-Barré syndrome **Temporary Exclusion Criteria** A prospective subject should not be included in the study until the following condition 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 trial inclusion

Statistical Methods:	**Non inferiority testing will only be carried out with seropositive subjects and providing that the number of evaluable subjects attains a global power of at least 80%. This applies to the co-primary objectives, and the secondary objective. Otherwise, descriptive analyses will be performed.** **Primary Objectives:** ***Tdap immunogenicity*** A non-inferiority testing approach will be used to compare geometric mean concentrations (GMCs) for PT, FHA, PRN, FIM2+3, 28 days after the booster dose of Tdap, for each antigen "i" based on the following individual hypotheses: $H_0^i: GMC^i_{Group1} / GMC^i_{Group2} \leq \frac{1}{\delta} \Leftrightarrow \log_{10}(GMC^i_{Group1}) - \log_{10}(GMC^i_{Group2}) \leq -\log_{10}(\delta)$ $H_1^i: GMC^i_{Group1} / GMC^i_{Group2} > \frac{1}{\delta} \Leftrightarrow \log_{10}(GMC^i_{Group1}) - \log_{10}(GMC^i_{Group2}) > -\log_{10}(\delta)$ with: i, antigen {PT, FHA, PRN, FIM 2+3}. δ, non-inferiority limit is set at 1.5, i.e., 0.176 (=$\log_{10}$ [1.5]), for each antigen "i". Non-inferiority for antigen "i" will be demonstrated if the lower bound of the 2-sided 95% CI is greater than -δ. For each of the 4 antigens, the statistical methodology will be based on the use of the age-stratified two-sided 95% CI of the ratio of GMCs between groups. The age-stratified CI will be calculated using an ANOVA model (type II analysis) of $\log_{10}$-transformed titers. The age groups (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years) will be used as the stratifying factor in the model. Additionally, a non-inferiority testing approach will be used to compare seroprotection rates of T and D, 28 days after the booster dose of Adacel®. Seroprotection is defined as anti-D and anti-T Ab concentration superior to 0.1 IU/mL. 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 10% for both T and D concentrations ≥ 0.1 IU/mL. 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 seroprotection rates and of the differences of the means of the $\log_{10}$ transformed post-vaccination concentrations/titers for GMCs (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 seroprotection rates and using the normal approximation of the $\log_{10}$ transformed post-vaccination titers for GMCs. ***CYD dengue vaccine immunogenicity*** A non-inferiority testing approach will be used to compare geometric mean titers (GMTs), for dengue serotypes 1, 2, 3, and 4, 28 days after the first injection of CYD dengue vaccine between Group 1 and Group 2 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, i.e., 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 two-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. Overall, non-inferiority among the groups will be demonstrated if, for each antigen of Tdap and each serotype of CYD dengue vaccine, the two-sided 95% CI lies above - δ. **<u>Secondary Objectives</u>** ***CYD dengue vaccine immunogenicity (non-inferiority analysis)*** A non-inferiority testing approach will be used to compare GMTs (dengue serotypes 1, 2, 3, and 4) 28 days after 3 injections of CYD dengue vaccine between Group 1 and Group 2 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, i.e., 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 two-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. Overall, non-inferiority among the groups will be demonstrated if, for each antigen of Tdap and each serotype of CYD dengue vaccine, the two-sided 95% CI lies above - δ. ***Descriptive analysis on CYD dengue vaccine and Tdap vaccine immunogenicity*** No hypotheses will be tested. Immunogenicity point estimates and their 95% CI will be presented for each and any group, before and after the first and third injections for CYD dengue vaccine and before and after the booster vaccination for Tdap. A complementary analysis on CYD dengue vaccine and Tdap vaccine immunogenicity after each dose will be conducted for each and any group according to the age groups (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years). 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. The 95% CIs will be calculated using: • The normal approximate method for GMCs/GMTs and geometric mean of concentration ratios [GMCRs]/geometric mean of the titer ratios [GMTRs]

	Assuming that log_{10} transformation of the titers/concentrations follows a normal distribution, at first, the mean and the 95% CI will be calculated on log_{10} (titers/concentrations) 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 and their 95% CI using: • The exact binomial distribution for percentages (Clopper-Pearson's method, quoted by Newcombe) In addition, the booster response against pertussis components (PT, FHA, PRN, and FIM2+3) will be calculated based on Ab concentration rises between pre- and post-vaccination defined as: • A post-vaccination Ab concentration ≥ 4 x the lower limit of quantification (LLOQ) when pre-vaccination concentration is < LLOQ • A post-vaccination Ab concentration ≥ 4 x pre-vaccination Ab concentration when pre-vaccination concentration is ≥ LLOQ but < 4 x LLOQ • A post-vaccination Ab concentration ≥ 2 x pre-vaccination Ab concentration when pre-vaccination concentration is ≥ 4 x LLOQ ***Safety*** All analyses will be descriptive; no hypotheses will be tested. Safety will be assessed for all subjects after the booster dose of Tdap vaccine and after each and any dose of CYD dengue vaccine. A complementary analysis will be conducted for each group according to the age groups (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years). A complementary analysis after each and any dose of CYD dengue vaccine will be conducted 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) for proportions. **<u>Calculation of Sample Size:</u>** A total of 688 subjects will be enrolled: 344 subjects per treatment group (86 subjects per age group). Considering a potential attrition rate of 10%, it was initially planned that such sample size would provide 618 evaluable subjects in the Per-Pprotocol population of Tdap and CYD dengue vaccine. This sample size (based on SAS proc Power) targeted a global power over 90.0% for the non-inferiority testing corresponding to the co-primary objectives (i.e., after the booster dose of Tdap and after the first dose of CYD), and over 99.0% for the non-inferiority corresponding to the secondary objective (ie, testing after the third dose of CYD dengue vaccine) However, as per protocol amendment 1, the number of evaluable subjects will be reduced since only dengue seropositive subjects will be included in the Per-Protocol populations. Thus, the non-inferiority testing will be carried out only if a global power of at least 80% for the co-primary objectives and secondary objective can be attained (i.e., if the number of evaluable subjects is at least 510 for the co-primary objectives and 324 for the secondary objective). The following assumptions were considered for the non-inferiority of Tdap: an alpha level of 2.5% (one-sided hypotheses), a maximum acceptable difference of 0.176 for GMCs and of 10% for seroprotection rates, and the following rates and standard deviations (SDs):

	• T ≥ 0.1 IU/mL – 99% of subjects • D ≥ 0.1 IU/mL – 99% of subjects • PT SD – 0.4 • FHA SD– 0.4 • PRN SD – 0.5 • FIM2+3 SD – 0.6 (Based on TD519, TD506 and TD526 studies and on Keith S. Reisinger). The following assumptions were considered for the non-inferiority after the first dose of CYD dengue vaccine: an alpha level of 2.5% (one-sided hypotheses), a maximum acceptable difference of 0.301 for GMTs, and a SD of 1.0 for serotype 1, 0.8 for serotypes 2 and 3, 0.7 for serotype 4 (based on CYD22 and CYD47 studies conducted in Asia Pacific). The following assumptions were considered for the non-inferiority after the third dose of CYD dengue vaccine: an alpha level of 2.5% (one-sided hypotheses), a maximum acceptable difference of 0.301 for GMTs, and a SD of 0.8 for serotypes 1 and 2, 0.7 for serotypes 3 and 4 (based on studies conducted in Asia Pacific). This sample size will also provide a 95% probability of observing an AE that has a true incidence > 0.87% in each group (N=344per group). **Interim analysis:** Two or three planned statistical analyses will be performed: • A first interim statistical analysis will be performed on results obtained after a partial database lock of data collected up to the 28 days post first dose of CYD dengue vaccine (V03; M2). • A second interim analysis might be performed on results collected up to the 28 days after the third dose of CYD dengue vaccine (V06; M13). • The final analysis will be performed on data collected at the end of the study. No statistical adjustment is necessary because there will be no repeated analyses of the primary objectives (as the primary tests will be performed at the time of the first statistical analysis).

Table of Study Procedures

Initial design: Phase IIIb Trial, 4 Vaccinations, 7 Visits and 3 or 4 Blood Samples (depending on group allocation), 19 Months Duration Per Subject. One Safety Follow-up Phone Call (PC) will be given 6 months after the last injection and 3 Interim phone calls will be given during the 6-month period after each CYD dengue vaccine injection (approximately 3 months after vaccination). Modifications introduced as per this protocol amendment 1 are included in this table.

Visit Number (V)	V01††††	V02††††	V03††††	V04‡‡‡‡	V05‡‡‡‡	V06‡‡‡‡	V07‡‡‡‡	Phone call**
Trial Timelines* (Days/Months)	D0	M1 (V01+28D)	M2 (V02+28D)	M7 (V02 +6 months)	M8 (V04+28D)	M13 (V02 +12 months)	M14 (V06+28D)	
Time Windows (Days)		+14	+14	±20	+14	±20	+14	+30
Intervening study-hold & Protocol Amendment1 preparation/implementation				*study-hold*				
Unscheduled Visit/Phone call****				*X*				
Assent or Informed Consent Addendum 1 at next planned visit after study-hold§§§§				*X (= V04, V05 or V06)*				
Assent or Informed Consent Protocol version1.0	X							
Inclusion/Exclusion Criteria	X	X (Group 1)						
Contraindication	X (Group 2)	X		X		X		
Contraindication at next planned visit after study-hold§§§§				*X (=V04, V05 or V06)*				
Significant Medical History	X							
History of Dengue Infection/Vaccination	X							
Temperature	X (Group 2)	X		X		X		
Physical Examination†	X	X	X	X	X	X	X	
Urine Pregnancy Test ‡	X (Group 2)	X		X		X		
Demography/Body Stature	X							
Randomization	X							
Blood Sampling (BL) for Immunogenicity ††								
T, D, PT, FHA, PRN, and FIM2+3	BL (Group 2)	BL	BL (Group 1)					
Dengue Serotypes 1, 2, 3, and 4		BL	BL				BL	

Visit Number (V)	V01††††	V02††††	V03††††	V04‡‡‡‡	V05‡‡‡‡	V06‡‡‡‡	V07‡‡‡‡	Phone call**
Tdap Vaccination §	**X (Group 2)**	**X (Group 1)**						
CYD dengue Vaccination §		**Dose 1**		**Dose 2**		**Dose 3**		
Post-injection phone calls (PC)**	Interim phone calls during the 6-month period after each CYD dengue vaccine injection; Last phone call 6 months after the last injection**							
30-Min. Observation Period	X (Group 2)	X		X		X		
Injection Site and Systemic Events Collected‡‡‡		X (Group 2)	X	X	X	X	X	
Diary Card (DC) **DC Provided**	X (Group 1 for SAE only, and Group 2)	X		X		X		
DC Collected		X		X		X	X	
Memory Aid (MA) **MA Provided** **MA Provided at next planned visit after study-hold§§§§**							X *X (=V04, V05 or V06)*	
MA Checked								X
Concomitant Therapy‡‡	X	X	X	X	X	X	X	
Telephone Contact								X
Blood Sampling (BL) for virological confirmation of hospitalized suspected dengue case§§	All acute febrile illness with diagnosis of hospitalized suspected dengue case within the first 5 days after fever onset, anytime throughout the trial period							
SAEs and AESIs collected***	Throughout the trial period (for SAEs) or in defined time windows according to the type of AESIs							
Termination Record§§§							X	

AESI: AE of special interest; BL: blood sample; D: Day;; M: Month; MA: Memory Aid; SAE: Serious adverse event; V: Visit

* Timelines must be calculated based on the date of vaccination, not the date of visit. Vaccinations and associated or subsequent procedures may be out of the defined time-windows in dengue-immune subjects continuing the study due to the pause of vaccine injections (as per Protocol Amendment 1).

** Interim phone calls during the 6-month period after each CYD dengue vaccine injection; 3 months after Visit 2 (PC1: M4 [M1 + 3 months]) already carried out at the time of protocol Amendment 1; 3 months after Visit 4 (PC2: M10 [M7 + 3 months], and 3 months after Visit 6 [PC3: M16 M13 + 3 months] will be made to subjects receiving, respectively, dose 2 and Dose 3 of the CYD dengue vaccine. The last PC will be held 6 months after the last CYD dose the subject received (whether 1, 2 or 3), provided the subject consents to continue in the study.

† Physical examination will be performed if necessary, based on the health status of the subject.

‡ For female subjects of childbearing potential (e.g., a female subject who has reached menarche).

§ CYD and Tdap will be administered in 2 different sites, with the CYD dengue vaccine administered in one deltoid and Tdap in the other deltoid

‡‡ Concomitant therapy and ongoing medication will be collected for Days 0–28 after each injection only

†† Blood samples planned during vaccination visits will be taken before vaccination

‡‡‡ 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.

§§ In such case, 1 unplanned acute blood sample (approximately 3 mL) will be collected for virological confirmation of hospitalized suspected dengue case

*** 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 within 30 days after each CYD dengue vaccine injection, serious dengue cases requiring hospitalization (hospitalized VCD case) will be reported during the entire study).

§§§ Termination form will be completed.

**** All subjects will either attend an unscheduled visit or have an unscheduled phone call after the hold of activities and before their next scheduled visit.

†††† All participants carried out V01-V03 before the start of the study-hold and implementation of Protocol Amendment 1

‡‡‡‡ V04 and/or V05 (if they were not carried out) and V06 and V07 will take place for those subjects dengue seropositive at baseline who consent continue participation in the study and consent administration of remaining CYD dengue doses. All other subjects who consent to continue in the study will only attend their next planned visit after study-hold (whether V04, V05 or V06).

§§§§ ICF/AF Addendum 1 signature, contraindications check and MA delivery at next planned visit (whether V04, V05 or V06) applies to subjects seropositive who consent continue participation in the study and refuse administration of remaining CYD dengue doses, and seronegative subjects who consent continue in the study.

List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AF	assent form
Ag	antigen
ALT	alanine transaminase
ap	acellular pertussis
AR	adverse reactions
AST	aspartate aminotransferase
BL	blood sample
$CCID_{50}$	cell-culture infectious dose 50%
CDM	clinical data management
CI	confidence interval
C&MQO	Clinical and Medical Quality Operations department
CRA	clinical research associate
CTA	clinical trial agreement
CLT	clinical teal leader
d	diphtheria
D	day
DC	diary card
dil	dilution
DF	dengue fever
DHF	dengue hemorrhagic fever
DSS	dengue shock syndrome
eCRF	electronic case report form
EDC	Electronic Data Capture
ELISA	enzyme-linked immunosorbent assay
EU	ELISA unit
FAS	full analysis set
FHA	filamentous hemagglutinin
FIM	fimbriae
FV	flavivirus
FVFS	first visit, first subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice

GM	geometric mean
GMC	geometric mean of concentration
GMCR	Geometric mean of concentration ratio
GMT	geometric mean of titer
GMTR	Geometric mean of the titer ratio
GPV	Global PharmacoVigilance
HIV	human immunodeficiency virus
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IRB	Institutional Review Board
LLOQ	lower limit of quantitation
LLT	lowest level term
LVLS	last visit of last subject
M	month
MA	memory aid
MedDRA	Medical Dictionary for Regulatory Activities
MIT-TNA	Micrometabolic Inhibition Test - Toxin Neutralization assay
mL	milliliter
NSAID	non steroidal anti-inflammatory drug
NS1	non-structural protein 1
PC	Phone call
PFU	plaque-forming unit
PPT	per-protocol analysis set for Tdap
PPC	per-protocol analysis set for CYD dengue vaccine
PPAS	per-protocol analysis set
PRN	Pertactin
$PRNT_{50}$	50% plaque reduction neutralization test
PSO	Product Safety Officer
PT	pertussis toxoid
RCTM	Regional Clinical Trial Manager
RMO	Responsible Medical Officer
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan

SafAS	safety analysis set
SC	subcutaneous
SET	safety evaluation team
SMT	safety management team
T	tetanus
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 CYD dengue vaccine when administered concomitantly or sequentially with a single booster dose of the tetanus (T), reduced-dose diphtheria (D), and 5-component acellular pertussis vaccine (ap), consisting of pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM2+3); known by preferred product trade names ADACEL®/Adacel®/COVAXIS®/Triaxis®/TRIAXIS®, and further referred to as Tdap in this document.

Dengue

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 (DF) 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.

Tetanus

Tetanus is an acute and often fatal infection caused by an extremely potent neurotoxin produced by a bacterium, *Clostridium tetani*, which is most commonly found in the soil. The disease is not communicable but is acquired through environmental contamination of flesh wounds by the bacteria which can lead to disease characterized by severe, painful muscle contractions accompanied by hypersensitivity, hyperreflexia, and increased autonomic stimulation of the affected body part(s). Complications associated with tetanus include laryngospasms, spinal and long bone fractures, and hypertension.

Diphtheria

Diphtheria is an acute infection caused by toxin-producing strains of the bacterium *Corynebacterium diphtheriae,* which can be transmitted from person to person via respiratory droplets. The main site of infection is the upper respiratory tract presenting as a sore throat often with a mild fever. Complications associated with severe diphtheria include airway obstruction, myocarditis, and aparalysis. The case fatality rate is as high as 30-95%, despite modern medical care.

Pertussis

Pertussis (whooping cough) is a highly contagious disease of the respiratory tract caused by the bacterium *Bordetella pertussis*, which is transmitted by the respiratory route. The illness is characterized by several coughing spasms, which may or may not be associated with classic inspiratory ‘whooping’. In severe disease, the coughing spasms can vary in length and severity but may become so severe, that respiration is compromised leading to hypoxia and even subsequent neurological damage. Pneumonia may also occur in severe cases. Although pertussis is most severe and complications most frequent in children < 1 year of age, pertussis can affect persons of any age. Antimicrobial therapy is effective in treating disease but does not alter progression of disease unless administered early when pertussis is rarely suspected, thus disease control is based on vaccine prophylaxis.

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, 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 EMA guidelines has been conducted (5), 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, a total of 4903 subjects aged 12 months-45 years were enrolled to 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 year olds has been completed in 2012. Subjects from CYD23 were followed for safety in a long-term follow-up study (CYD57) for a total of 5 years post-dose 3.
- In Phase III trials, a total of 23,140 subjects aged 9 months to 60 years 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 (6) and CYD15 (7) conducted in Asia Pacific (10,275 subjects aged 2 to 14 years) and Latin America (20,869 subjects aged 9 to 16 years) respectively, have completed the 25-month active phase and the 1st year of the Hospital Phase of the 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 (8). To include the totality of efficacy studies (CYD14, CYD15) analyzed over the 25 month 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 was performed with improved point estimate precision for descriptive outcomes (6). Consistent VE was demonstrated during the 25-month 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) 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 (6). No safety issues have been identified in subjects 9-16 years of age during the 25 month active period or during the first year of long term follow-up in the Hospital Phase (6) (7) (9). This included no observed increase in dengue disease severity compared to the placebo group (6).

In interim results of the long term follow-up, for the first year (year 3) of the Hospital Phasepooled efficacy results demonstrated a continued benefit in subjects who were 9 years and above with lower risk of hospitalized VCD, RR 0.50 in the vaccine compared to the placebo group. All subjects who were hospitalized due to dengue fully recovered after receiving appropriate supportive treatment. However, in CYD14, in the first year of the Hospital Phase (year 3), the relative risk 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 1.58; in particular in the 2 to 5 years old age group.

Up to November 2016, a total of 28 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 to 60 years of age. Of these subjects, 21,215 were aged 9 through to 60 years and received at least 1 dose of CYD dengue vaccine formulation. Furthermore, the CYD dengue vaccine has demonstrated a consistent and acceptable safety profile, comparable with placebo during its clinical development 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.

Considering the totality of the efficacy and safety of CYD dengue vaccine studies, a favorable benefit-risk ratio supports the claimed indication for the prevention of dengue disease caused by all 4 serotypes in individuals 9 to 60 years of age living in endemic regions.

As of October 2017, the CYD dengue vaccine (commercial name Dengvaxia®) has been licensed in 19 countries (in alphabetical order): Argentina, Australia, Bangladesh, Bolivia, Brazil, Cambodia, Costa Rica, El Salvador, Guatemala, Honduras, Indonesia, Malaysia, Mexico, Paraguay, Peru, the Philippines, Singapore, Thailand, and Venezuela for the prevention of dengue disease caused by all 4 virus serotypes (1, 2, 3, 4) in individuals 9/12 to 16/45/60 years living in endemic areas.

As of December 2017, the Sanofi label proposal is being reviewed by national regulatory agencies in each country where the vaccine is registered or under registration.

1.3 Potential Benefits and Risks

Detailed risk/benefit analysis is presented in the Investigator's Brochure version 19.0 dated 9 February 2017, and recent Investigator's Brochure Amendment version 1.0 dated 21 December 2017.

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.

Results from the two large-scale Phase III efficacy trials showed the potential for CYD dengue vaccine to reduce the probability of a subject's having symptomatic VCD, hospitalized VCD due to any of the 4 serotypes (vaccine efficacy [VE] estimates against symptomatic VCD during the whole Active Phase due to any of the 4 serotypes were 56.5% [95%CI: 43.8; 66.4] for CYD14 and 60.8% [95%CI: 52.0; 68.0] for CYD15). In addition, efficacy was observed against each of the 4 serotypes with high efficacy seen against severe VCD cases and hospitalized VCD cases during the Active Phase.

A number of supplemental exploratory analyses (see section 1.4) have provided strong evidences that, for subjects that were dengue seropositive prior to CYD dengue vaccination, the vaccine protects against symptomatic dengue, hospitalized dengue, and severe dengue disease.

The subjects receiving Adacel® may increase their current immunity and protection against diphtheria, tetanus and pertussis disease.

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 also 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 3 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 the efficacy trials during year 3 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 (6).

Considering the totality of long-term follow-up data during the Hospital Phase across the 3 efficacy studies, no evidence of increased severity of dengue disease or increase in frequency of hospitalized dengue cases has been observed in subject from 9 to 16 years old vaccinated with the dengue vaccine.

Following a number of supplemental exploratory analyses (see Section 1.4), it was shown that subjects that were dengue seronegative prior to CYD dengue vaccination have an increased risk of hospitalized or severe disease, as compared to subjects who received the placebo, with an onset from the third year after the first injection.

Tdap vaccine (Adacel®)

Tdap vaccine (Adacel®) may not protect 100% of vaccinated individuals. Following vaccination with Adacel®, the most common local adverse reactions include injection site pain, erythema, and swelling; the most common systemic adverse events include headache, body ache, tiredness, and fever. Adacel® is contraindicated in persons with known systemic hypersensitivity to any of their components or a life-threatening reaction after previous administration of either vaccine or a vaccine containing the same substances. Because of uncertainty as to which vaccine component

may be responsible, no further vaccination with the diphtheria, tetanus, or pertussis components found in Adacel® should be carried out.

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 Adacel®), 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 Adacel® for additional information regarding potential risks. Full list of expected adverse events (AEs) for the CYD dengue vaccine can be found in the Investigator's Brochure.

1.4 Rational for the Trial

Preventive measures presently rely 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.

It is preferable that CYD dengue vaccine is administered at an existing scheduled visit as part of the routine immunization schedule. There is currently no data on concomitant administration of CYD dengue vaccine with other vaccines in the indicated population aged 9-60 years of age. Co-administration of CYD dengue vaccine with other vaccines has been assessed in clinical studies outside the age indication, in infants and 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) (CYD08) (10), 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) (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.

The present post-licensure Phase IIIb study CYD66 will investigate the immunogenicity and safety of CYD dengue vaccine and Tdap vaccine when both vaccines are administered concomitantly or sequentially to subjects aged 9 to 60 years living in the Philippines. CYD dengue vaccine may be given concomitantly with Tdap. Tdap vaccine is indicated for the prophylaxis of diphtheria caused by *Corynebacterium diphtheriae*, tetanus caused by *Clostridium tetani*, and pertussis (whooping cough) caused by *Bordetella pertussis* in individuals 4 through 64 years of age as a booster according to the national vaccination policies. Tdap vaccine is a sterile liquid suspension of adsorbed tetanus, low-dose diphtheria toxoids, and acellular pertussis

components, intended for intramuscular administration. Tdap vaccine is licensed in a total of 67 countries, and is administered as a single booster dose in adolescent and adult public and private vaccination schedules in the Philippines. Dengvaxia® is currently indicated in subjects 9 to 45 years of age. In order to generate further data in older subjects, it was decided to also administer the Dengvaxia® to 46-60 year-old subjects in the present study.

As multiple Ags are administered concurrently, it is necessary to demonstrate that there is no impact on either the immunogenicity or safety profile of CYD vaccination on Tdap or the inverse. Furthermore, the administration of CYD dengue vaccine at the same time as a booster dose of Tdap vaccine might reduce the number of vaccination visits, and thereby increase vaccine compliance and coverage of co-administered vaccines, and facilitate dengue program. implementation.

Protocol Amendment 1

This amended protocol introduces important changes to the original protocol of the ongoing CYD66 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 (11) (12). 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 (when 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 not exposed 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 occur 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 is amending this study protocol. As a general rule, only subjects assessed as dengue exposed at baseline (ie, before receiving the first injection) will be eligible to receive any further dose of CYD dengue vaccine in an ongoing study. In this study (CYD66), all subjects will be informed about these latest results and 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 ICF and/or AF, as applicable. Subjects assessed as dengue exposed will confirm their participation in the study and will continue to be eligible to receive remaining CYD dengue doses planned. Subjects classified as unexposed at baseline, will only be able to continue in the study for a 6-month safety follow-up. Their consent will also be asked for.

To determine the basal serostatus of the subjects already included in the study, the Dengue PNRT will be used.

2 Trial Objectives

2.1 Primary Objectives

Tdap immunogenicity

- To demonstrate the non-inferiority of the humoral immune response to the Tdap booster dose concomitantly administered with the first dose of CYD dengue vaccine as compared to sequential administration, measured 28 days after Tdap booster dose

CYD dengue vaccine immunogenicity

- To demonstrate the non-inferiority of the humoral immune response to the first dose of CYD dengue vaccine concomitantly administered with Tdap as compared to sequential administration, measured 28 days after the first dose of CYD dengue vaccine

The endpoints for the primary objective(s) are presented in Section 9.1.

2.2 Secondary Objectives

CYD dengue vaccine Immunogenicity:

- To demonstrate the non-inferiority of the humoral immune response of 3 doses of CYD dengue vaccine with the first dose concomitantly administered with Tdap as compared to sequential administration, measured 28 days after the third dose of CYD dengue vaccine
- To describe the humoral immune response at baseline and 28 days after the first and third doses of CYD dengue vaccine, in each and any group

Tdap Immunogenicity:

- To describe the humoral immune response of Tdap vaccine at baseline and 28 days after concomitant administration with the first dose of CYD dengue vaccine as compared to the sequential administration, in each and any group

Safety

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

The endpoints for the secondary objective(s) are presented in Section 9.2.

3 Investigators and Trial Organization

This trial will be conducted in approximately 4 centers in the Philippines. 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 Independent Data Monitoring Committee (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 Global Clinical Immunology (GCI) (Swiftwater, Pennsylvania, USA) or outsourced laboratory under the management of GCI.

Sponsor's Responsible Medical Officer

The Sponsor's Responsible Medical Officer [redacted]

4 Independent Ethics Committee/Institutional Review Board

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

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

The Investigator 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.

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 688 healthy subjects aged 9 to 60 years in the Philippines.

Subjects received the first dose of the CYD dengue vaccine either concomitantly or sequentially with a booster dose of Tdap vaccine (Adacel®)

Subjects were randomized according to a 1:1 ratio into one of the 2 following groups with stratification on age (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years):

- **Group 1**: subjects were administered the first dose of CYD dengue vaccine concomitantly with the booster dose of Tdap vaccine at the second visit (V02; M1)
- **Group 2**: subjects were administered Tdap vaccine at the first visit (V01; D0), and then CYD dengue vaccine 28 days later at the second visit (V02; M1)

The stratification will be considered in order to balance the potential difference in terms of booster response by age group for the pertussis antigens (PT, FHA, PRN and FIM2+3).
Since the CYD dengue is administered according to a 3-dose schedule, given 6 months apart, initial trial design included administration of the second and third doses of CYD dengue vaccine at V04 (Month 7 [M7] and at V06 (M13) in all subjects.

All but 19 subjects (from both, Group1 and Group 2) did receive dose 2 of the CYD dengue vaccine as planned. However, as per changes in the conduct of the study reflected in this Protocol Amendment 1 (see also Section 1.4), the following will be applied:

- All vaccinated subjects will be informed about their baseline dengue serostatus and what it means as soon as possible
- All subjects will be asked about their willingness to continue participating in this study, and consent will be formalized by signing an ICF and/or AF addendum, as applicable.
- Subjects seropositive at baseline will additionally be asked for consent to receive remaining CYD dengue doses.
- Subjects seronegative at baseline will be able to continue in the study for safety follow-up if they consent to, but will not receive further injections of CYD dengue vaccine.
- Subjects seronegative at baseline who were vaccinated during this study will have timely access to appropriate care in the event of suspected dengue, for 10 years from the date of last dengue vaccination.

Time between communication of the results from the exploratory analyses and approval of Protocol Amendment 1 by the competent authorities and for the associated logistic tasks will result into a hold of study activities of several months (approximately 4-6 months). Study-hold intervenes after V03, V04 or V05, depending on each subject's visit-calendar at the time of study-hold.

Blood samples collected before dose 1 of the vaccine (at V01 for Group 2 and at V02 for Group 1) will be used to determine dengue serostatus at baseline. Dengue serostatus will be determined using the Dengue PRNT. A "seropositive" subject has been generally defined by a PRNT titer ≥ 1:10 to any dengue serotype at baseline, and a "seronegative" subject has been defined by a PRNT titer <10 for all four dengue serotypes. Only subjects identified as dengue seropositive will be eligible to receive further vaccine injections.

In order to communicate to each subject his/her dengue serostatus at baseline, there will be either 1 unscheduled visit and /or phone call during the study-hold, before the next visit initially planned (at V06 at the latest):

The subject will consent to continue participation in the study by signing an ICF/AF addendum 1 at subject's next planned visit (either V04, V05 or V06).

Thus, dose 2 and 3, or dose 3 only (provided that dose 2 was received, as planned) will be administered only to those subjects dengue seropositive at baseline who consent continue participation in the study and consent receiving the remaining CYD dengue doses planned.

A 6 months safety follow up is planned for all subjects who received at least 1 dose and who consent to continue participation in the study. This period will start after the last CYD dose the subject received (whether 1, 2 or 3 doses).

At the time vaccinations were paused, subjects had already provided 2 to 3 blood samples (BL), depending on the allocation group. Only dengue-exposed subjects who will continue in the study and choose to receive remaining CYD dengue doses will provide 1 subsequent BL, as initially planned in Protocol Version 1.0.

Additional blood samples might be collected in case of SAEs (including AEs of special interest [AESIs]) and to assess AEs that may be indicative of viscerotropic or neurotropic disease (see Guidelines for Assessing Viscerotropic and Neurotropic AE).

In case of hospitalized suspected dengue case, one unplanned BL (= acute BL) will have to be collected within the first 5 days after fever onset for virological confirmation of dengue disease. (If this cannot be accomplished, this sample should still be obtained as soon as possible thereafter, for IDMC severity assessment).

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

Immunogenicity of the Tdap booster dose will be evaluated before and 28 days after injection in both groups. Immunogenicity of the CYD dengue vaccine will be evaluated before the first injection and 28 days after the first and the third injections in both groups. The safety of the two vaccines will be assessed after each injection in both groups.

For seropositive subjects who consent continue participation in the study and administration of remaining CYD dengue doses, due to period of study-hold, the duration of each subject's participation in the trial will be approximately 23-25 months, since it will be extended by 4-6 months with respect to the initial plan (ie, as per protocol version1.0: approximately 19 months, including a vaccination phase of 12 months for subjects in Group 1 and 13 months for subjects in Group 2, followed by a safety follow-up period of 6 months after the third injection of CYD dengue vaccine).

For seropositive subjects who consent continue participation in the study but refuse to receive remaining CYD dengue doses and seronegative subjects who provide their consent to continue participation in the study, their participation in the trial will be less than 19 months as initially planned. (i. e., taking into account the study-hold and the 6 months safety follow up

Subjects declining continue participation in the study will end the study on the date this decision is communicated to the Sponsor.

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 9-60 years of age. Based on the current age indication of the dengue vaccine, co-administration with Adacel®, currently used in public sector school-based vaccination programs in subjects aged 9 years and above, is needed and will be incorporated into the post-licensure plan. Therefore, the present CYD66 study will investigate the immunogenicity and safety of the CYD dengue vaccine when it is administered concomitantly or sequentially (at least 28 days apart) with Adacel®. In the Philippines, the CYD dengue vaccine received an indication for use in the 9-45 year-old subjects. In order to generate further data in older subjects, it was decided to also administer the CYD dengue vaccine to 46-60 year-old subjects in the present study.

5.1.3 Trial Plan

A schedule of assessments and study vaccinations is provided in the table of study 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 electronic case report form (eCRF).

5.1.4 Visit Procedures

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/vaccination.
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) Allocate a subject number to the subject.
7) Scratch-off the randomization list to obtain the group allocation, and sign it.
8) Perform a physical examination
9) Record the subject's axillary temperature (Group 2).
10) For female subjects of childbearing potential[a], perform a urine pregnancy test (Group 2).

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

11) Obtain blood sample[a] from subjects in Group 2 (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 be used for vaccination.
12) Review temporary and definitive contraindications to vaccination.
13) Inject Tdap vaccine to subjects from Group 2.
14) Keep the subject from Group 2 under observation for 30 minutes, and record any immediate AE in the source document (Group 2).
15) 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).
16) Give the subject or parent/legally acceptable representative of subjects in Group 2 a diary card (DC), a thermometer, and a ruler, and go over the instructions for their use. Subjects from Group 1, who will not be vaccinated at V01, will receive a DC for the collection of SAE only.
17) Remind the subject or parent/legally acceptable representative to bring back the DC when they return for Visit 2 at a specified date and time.
18) Remind the subject or parent/legally acceptable representative to notify the site in case of an SAE.
19) Complete the relevant electronic case report form (eCRF) pages for this visit.

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) Review the DC pages.
3) Recheck inclusion and exclusion criteria for Group 1.
4) Perform a physical examination
5) Record the subject's axillary temperature.
6) Collect information regarding the subject's medication status since the previous visit.
7) For female subjects of childbearing potential, perform a urine pregnancy test.
8) Obtain blood sample (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 be used for

[a] 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 eCRF. In that case, and if the subject wants to participate in the trial, he/she will be vaccinated.

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).

9) Review temporary and definitive contraindications to vaccination
10) Inject the first dose of CYD dengue vaccine to all subjects.
11) Inject Tdap vaccine to subjects in Group 1 on the opposite side (the one who did not receive the CYD dengue vaccine).
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 subject or parent/legally acceptable representative a DC (both Groups).
15) Remind the subject or parent/legally acceptable representative to bring back the DC when they return for Visit 3 at a specified date and time.
16) Complete the relevant eCRF pages for this visit.

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

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) Check concomitant medications and record every reportable medication ongoing at the time of vaccination.
3) Collect information regarding the subject's medication status since the previous visit.
4) Perform a physical examination
5) Obtain blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
6) Remind the subject or parent/legally acceptable representative to bring back the DC when they return for Visit 4 at a specified date and time.
7) Complete the relevant eCRF pages for this visit.

Phone Call 1 (PC1) (Month 4; initially planned 3 months after Visit 2)

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.

Unscheduled visit/phone call comprised between V03 [28+14 days after first dose of CYD dengue vaccine] and V06 [initially planned at M13+20 day]

As per Protocol Amendment 1, this unscheduled visit/phone call is to take place as soon as possible after study-hold (between V03 and V06). During this visit/phone call, subjects will be informed about their dengue serostatus at baseline, and about the increased risk of hospitalized or severe dengue for subjects not exposed to dengue infection prior to the first injection with the CYD dengue vaccine.

The subject will consent to continue participation in the study by signing an ICF/AF addendum 1 at subject's next planned visit (either V04, V05 or V06). At the latest, this visit will take place at the same time as V06.

The scheduled calendar for the next visits and phone calls may be impacted (delayed) by the length of the study hold. It will be adapted accordingly.

Visit 4 (initially planned at Month 7; 6 months [± 20 days] after Visit 2)

The Investigator or designated study personnel will:

1) Review the DC pages with the parent/legally acceptable representative.
2) Perform a physical examination
3) Record the subject's axillary temperature.
4) Collect information regarding the subject's medication status since the previous visit.
5) For female subjects of childbearing potential, perform a urine pregnancy test.
6) Review temporary and definitive contraindications to vaccination.
7) Inject the second dose of CYD dengue vaccine to all subjects.
8) Keep the subject under observation for 30 minutes, and record any immediate AE in the source document.
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 subject or parent/legally acceptable representative a DC.
11) Remind the subject or parent/legally acceptable representative to bring back the DC when they return for Visit 5 at a specified date and time.
12) Complete the relevant eCRF pages for this visit.

Visit 5 (initially planned at Month 8; 28 [+14] days after Visit 4)

This visit is performed only to collect safety data post-second injection with CYD dengue vaccine. The same procedures as those described for Visit 3 will be followed, except that no blood sample will be performed.

Phone Call 2 (PC2) (initially planned at Month 10;3 months after Visit 4)

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

Visit 6 (initially planned at Month 13; 12 months [± 20 days] after Visit 2)

The same procedures as those described for Visit 4 will be followed.

Phone Call 3 (PC3) (initially planned at Month 16;3 months after Visit 6)

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

Visit 7 (initially planned at Month 14; 28 [+14] days after Visit 6)

The same procedures as those described for Visit 3 will be followed. In addition, subject or parent/legally acceptable representative will be given a memory aid (MA).

6-Month Safety Follow-up After the Last Vaccination

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 the last vaccination): Collection of SAEs

After the last CYD dengue dose received (whether 1, 2 or 3 doses), subjects will still be contacted by telephone. This contact will be made 6 months after the last vaccination or the closest possible to that date, considering the potential delay triggered by the study-hold. During this contact, the Investigator or designated study personnel will:

1) 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.
2) Complete the relevant eCRF 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 they may be impacted by the study-hold and they depend on the obtention of the appropriate regulatory and ethical approvals..

Planned trial period (FVFS to LCLS[a]): Q3 2016 to Q2 2019

Planned vaccination period: Q3 2016 to Q3 2018

Planned end of trial[b]: Q2 2019

Planned date of final clinical study report: Q4 2019

The initial expected duration of each subject's participation in the trial is approximately 19 months, including a safety follow-up period of 6 months after the third injection of CYD dengue vaccine.

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 the Philippines 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 SET will perform 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.

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

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

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 documented by means of a written, signed, and dated ICF or AF (according to local EC regulation).

Following the amendment of the original protocol, subject/subject's parent(s) or legally acceptable representative(s) are to sign an addendum to the AF and /or the 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 and AF 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/AF provided by the Sponsor. Any change to the content of the ICF and/or 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/or AF or an addendum to the original ICF and/or 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) Subject aged 9 to 60 years (i.e., from the day of the 9th birthday to the day prior to the 61th birthday) on the day of inclusion
2) Subject in good health, based on medical history and physical examination
3) 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)

4) For subject aged 9 to 11 years: known (documented) receipt of at least 4 previous doses of diphtheria toxoid, tetanus toxoid and acellular pertussis-containing (DTaP) vaccines, with the last dose not within the last 5 years prior to enrolment
OR
For subject aged at least 12 years: known (documented or self-reported) receipt of at least 3 previous doses of diphtheria toxoid , tetanus toxoid, and whole cell pertussis-containing (DTwP) vaccines, with the last dose not within the last 5 years prior to enrolment

5) Subject (or subject and parent[s]/legally acceptable representatives) able to attend all scheduled visits and to comply with all trial procedures

5.2.5 Exclusion Criteria

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

1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche[a] or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination 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 CYD dengue vaccine

5) Receipt of immune globulins, blood or blood-derived products in the past 3 months, which might interfere with assessment of the immune response

6) 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 corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

7) A previous severe reaction to pertussis, diphtheria or tetanus vaccine including immediate anaphylaxis, encephalopathy within 7 days or seizure within 3 days of receiving the vaccine

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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) 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.

8) Known systemic hypersensitivity to any of the vaccine components[a], or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances
9) Thrombocytopenia, contraindicating intramuscular vaccination
10) Bleeding disorder or receipt of anticoagulants within 3 weeks preceding inclusion, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator
11) Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily
12) Current alcohol abuse or drug addiction that, based on Investigator's judgment, may interfere with the subject's ability to comply with trial procedures
13) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion
14) Identified as an Investigator or employee of the Investigator with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
15) Self-reported Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection
16) Personal history of Guillain-Barré syndrome

Temporary Exclusion Criteria:

A prospective subject should not be included in the study until the following condition 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 trial inclusion

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 eCRF. The significant medical history section of the eCRF 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)

[a] The components of the vaccines used in the trial are listed in Section 6.1 and in the Investigator's Brochure or summary of product characteristics.

- 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.

1) Febrile illness (temperature ≥ 38.0°C) or moderate or severe acute illness/infection on the day of vaccination, according to Investigator judgment
2) Receipt of any vaccine other the trial vaccination 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
6) Subject classified as a dengue unexposed subject (seronegative) at baseline

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

If a subject has been classified as a “dengue unexposed”, she/he will have the possibility to continue participating in the safety follow-up.

5.2.8 Conditions for Withdrawal

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

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject’s permission
- At the request of the subject/parents or legally acceptable representatives (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 eCRF.

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 (i.e., documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the eCRF 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 eCRF. Reasons are listed below from the most significant to the least significant (refer to the eCRF 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 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 10.

N**on-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 (i.e., 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 unexposed subjects who discontinued after dengue vaccine injection(s) to inform them about their dengue status and their rights to access medical care 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.

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 1 month after identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome—i.e., details about the delivery and the newborn, or about pregnancy termination—and must update the 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 an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the Global PharmacoVigilance (GPV) Department regardless of when the SAE occurs (e.g., even after the end of the trial).

5.3 Modification of the Trial and Protocol

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

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

Subjects will receive the CYD dengue vaccine according to a 3-dose schedule, given 6 months apart, with the first dose of CYD dengue vaccine administered either concomitantly or sequentially with a booster dose of Tdap vaccine (Adacel®).

6.1 Identity of the Investigational Products

6.1.1 Identity of CYD Dengue Vaccine

CYD dengue vaccine:	Live, attenuated, tetravalent dengue virus vaccine
Presentation:	Monodose
Form:	Powder and solvent for suspension for injection
Dose:	0.5 milliliters (mL) of the reconstituted vaccine
Route:	Subcutaneous (SC) injection
Batch number:	To be determined

6.1.1.1 Composition

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

- **Active Ingredients:** 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, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminomethane, and urea
- **Solvent**: NaCl 0.4%

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.

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 eCRF. 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 dengue virus seroptype 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 group and with different flavivirus 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 (13). 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) (14).

The choice of the final 3 dose schedule at 6 month intervals apart of 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 (15).

6.1.2 Identity of Adacel

Adacel®:	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed
Form:	Suspension for injection in a vial
Dose:	0.5 mL
Route:	Intramuscular (IM) injection
Batch number:	Commercial

6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

- Active Ingredients:
  - Tetanus toxoid 5 Lf
  - Diphtheria toxoid 2 Lf
  - Pertussis toxoid 2.5 µg
  - Filamentous Hemagglutinin 5 µg
  - Pertactin 5 µg
  - Fimbriae types 2 and 3 5 µg
- Excipients:
  - aluminum phosphate (adjuvant) 1.5 mg
  - 2-phenoxyethanol 0.6% v/v

6.1.2.2 Preparation and Administration

Sanofi Pasteur's Tdap 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 Tdap vaccine is to be administered intramuscularly in the deltoid region of the upper arm, on the opposite side (the one who did not receive the CYD dengue vaccine).

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 eCRF. 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

Not applicable.

6.2 Identity of Other Product

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 (for clinical trial use only)
- Storage conditions
- Batch number
- Dose number

- Name of Sponsor
- Expiry date

For Adacel®, a commercial batch will be used, and the manufacturer's packaging will be used and labeled 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 (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, 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 and must be protected from light. 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 eCRF. 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 eCRF.

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 CYD66 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. Stratification according to age will be applied (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years) to balance the potential difference in terms of booster response by age group for the pertussis antigens (PT, FHA, PRN and FIM2+3).

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, Subject 001-00001 is the first subject enrolled in center number 1 and Subject 002-00001 is the first subject enrolled in center number 2.

Subject numbers will be an 8-digit string, consisting of a 3-digit study center identifier and a 5-digit subject identifier. The 5-digit subject identifier will correspond to the age group (the first digit will be used to identify the age group, with “0” for subjects aged 9 to 11years, “1” for subjects aged 12 to 17 years, “2” for subjects aged 18 to 45 years, and “3” for subjects aged 46 to 60 years) and to chronological order of enrollment in the center. Subject identifier will be:

- From 00001 to 09999 for subjects aged 9 months through 11 years
- From 10001 to 19999 for subjects aged 12 years through 17 years
- From 20001 to 29999 for subjects aged 18 years through 45 years
- From 30001 to 39999 for subjects aged 46 years through 60 years

For example, Subject 001-10001 is the first subject in the 12-17 year-old age group enrolled in the study center number 1 and Subject 002-20001 is the first subject from the 18-45 year-old age group enrolled in the study center number 2.

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 eCRF 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 eCRF from the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 28 day 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:

- 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):
  - Vaccines (other than the trial vaccines) in the 4 weeks before and after each trial vaccination
  - 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

The information reported in the eCRF 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 eCRF 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 Ab responses will be collected at Visits 1, 2, 3, and 7. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

7.1.1 Serum Samples for Neutralizing Ab Assessment

At Visits 1, 2, 3, and 7, 2 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 1), or from the limb that will be used for Tdap opposite to the one that will be used for CYD dengue vaccine for concomitant injection (Group 2).

At the time of study-hold, subjects already provided 2 or 3 blood samples (BL), depending on their allocation group. Blood samples collected before administration of the first dose of CYD dengue vaccine will be used for baseline dengue serostatus assessment. No additional BL will be provided by dengue unexposed participants. Dengue exposed subjects will provide the remaining BL as initially planned.

Table 7.1: Blood sampling volume (mL) per visit

Visit Number Trial Timelines (Days/Months) Time Windows (Days)	V01 D0	V02 M1 (D0+28D) +14	V03 M2 (M1+28D) +14	V07 M14 (M13+28D) +14
Dengue Neutralizing Abs		4 (Group 1) 4 (Group 2)	4 (Group 1) 4 (Group 2)	4 (Group 1) 4 (Group 2)
T, D, PT, FHA, PRN, and FIM2+3 Abs	0 (Group 1) 2 (Group 2)	2 (Group 1) 2 (Group 2)	2 (Group 1) 0 (Group 2)	-
TOTAL (mL)	**0 (Group 1)** **2 (Group 2)**	**6 (Group 1)** **6 (Group 2)**	**6 (Group 1)** **4 (Group 2)**	**4 (Group 1)** **4 (Group 2)**

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

In case of hospitalized suspected dengue case, one 3 mL acute blood sample will be collected (within the 5 days after the fever onset) as described 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], creatinine, blood cell count, total bilirubin, and hematocrit count) have been checked or are planned to be checked as part of local standard of care at the hospital. If these parameters have not been measured, additional blood specimens will be taken to perform these tests for 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. More detailed instructions are detailed in the Guidelines for Assessing Viscerotropic and Neurotropic AE (16) (17) (18) document.

7.1.4 Urine Samples

Pregnancy tests are applicable only for any female subjects of childbearing potential. Urine samples for pregnancy tests at the vaccination visits (V01 [Group 2], V02, V04, and V06) will be taken and analyzed at the trial center.

7.2 Serum Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of Ab 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, AFs, eCRFs, DCs, MAs, 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 endpoints for the evaluation of immunogenicity are:

Tdap vaccine immunogenicity

- Ab concentrations against pertussis antigens (PT, FHA, PRN, FIM2+3) as measured by ELISA, 28 days after the dose of Tdap vaccine
- Seroprotection against D and T, defined as anti-D and anti-T Ab concentrations ≥ 0.1 international units (IU)/mL, as measured by ELISA for T and by Diphtheria Micrometabolic Inhibition Test - Toxin Neutralization assay (MIT-TNA) for D, 28 days after the dose of Tdap vaccine

CYD dengue vaccine immunogenicity

- Neutralizing Ab titers against each of the 4 dengue serotypes, as measured by dengue 50% plaque reduction neutralization test ($PRNT_{50}$), 28 days after the first dose of CYD dengue vaccine

9.1.1.2 Immunogenicity Assessment Methods

Anti-Bordetella Pertussis Antibodies (US Methods)

Assays will be performed by ELISA at Sanofi Pasteur. Purified PT, FHA, PRN, or FIM2+3 Ag is adsorbed to the wells of a microtiter plate. Diluted serum samples (test samples, reference standards, and quality controls) are incubated in the wells. Specific Abs in the serum samples bind to the immobilized Ag to form Ag-Ab complexes. Unbound Abs are washed from the wells, and enzyme-conjugated anti-human IgG is added. The enzyme conjugate binds to the Ag-Ab complex. Excess conjugate is washed away and a specific colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction causing color development. The intensity of the generated color is proportional to the amount of specific Ab bound to the wells. The results are read on a spectrophotometer (ELISA plate reader). An in house reference standard serum assayed on each plate is used to calculate the amount of specific PT, FHA, PRN, or FIM2+3 Ab in the test samples in ELISA unit (EU)/mL by comparison to the reference standard curves. The LLOQ for the anti-PT, PRN, and FIM ELISA is 4 EU/mL and the LLOQ for the anti-FHA ELISA is 3 EU/mL.

Antibodies to Tetanus Toxin

Assays will be performed by ELISA at Sanofi Pasteur. Purified Tetanus Ag is adsorbed to the wells of a microtiter plate. Diluted serum samples (test samples, reference standard, and quality control) are incubated in the wells. Specific Abs in the serum samples bind to the immobilized Ag. Unbound Abs are washed from the wells, and enzyme-conjugated anti-human IgG is added. The enzyme conjugate binds to the Ag-Ab complex. Excess conjugate is washed away and a specific colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction, which

causes color development. The intensity of the generated color is proportional to the amount of specific Ab bound to the wells. The results are read on a spectrophotometer (ELISA plate reader). A reference standard assayed on each plate, WHO human standard lot TE3, is used to calculate the amount of specific anti-Tetanus Ab in the unitage assigned by the reference standard (IU/mL of serum). The LLOQ for the anti-Tetanus ELISA is 0.01 IU/mL.

Antibodies to Diphtheria Toxin (MIT Method)

Assays will be performed by an MIT-TNA at Sanofi Pasteur. Serial dilutions of human sera are mixed with diphtheria challenge toxin and incubated with Vero cells that are sensitive to the toxin. Neutralizing Abs specific to diphtheria toxin contained in the serum samples bind to and neutralize the toxin. The neutralized toxin does not affect cellular viability, therefore the cultured cells continue to metabolize and release CO_2, reducing the pH of the culture medium. Cell survival correlates with the change in the color of the pH indicator (phenol red to yellow at pH $\leq$ 7.0) contained in the medium. In the absence of neutralizing Abs, the challenge toxin reduces cellular metabolism and CO_2 production, therefore the pH does not decrease and a color change is not detected. The LLOQ is 0.005 IU/mL.

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 $\geq$ 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 LLOQ of the assay is 10 (1/[dil]).

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

CYD dengue vaccine Immunogenicity:

- Neutralizing Ab titers against each of the 4 dengue serotypes, as measured by dengue $PRNT_{50}$, at baseline (M1) and 28 days after the first and third doses of CYD dengue vaccine
- Neutralizing Ab titers ≥ 10 1/dil against each of the 4 dengue serotypes and against at least 1, 2, 3, or 4 dengue serotypes, as measured by dengue $PRNT_{50}$, at baseline (M1) and 28 days after the first and third doses of CYD dengue vaccine
- Neutralizing Ab titers ≥ different titer thresholds (1/dil) against each of the 4 dengue serotypes, as measured by dengue $PRNT_{50}$, at baseline (M1) and 28 days after the first and third doses of CYD dengue vaccine

Tdap Immunogenicity:

- Ab concentrations against PT, FHA, PRN, and FIM2+3, as measured by ELISA, at baseline (D0 for group 2, M1 for Group 1) and 28 days after the dose of Tdap vaccine
- Anti-T and anti-D Ab concentrations ≥ 0.1 IU/mL, as measured by ELISA for T and by MIT-TNA for D, at baseline (D0 for group 2, M1 for Group 1) and 28 days after the dose of Tdap vaccine

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:

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:

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

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

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

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

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

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

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

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:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

Unexpected Adverse Reaction (UAR):

An UAE 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 eCRF**.** 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 (i.e., solicited) in the eCRF 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 eCRF in terms of diagnosis and/or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D14 is a solicited reaction (i.e., prelisted in the eCRF), 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.

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.

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

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

Safety endpoints for Tdap vaccine and CYD dengue vaccine safety in each group are:

- Occurrence of immediate AEs reported in the 30 minutes after each/any injection
- Occurrence of solicited (i.e., pre-listed in the subject's DC and eCRF) injection site reactions (pain, erythema and swelling) within 7 days following each/any injection
- Occurrence of solicited systemic reactions (fever, headache, malaise, myalgia, and asthenia) occurring up to 14 days following each/any injection
- Occurrence of unsolicited (spontaneously reported) AEs within 28 days following each/any injection
- Occurrence of non-serious AESIs* occurring up to 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 (i.e., from D0 through the 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 (i.e., hospitalized suspected dengue case) occurring in all subjects at any time during the study.

** Subjects from Group 1 will not be vaccinated at V01 but will receive the first vaccinations at V02. However, SAEs will be recorded from inclusion and subjects from Group 1 will receive a SAE-specific DC at V01 that will be collected at V02.

Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

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 eCRF 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 eCRF, as follows:

- Any unsolicited systemic AE occurring during the first 30 minutes post-vaccination will be recorded on the eCRF 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 (i.e., D0 to D7) for the solicited injection site reactions and for the next 14 days (i.e., 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 eCRF 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 eCRF, 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
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: 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 for all subjects

CRF term (MedDRA LLT)	Injection site pain	Injection site erythema	Injection site swelling
DC term	Pain	Redness	Swelling
Definition		Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	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 DC. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 9.3: Solicited 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, **or** ≥ 100.4°F to ≤ 101.1°F Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	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 eCRF. The preferred route for this trial is axillary. Pre-vaccination temperature is also systematically collected by the Investigator in the eCRF for subjects aged between 9 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 eCRF 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

[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] Serious dengue case requiring hospitalization is a hospitalized suspected dengue case.

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 Case Severity

In the event of a hospitalized suspected dengue case, the following tests will be performed on the acute BL 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 $\log_{10}$ plaque forming unit (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 within the microplate wells coated with MAb. If NS1 Ag is present in the sample, an immune-

[a] ICH Guidelines, Clinical Safety Data Management E2A

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 dengue screen 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 (i.e., $\geq$ 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 (i.e., 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 the Philippines. 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 eCRF.

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 eCRF.

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 i.e., 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 a hospitalized VCD case as severe will be made on a case by case basis by the IDMC.

9.2.4 Efficacy

There are no secondary objectives for efficacy.

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 and 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: +33 4 37 37 71 32
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: pv.outsourcing@sanofipasteur.com
- By express mail, to the following address, using a method of transmission that includes password protection:
  Sanofi Pasteur SA
  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 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 eCRF 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 AESIs, 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 eCRF. 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 MA 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 eCRF. (Any information that was not documented in the DC will first be captured in the source document and then reported electronically.) The eCRF 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 eCRF, 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 eCRF; must provide explanations for all missing information; and must sign the eCRF using an e-signature.

11.2 Data Management

11.2.1 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 eCRF, 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 eCRF 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.

11.2.2 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.

11.2.3 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 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.

Non-inferiority testing will only be carried out with seropositive subjects and providing that the number of evaluable subjects attains a global power of at least 80%. This applies to the co-primary objectives and the secondary objective. Otherwise, descriptive analyses will be performed

12.1.1 Hypotheses and Statistical Methods for Primary Objectives

12.1.1.1 Hypotheses

Non-inferiority on Tdap vaccine

The objective is to demonstrate that the humoral immune response to the Tdap booster dose administered concomitantly with the first dose of CYD dengue vaccine is non-inferior to the humoral immune response to the Tdap booster dose administered alone 28 days before the first dose of CYD dengue vaccine.

Individual hypotheses on Tdap response for each antigen:

A non-inferiority testing approach will be used to compare geometric mean concentrations (GMCs) for PT, FHA, PRN, FIM2+3, 28 days after the booster dose of Tdap, for each antigen "i" based on the following individual hypotheses:

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

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

with:

i, antigen {PT, FHA, PRN, FIM 2+3}.

δ, non-inferiority limit is set at 1.5, i.e., 0.176 (=$\log_{10}$ [1.5]), 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). For each of the 4 antigens, the statistical methodology will be based on the use of the age-stratified two-sided 95% CI of the ratio of GMCs between groups. The age-stratified CI will be calculated using an ANOVA model (type II analysis) of $\log_{10}$-transformed titers. The age groups (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years) will be used as the stratifying factor in the model.

Additionally, a non-inferiority testing approach will be used to compare seroprotection rates of T and D, 28 days after the booster dose of Tdap vaccine. Seroprotection is defined as anti-D and anti-T Ab concentration superior to 0.1 IU/mL.

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

$$H_0^i : P_{Group1}^i - P_{Group2}^i \leq -\delta$$
$$H_1^i : P_{Group1}^i - P_{Group2}^i > -\delta$$

with:

i, antigen {T, D}

δ, non-inferiority limit is set at 10% for both T and D.

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

Global hypotheses for non-inferiority on Tdap response:

The global hypotheses are:

H_{0G}: Non inferiority of Tdap booster dose co-administered with the first dose of CYD dengue vaccine versus Tdap booster dose administered alone is not demonstrated for at least one antigen.

H_{1G}: Non-inferiority of Tdap booster dose co-administered with the first dose of CYD dengue vaccine versus Tdap booster dose administered alone is demonstrated for all the antigens.

$$H_0^G : \text{at least one } H_0^i \textit{ not rejected}$$
$$H_1^G : \text{all } H_0^i \textit{ are rejected}$$

Non-inferiority on CYD dengue vaccine after 1 dose

The objective is to demonstrate that the humoral immune response to the first dose of CYD dengue vaccine administered concomitantly with Tdap booster dose is non-inferior to the humoral immune response to the first dose of CYD dengue vaccine administered sequentially 28 days after the Tdap booster dose.

Individual hypotheses on CYD response after one dose for each serotype:

A non-inferiority testing approach will be used to compare geometric mean of titers (GMTs), for dengue serotypes 1, 2, 3, and 4, 28 days after the first injection of CYD dengue vaccine between Group 1 and Group 2 for each serotype "i" 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, serotypes in {1, 2, 3, 4}.

δ, non-inferiority limit is set at 2, i.e., 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 after one dose:

H_0^G : at least one H_0^i *not rejected*

H_1^G : all H_0^i *are rejected*

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

12.1.1.2 Statistical Methods

Non-inferiority on Tdap vaccine

The non-inferiority test will be performed using the 95% 2-sided CI of the difference between Group 1 and Group 2 for seroprotection rates and of the differences of the means of the $\log_{10}$ transformed post-vaccination concentrations/titers for GMCs/GMTs (α=2.5% one-sided). The 95% CIs will be calculated based on the Wilson score method without continuity correction as quoted by Newcombe (19) for seroprotection rates and using normal approximation of log-transformed titers for GMCs/GMTs.

Non-inferiority on CYD dengue vaccine after one dose

The statistical methodology will be based on the use of the two-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.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses

Non-inferiority on CYD dengue vaccine after three doses

The objective is to demonstrate that the humoral immune response of 3 doses of CYD dengue vaccine with the first dose administered concomitantly with the Tdap booster dose is non-inferior to the humoral immune response of 3 doses of CYD dengue vaccine administered sequentially with the Tdap booster dose administered 28 days before the first dose of CYD dengue vaccine.

Individual hypotheses on CYD response after three doses for each serotype:

A non-inferiority testing approach will be used to compare GMTs (dengue serotypes 1, 2, 3, and 4) 28 days after 3 injections of CYD dengue vaccine between Group 1 and Group 2 for each serotype "i" 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, serotypes in {1, 2, 3, 4}.

δ, non-inferiority limit is set at 2, i.e., 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 after three doses:

H_0^G : at least one H_0^i *not rejected*

H_1^G : all H_0^i *are rejected*

Overall, non-inferiority among the groups will be demonstrated if, for each serotype of CYD dengue vaccine, the two-sided 95% CI lies above -δ.

Non-inferiority on Tdap vaccine

No statistical hypothesis will be tested on Tdap for secondary objectives.

12.1.2.2 Statistical Methods

Non-inferiority on CYD dengue vaccine after 3 doses

The statistical methodology will be based on the use of the two-sided 95% CI of the differences 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.

Descriptive analysis on CYD dengue vaccine and Tdap vaccine immunogenicity

No hypotheses will be tested. Immunogenicity point estimates and their 95% CI will be presented for each and any group, before and after the first and third injections for CYD dengue vaccine and before and after the booster vaccination for Tdap.

A complementary analysis on CYD dengue vaccine and Tdap vaccine immunogenicity after each dose will be conducted for each and any group according to the age groups (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years).

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.

The 95% CIs will be calculated using:

- The normal approximate method for GMCs/GMTs and Geometric mean of concentration ratios [GMCRs]/Geometric mean of the titer ratios [GMTRs]

Assuming that log_{10} transformation of the titers/concentrations follows a normal distribution, at first, the mean and the 95% CI will be calculated on log_{10} (titers/concentrations) 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 percentages (Clopper-Pearson's method, quoted by Newcombe (20))

In addition, the booster response against pertussis components (PT, FHA, PRN, and FIM2+3) will be calculated based on Ab concentration rises between pre- and post-vaccination defined as:

- A post-vaccination Ab concentration ≥ 4 x the lower limit of quantification (LLOQ) when pre-vaccination concentration is < LLOQ
- A post-vaccination Ab concentration ≥ 4 x pre-vaccination Ab concentration when pre-vaccination concentration is ≥ LLOQ but < 4 x LLOQ
- A post-vaccination Ab concentration ≥ 2 x pre-vaccination Ab concentration when pre-vaccination concentration is ≥ 4 x LLOQ

Safety

All analyses will be descriptive; no hypotheses will be tested. Safety will be assessed for all subjects after the booster dose of Tdap vaccine and after each and any dose of CYD Dengue vaccine.

A complementary analysis will be conducted for each group according to the age groups (9 to 11 years, 12 to 17 years, 18 to 45 years and 46 to 60 years). A complementary analysis after each and any dose of CYD dengue vaccine will be conducted 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 (20)) for proportions.

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

The FAS is defined as the subset of subjects who received at least one dose of each of the study vaccines (CYD and Tdap). Subjects will be analyzed by the vaccine group to which they were randomized.

12.2.2 Per-Protocol Analysis Set

Three PPASs will be defined: one for Tdap (PPT), one for CYD dengue vaccine after first dose (PPC1) and one for CYD dengue vaccine after the three doses (PPC3).

PPT

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject had dengue seronegative status at baseline
- Subject did not complete the vaccination schedule (at V02 for Group 1, V01 for Group 2)
- Subject received a vaccine other than the one that he/she was randomized to receive (at V02 for Group 1, V01 for Group 2)
- Administration of vaccine was not done as per-protocol (site and route of administration) (at V02 for Group 1, V01 for Group 2)
- Subject did not receive vaccine in the proper time window (at V02 for Group 1)
- Subject did not provide after Tdap injection a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn (V03 for Group 1, V02 for Group 2)
- Subject received a protocol-prohibited medication (prohibited therapies/medications/vaccines are indicated in Section 6.7) (until V03 for Group 1, V01 to V02 for Group 2)
- Subject's serology sample did not produce a valid test result, i.e., no Tdap Ab concentration available (at V03 for Group 1, V02 for Group 2)

PPC1

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPC1:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject had dengue seronegative status at baseline
- Subject did not complete the vaccination schedule (at V02 for Group 1, at V01 and V02 for Group 2)
- Subject received a vaccine other than the one that he/she was randomized to receive (at V02 for Group 1, at V01 or V02 for Group 2)
- Administration of vaccine was not done as per-protocol (site and route of administration) (at V02 for Group 1, at V01 and V02 for Group 2)
- Subject did not receive vaccine in the proper time window (at V02 for Group 1 and Group 2)

- Subject did not provide after the first CYD dengue vaccine injection a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn (at V03 for Group 1 and Group 2)
- Subject received a protocol-prohibited medication (prohibited therapies/medications/vaccines are indicated in Section 6.7) (until V03 for Group 1 and Group 2)
- Subject's serology sample did not produce a valid test result, i.e., no Neutralizing Ab titers against any of the four parental dengue virus serotypes of CYD dengue vaccine available (at V03 for Group 1 and Group 2)

PPC3

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPC3:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject had dengue seronegative status at baseline
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he/she was randomized to receive
- Administration of vaccine was not done as per-protocol (site and route of administration)
- Subject did not receive vaccine in the proper time window (at V02, V04 or V06)
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn (at V07)
- 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, i.e., no neutralizing Ab titers against any of the four parental dengue virus serotypes of CYD dengue vaccine available (at V07)

12.2.3 Safety Analysis Set

The SafAS is defined as the 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 the first dose.

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

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

12.2.4 Other Analysis Set

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 FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

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

The SafAS will be performed on the safety analysis set. 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. Imputations may be done for a limited number of scenarios. These will be described in the SAP.

12.3.2 Immunogenicity

For the computation of GMT/GMCs, any titer/concentration reported as < LLOQ will be converted to a value of ½ LLOQ.

While a single approach was used for GMT/GMCs, two different approaches for GMTR/GMCR will be applied:

- For Tdap Vaccine, < LLOQ will be converted to ½ LLOQ for a numerator and < LLOQ will be converted to LLOQ for a denominator when only one of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.
- For CYD dengue vaccine, < LLOQ will be converted to ½ 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 or three planned statistical analyses will be performed:

- A first interim statistical analysis (interim analysis) will be performed on results obtained after a partial database lock of data collected up to the 28 days post first dose of CYD dengue vaccine (V03; M2).
- A second interim analysis might be performed on results collected up to the 28 days after the third dose of CYD dengue vaccine (V06; M13).
- The final analysis will be performed on data collected at the end of the study.

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

12.5 Determination of Sample Size and Power Calculation

A total of 688 subjects will be enrolled: 344 subjects per treatment group (86 subjects per age group).

Considering a potential attrition rate of 10%, it was initially planned that such sample size would provide 618 evaluable subjects in the PPAS of Tdap and CYD dengue vaccine (PPT and PPC1). This sample size (based on SAS proc Power) targeted a global power over 90.0% for the non-inferiority testing corresponding to the co-primary objectives (i.e., after the booster dose of Tdap and after the first dose of CYD), and over 99.0% for the non-inferiority corresponding to the secondary objective (ie, testing after the third dose of CYD dengue vaccine)

However, as per this protocol amendment 1, the number of evaluable subjects will be reduced since only dengue seropositive subjects will be included in the Per-Protocol populations. Tus, the non-inferiority testing will be carried out only if a global power of at least 80% for the co-primary objectives and secondary objective can be attained (i.e., if the number of evaluable subjects is at least 510 for the co-primary objectives and 324 for the secondary objective).

The following assumptions were considered for the non-inferiority on Tdap: an alpha level of 2.5% (one-sided hypotheses), a maximum acceptable difference of 0.176 for GMCs, and of 10% for seroprotection rates, and the following rates and standard deviations (SDs):

- T ≥ 0.1 IU/mL – 99% of subjects
- D ≥ 0.1 IU/mL – 99% of subjects
- PT SD – 0.4
- FHA SD– 0.4
- PRN SD – 0.5
- FIM2+3 SD – 0.6

(Based on TD519, TD506 and TD526 studies and on Keith S. Reisinger (21)).

The following assumptions were considered for the non-inferiority after the first dose of CYD dengue vaccine: an alpha level of 2.5% (one-sided hypotheses), a maximum acceptable difference of 0.301 for GMTs, and a standard deviation of 1.0 for serotype 1, 0.8 for serotypes 2 and 3, 0.7 for serotype 4 (based on CYD22 and CYD47 studies conducted in Asia Pacific).

The following assumptions were considered for the non-inferiority after the third dose of CYD dengue vaccine: an alpha level of 2.5% (one-sided hypotheses), a maximum acceptable difference

of 0.301 for GMTs, and a standard deviation of 0.8 for serotypes 1 and 2, 0.7 for serotypes 3 and 4 (based on studies conducted in Asia Pacific).

The following tables indicate the individual powers for the non-inferiority testing considering a number of evaluable subjects of 309 per group for the co-primary and secondary objectives, or 255 per group for the co-primary objective (Table 12.3) and 162 per group for the secondary objective (Table 12.1and Table 12.2).

Table 12.1: Powers for Non-inferiority of seroprotection/GMC/GMT for each antigen and serotype between groups- Primary objective

Antigen/Serotype	Alpha	δ	Reference rate/SD	Power (%) for 309 evaluable subjects per group	Power (%) for 255 evaluable subjects per group
D	0.025	10%	99%	> 99.9	> 99.9
T	0.025	10%	99%	> 99.9	> 99.9
PT	0.025	0.176	0.4	> 99.9	> 99.9
FHA	0.025	0.176	0.4	> 99.9	> 99.9
PRN	0.025	0.176	0.5	99.2	97.8
FIM2+3	0.025	0.176	0.6	95.4	91.1
Dengue serotype 1	0.025	0.301	1.0	96.2	92.4
Dengue serotype 2	0.025	0.301	0.8	99.7	98.9
Dengue serotype 3	0.025	0.301	0.8	99.7	98.9
Dengue serotype 4	0.025	0.301	0.7	> 99.9	99.8
Global power				**90%**	**80%**

Table 12.2: Powers for Non-inferiority of GMT for each serotype between groups- Secondary objective

Serotype	Alpha	δ	Reference SD	Power (%) for 309 evaluable subjects per group	Power (%) for 162 evaluable subjects per group
Dengue serotype 1	0.025	0.301	0.8	99.7	96.4
Dengue serotype 2	0.025	0.301	0.8	99.7	96.4
Dengue serotype 3	0.025	0.301	0.7	> 99.9	99.0
Dengue serotype 4	0.025	0.301	0.7	> 99.9	99.0
Global power				**99%**	**80%**

This sample size will also provide a 95% probability of observing an AE that has a true incidence > 0.87% in each group (N=344).

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 DC, and transfer the information to the eCRF.

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.

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the trial (i.e., 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, eCRF 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 eCRF Completion Guidelines for entering data into the eCRF, and the Operating Guidelines for detailed trial procedures such as the product management and sample-handling procedures.

After the start of the trial, the Sponsor's 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 eCRF. 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 eCRF 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 eCRF, 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 CTA 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 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 Signature

I confirm that this protocol (version 2.0 dated 04 January 2018) is in accordance with applicable regulations and Good Clinical Practice.

Sponsor Signature

I confirm that this protocol (version 2.0 dated 04 January 2018) is in accordance with applicable regulations and Good Clinical Practice.