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Sponsor: Sanofi Pasteur **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** U1111-1116-4957, IND 11219, NCT01373281, 2014-001708-24 **Study code:** CYD14
Title of the study: Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 14 years in Asia	
Study center(s): This was a multi-center trial conducted across 11 sites in Indonesia, Malaysia, Thailand, the Philippines, and Viet Nam (2 to 3 sites in each country).	
Study period: Date first subject/patient enrolled: 03/Jun/2011 Date last subject/patient completed: 21/Nov/2017	
Phase of development: Phase 3	

Objectives:

Primary objective:

To assess the efficacy of chimeric-yellow-fever dengue (CYD) vaccine after 3 vaccinations at 0, 6 and 12 months in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the 4 serotypes in children aged 2 to 14 years at the time of inclusion.

Secondary objectives:

ALL SUBJECTS (N=10 278):

Efficacy during the Active Phase

1) To describe the efficacy of CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases after the third dose to the end of the Active Phase:
   a. due to at least 3 serotypes
   b. due to each of the 4 serotypes
2) To describe the efficacy of CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases after at least 1 dose:
   c. due to any of the 4 serotypes
   d. due to at least 3 serotypes
   e. due to each of the 4 serotypes
3) To describe the efficacy of CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases after 2 doses:
   f. due to any of the 4 serotypes
   g. due to at least 3 serotypes
   h. due to each of the 4 serotypes

Safety

4) To describe the occurrence of SAEs, including serious adverse events of special interest (AESIs), in all subjects throughout the trial period.

5) To describe the occurrence of hospitalized virologically-confirmed dengue cases and the occurrence of severe (clinically-severe or as per WHO criteria) virologically-confirmed dengue cases, throughout the Surveillance Expansion Period (SEP) and throughout the trial (from D0 until the end of the trial).

IMMUNOGENICITY AND REACTOGENICITY SUBSET (N=2000):

Immunogenicity

6) To describe the antibody (Ab) response to each dengue serotype after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3.

Reactogenicity

7) To describe the reactogenicity of CYD dengue vaccine after each dose.

Methodology:

CYD14 was a randomized, observer-blind, placebo-controlled, multi-center, Phase III trial in 10 278 subjects.

There were 3 injections and subjects were randomized in a 2 to 1 ratio to 2 groups:

CYD Dengue Vaccine Group (N=6852): CYD dengue vaccine at 0, 6, and 12 months

Control Group (N=3426): placebo (NaCl 0.9%) at 0, 6, and 12 months

A licensed non-dengue vaccine appropriate for the age group was offered to participants at least 6 months after the last dose. This active non-dengue vaccine was intended to offer benefit to the subjects. The choice of this vaccine and the timing of its administration were site-specific and are described in the site-specific annexes of the protocol.

A subset of subjects from each country was evaluated for reactogenicity and immunogenicity to enable the generation of country-specific data on reactogenicity, immunogenicity, and baseline dengue and Japanese encephalitis (JE) antibody (Ab) levels. It was planned that subjects were to be randomized to the subset during the first 2 months of enrollment in each country; this period was extended in some countries because of lower inclusion rate. Between 300 and 600 subjects were targeted to be enrolled in each participating country, to a total of 2000 subjects (1333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) was involved in the regular review of safety data and confirmed dengue cases including assessment of dengue severity. Additionally, any related serious adverse event (SAE) or death was promptly reviewed by the IDMC. The IDMC was involved in the regular blinded review of safety.

Detection of dengue cases

Suspicion of dengue was based on the presence of an acute febrile episode. Two consecutive febrile episodes were considered as separate episodes if the interval between these 2 episodes is > 14 days. An acute febrile episode was considered to have ended once the temperature is < 38°C.

Dengue cases were detected using different methodologies throughout the trial, as described below:

Active Phase

For each subject, the Active Phase of dengue case detection began from Dose 1 and was expected to continue until 13 months after Dose 3. It was assumed that 12 months of surveillance resulted in the detection of a sufficient number of virologically-confirmed dengue cases to allow for an assessment of efficacy. The continuation of the Active Phase for 13 months post-Dose 3 was based on this 12 month period beginning 28 days after Dose 3.

This phase involved regular contact with parents/guardians of the subjects (eg, phone calls, short message service [SMS], home visits, and school based surveillance; the method of contact could be different at each site and was detailed in the site-specific annexes). The purpose of this contact was to provide a reminder to take their child to the trial center or health care center in the event of acute febrile illness. There was an initial minimum frequency of one contact every week; however this frequency could be changed following written notification to sites.

Hospital Phase

This phase began after the Active Phase. Subjects with febrile illness and requiring hospitalization were screened for dengue. This phase continued until consent to participate in the SEP was given or otherwise, until trial completion.

During this phase, there was a minimum frequency of one contact every 3 months and surveillance of identified non-study healthcare sites was performed.

Surveillance Expansion period

Subjects consenting to take part into the SEP were actively followed for dengue case detection similar to the Active Phase. Thus, surveillance was designed to maximize the detection of symptomatic confirmed dengue (hospitalized or not) in order to describe CYD dengue vaccine efficacy and safety in preventing symptomatic dengue. Subjects who declined participation continued surveillance as in the Hospital Phase (HP) until trial completion (up to 60 months post-Dose 3).

Management of suspected dengue cases

In addition to the tests performed as part of the local standard of care, 2 blood samples (acute and convalescent) were taken to confirm the dengue case in the event of any acute febrile illness (ie, temperature ≥ 38°C on at least 2 consecutive days) during the Active Phase. Likewise, acute and convalescent samples were taken in the event of hospitalized acute febrile illness during the HP until the Surveillance Expansion visit (Vse), when the subject consented or declined to enter the SEP. From this timepoint (Vse), whenever it occured, and until the end of the trial, only the first blood sample (acute sample) was taken:

1) The first blood sample was taken, throughout the trial, during the acute phase of the disease, as soon as possible and within 5 days of the onset of fever. Testing included dengue non-structural protein (NS) 1 antigen (Ag) enzyme-linked immunosorbent assay (ELISA), dengue screen (DS) reverse transcriptase-polymerase chain reaction (RT-PCR), dengue serotype- specific RT-PCR, hematocrit, platelet count, aspartate aminotransferase (AST) and alanine transaminase (ALT). Dengue immunoglobulin (Ig) M/IgG ELISA was performed in acute samples from D0 until Vse. It may have also been performed from Vse until the end of the trial. Acute samples were used for the virological confirmation of dengue cases.
2) The second blood sample was taken, from D0 until Vse, during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample). Testing included dengue IgM/IgG ELISA, hematocrit, platelet count, AST and ALT.

Acute and convalescent sample pairs were used to explore IgG and IgM levels from subjects developing subsequent dengue infections from D0 until Vse.

Note: Acute and convalescent blood samples for all suspected dengue cases were collected within the pre-specified timeframe as described above. If this could not be accomplished, these samples were obtained as soon as possible thereafter.

A tourniquet test was also performed during the acute phase before the blood sample was taken. However, if a subject presented with other clinical signs of spontaneous haemorrhage, the tourniquet test was not mandatory.

Number of subjects:	Planned: 10278 Randomized: 10275 Treated: 10272
Evaluated:	Efficacy: 10059 Immunogenicity: 1983 Safety: 10272

Diagnosis and criteria for inclusion:

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

1) Aged 2 to 14 years on the day of inclusion and resident of the site zone
2) Subject in good health, based on medical history and physical examination
3) Assent form or informed consent form has been signed and dated by the subject (based on local regulations), and informed consent form 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) Subject able to attend all scheduled visits and to comply with all trial procedures

Study treatments

Investigational medicinal product: CYD dengue vaccine (Phase III lot)

Form: Powder and solvent for suspension for injection

Composition: Each 0.5 mL dose of reconstituted vaccine contains:

4.5 – 6 log10 cell-culture infectious dose 50% (CCID50) of each live, attenuated, dengue serotype 1, 2, 3, 4 virus

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 of administration: Subcutaneous (SC)

Dose regimen: 3 vaccinations at 0, 6, and 12 months

Investigational medicinal product: Placebo (NaCl)

Form: Solution

Composition: NaCl 0.9%

Route of administration: SC

Dose regimen: 3 injections at 0, 6, and 12 months

Duration of participation:

The duration of each subject's participation in the trial was approximately 6 years, except for prematurely discontinued subjects:

- The duration of the Active Phase for each subject was 25 months.
- The duration of the HP for subjects consenting to participate in the SEP was expected to be from the end of the Active Phase until consent for SEP was given. For subjects declining participation in the SEP, the duration of the HP was expected to be 47 months (from the end of Active Phase until the end of the trial).
- The duration of the SEP for subjects consenting to participate was expected to start at the time of consent (ie, after at least one year HP) and to last until the end of the trial.

Criteria for evaluation:

Primary endpoint:

Symptomatic virologically-confirmed dengue cases occurring > 28 days after Dose 3 (during the Active Phase) and defined as:

- Acute febrile illness (ie, temperature ≥ 38°C on at least 2 consecutive days)
- Virologically-confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test

It was expected that the number of symptomatic dengue cases virologically-confirmed in a 12-month period was sufficient to demonstrate efficacy. As this period began after 28 days after Dose 3, the Active Phase of dengue surveillance continued for each subject until 13 months after Dose 3.

Secondary endpoints:

ALL SUBJECTS (N=10,278):

Efficacy During the Active Phase

For the secondary efficacy objectives, dengue cases were taken into account if they occurred more than 28 days after the respective vaccination. In addition, the analysis on vaccine efficacy (VE) during the whole Active Phase (including the 28 days post vaccination) was performed.

Safety

Occurrence of SAEs, including serious AESIs, in all subjects is collected throughout the entire study.

Occurrence of hospitalized virologically-confirmed dengue cases and occurrence of severe (clinically-severe or as per WHO criteria) confirmed dengue cases, occurring during the SEP and during the trial.

IMMUNOGENICITY AND REACTOGENICITY SUBSET (N=2000):

Immunogenicity

Neutralizing Ab level against each of the 4 parental dengue virus strains of CYD dengue vaccine constructs (and potentially against recently isolated strains) are measured at baseline, after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3 (dengue neutralization assay). Likewise, neutralizing Ab level will be measured at Vse, whenever it occurs.

In addition, baseline neutralizing Abs against JE are described.

Reactogenicity

Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each dose.

Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (ie, pre-listed in the subject's diary and electronic case report form), injection site reactions occurring up to 7 days after each dose.

Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited systemic reactions occurring up to 14 days after each dose.

Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each dose.

Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination of non-serious AESIs occurring up to 7 days after each dose.

Statistical methods:

The first analysis was performed to assess the vaccine efficacy (VE) after the complete schedule of injections had been received by the subjects. This analysis was done on the per-protocol analysis set for efficacy (PPSE) after the completion of the Active Phase, and then was confirmed on the modified full analysis set for efficacy (mFASE).

Additional descriptive statistical analyses was performed after completion of each year of follow-up of the Hospital Surveillance Phase/SEP or when data became available, with a final analysis performed at the end of the study.

Analysis for the Primary Objective

The following hypotheses (H) were tested using an alpha=2.5%

H0: VE ≤ 25%

H1: VE > 25%

The statistical methodology was based on the use of the two-sided 95% Confidence Interval (CI) of the VE. The CI was calculated using the exact method described by Breslow & Day.

Then a second analysis of VE was also performed on the mFASE population. All subjects with a virologically-confirmed dengue case occurring more than 28 days after the third dose were considered as cases for this mFASE during the Active Phase. Additional stratified analyses were conducted to take into account the different countries and/or other covariates.

Analyses for the Secondary Objectives

The main efficacy, safety, and immunogenicity parameters were described with 95% CI using normal assumption for quantitative data, exact binomial distribution for proportions (Clopper-Pearson method) and exact method (Breslow & Day) for VE.

For efficacy against at least 3 serotypes, each combination was calculated:

- VE against Serotypes 1-2-3
- VE against Serotypes 1-2-4
- VE against Serotypes 2-3-4
- VE against Serotypes 1-3-4

Reactogenicity Evaluation

A subset of 2000 subjects (1333 in the CYD Dengue Vaccine Group and 667 in the Control Group) were to be included in the reactogenicity analysis that described both solicited and unsolicited events.

Subjects were randomized to the subset during the first 2 months of enrollment in each country; this period may have been extended in case of a lower inclusion rate. Between 300 and to 600 subjects were to be targeted to be enrolled in each participating country, to a total of 2000 subjects.
1333 subjects in the CYD Dengue Vaccine Group gave a probability of 95% of observing an event with a true incidence of 0.23% (rule of three). Furthermore, with this sample size, the 95% CIs of proportion had a range < 5.5%.

Immunogenicity Evaluation

The same subset as for reactogenicity was used for the immunogenicity evaluation. Immunogenicity parameters were described with 95% CI.

Summary:

Subjects Disposition

Between 03 June 2011 and 01 December 2011, a total of 10 275 subjects were randomized: 6851 in the CYD Dengue Vaccine Group and 3424 in the Control Group. A total of 2000 subjects, 1336 in the CYD Dengue Vaccine Group and 664 in the Control Group, were randomized in the immunogenicity and reactogenicity subset, and they were included between June 2011 and October 2011.

The distribution by country and treatment group of the overall subjects randomized in the study and the subset is summarized hereafter:

Country distribution and randomized treatment group in the overall population and in the immunogenicity & reactogenicity subset- Randomized Subjects

	CYD Dengue Vaccine Group (N=6851)		Control Group (N=3424)		All Subjects (N=10275)	
	n	n subset	n	n subset	n	n subset
Indonesia	1246	234	624	116	1870	350
Malaysia	937	204	464	96	1401	300
Philippines	2335	402	1166	200	3501	602
Thailand	778	225	392	116	1170	341
Viet Nam	1555	271	778	136	2333	407

n: number of subjects fulfilling the item listed

Overall, 10 194 subjects (99.2%) completed the Active Phase of the study, and 9874 (96.1%) completed the long term follow-up (LTFU). The same percentage was observed in the subset (99.2% and 96.5%, respectively for the Active Phase and the LTFU).

A total of 10 272 subjects (3 were not vaccinated) were included in the full analysis set for efficacy (FASE) and 10 059 subjects were included in the PPSE.

Demographic Characteristics

In the PPSE, there were similar percentages of female (51.5%) and male subjects (48.5%). Overall, 24.0% of the subjects were in the age group 2 to 5 years old, 53.3% in the age group 6 to 11 years old, and 22.8% in the age group 12 to 14 years old.

The mean age at enrollment was 8.8 years. The demographic characteristics were well balanced between the treatment groups and comparable across the different populations (randomized subjects, FASE, SafAS, and FASI) and across countries.

	CYD Dengue Vaccine Group	Control Group	Total
Per-protocol analysis set for efficacy (PPSE)			
Number	6709	3350	10059
Mean age, years (SD)	8.8 (3.5)	8.8 (3.4)	8.8 (3.4)
Male, n (%)	3252 (48.5)	1623 (48.4)	4875 (48.5)
Female, n (%)	3457 (51.5)	1727 (51.6)	5184 (51.5)
Full analysis set for immunogenicity (FASI)			
Number	1323	660	1983
Mean age, years (SD)	8.6 (3.8)	8.6 (3.8)	8.6 (3.8)
Male, n (%)	652 (49.3)	310 (47.0)	962 (48.5)
Female, n (%)	671 (50.7)	350 (53.0)	1021 (51.5)
Seroprevalence at baseline n (%)			
Dengue or Japanese encephalitis	1042 (78.8)	509 (77.1)	1551 (78.2)
Dengue	896 (67.7)	444 (67.3)	1340 (67.6)
Japanese encephalitis	702 (53.1)	341 (51.7)	1043 (52.6)
Safety analysis set (SafAS)			
Number	6848	3424	10272
Mean age, years (SD)	8.8 (3.5)	8.8 (3.4)	8.8 (3.4)
Male, n (%)	3324 (48.5)	1657 (48.4)	4981 (48.5)
Female, n (%)	3524 (51.5)	1767 (51.6)	5291 (51.5)

In the immunogenicity and reactogenicity subset, the proportion of dengue-immune subjects at baseline (neutralizing Ab response ≥10 (1/dil) using Dengue PRNT50) increased with age: from 51.3% for the 2 to 5 years age group to 81.0% for the 12 to 14 years age group. Differences in terms of dengue status at baseline were observed across countries: from 47.8% of dengue-immune subjects at baseline in Malaysia to 80.8% in Indonesia.

Efficacy

Overall, 8927 febrile episodes were reported during the Active Phase, with 65.2% in CYD Dengue Vaccine Group and 34.8% in the Control Group; 98.4% of these febrile episodes had an acute blood sample collected within the first 5 days after the fever onset, and less than 0.1% did not have any acute blood sample collected. Also, for 5 subjects in Thailand, the acute blood samples taken more than 5 days after fever onset were excluded from the main analysis. Among these febrile episodes, 612 (293 in the CYD Group and 319 in the Control Group in SafAS) were virologically-confirmed as being dengue episodes. Of these, 1 subject in each treatment group presented 2 virologically-confirmed dengue (VCD) episodes of the same serotype (serotype 1), so the second episode was not considered in the analyses, and 14 subjects reported 2 VCD episodes of different serotypes during the Active Phase (sequential infections). In addition 5 subjects in the Control Group presented co-infections (3 subjects co-infected with serotypes 1 and 2, 1 subject co-infected with serotypes 1 and 4, and 1 subject co-infected with serotypes 1 and 3).

During the Active Phase, all 4 serotypes were circulating in the 5 countries and within each individual country with a different serotypes distribution. The density incidence of VCD in children in the Control Group was 4.7% during the 25-month active surveillance period (ie, the Active Phase) and 4.1 % during the post-Dose 3 period (ie, from 28 days post-Dose 3 until the end of the Active Phase). During the Active Phase, the density incidence varied across serotypes with 1.9%, 1.1%, 0.6%, and 1.0% in the Control Group for serotypes 1, 2, 3, and 4, respectively. This serotype distribution was similar between the Active Phase and the post-Dose 3 period.

Overall, in the FASE, 595 subjects presented symptomatic VCD cases due to any serotype during the Active Phase. In the PPSE, a total of 250 subjects presented VCD cases more than 28 days post-Dose 3.

Primary Objective

Vaccine Efficacy (VE) Against VCD Due to Any Serotype – Post-Dose 3 PPSE)

	CYD Dengue Vaccine Group (N=6709)				Control Group (N=3350)				Vaccine Efficacy	
	Cases	Person-years at risk	Density incidence (95% CI)	n Episodes	Cases	Person-years at risk	Density incidence (95% CI)	n Episodes	%	(95% CI)
Symptomatic VCD	117	6525	1.8 (1.5; 2.1)	117	133	3227	4.1 (3.5; 4.9)	134	56.5	(43.8;66.4)

Cases: number of subjects with at least one symptomatic VCD episode from 28 days post-injection 3 to the end of Active Phase.
Density incidence: data are cases per 100 person-years at risk.
The person-years at risk was the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first. The person-years at risk calculation presented in the tables is the sum of individual units of time for which the participants contributed to the analyses. Incidence density was calculated as the number of VCD cases divided by the cumulative person-years at risk.
n Episodes: number of symptomatic VCD episodes in the considered period.

The vaccine efficacy is considered as significant if the lower bound of its 95% CI (exact method described by Breslow & Day) is greater than 25%.

A total of 250 subjects reported at least 1 VCD episode in the 12 months between 28 days post-injection 3 and the end of the Active Phase.

The overall primary estimate of VE against symptomatic VCD post-Dose 3 due to any serotype was 56.5% (95% CI: 43.8; 66.4), and the primary objective was met with a lower bound of 95% CI above 25%.

Similar results were observed in the mFASE.

Secondary Objectives

VE against VCD due to any and each serotype post-Dose 2, post-Dose 3 and during the Active Phase are summarized in the table below:

	Post-Dose 2			Post-Dose 3			Active Phase		
	Number of cases CYD vs Control	VE (%)	(95% CI)	Number of cases CYD vs Control	VE (%)	(95% CI)	Number of cases CYD vs Control	VE (%)	(95% CI)
Any serotype	205/238	57.9	(49.0; 65.2)	118/134	56.5	(43.8; 66.3)	286/309	54.8	(46.8; 61.7)
Serotype 1	80/91	56.7	(40.9; 68.3)	51/50	50.0	(24.6; 66.8)	116/126	54.5	(40.9; 64.9)
Serotype 2	70/56	37.9	(10.1; 56.9)	38/29	35.0	(-9.2; 61.0)	97/74	34.7	(10.4; 52.3)
Serotype 3	20/34	70.7	(47.7; 84.0)	10/23	78.4	(52.9; 90.8)	30/43	65.2	(43.3; 78.9)
Serotype 4	32/60	73.6	(58.7; 83.3)	17/34	75.3	(54.5; 87.0)	40/72	72.4	(58.8; 81.7)

Cases: number of subjects with at least one symptomatic VCD episode in the considered period.
Post-Dose 2: period from 28 days post-Dose 2 to the end of the Active Phase (OEAS)
Post-Dose 3: period from 28 days post-Dose 3 to the end of the Active Phase (mFASE)
Active Phase: period from Day 0 to the end of the Active Phase (FASE)

Descriptive analyses by serotype post-Dose 3 showed different VE estimates ranging from 35.0% (serotype 2) to 78.4% (serotype 3). Over this period, VE was 35.0% against serotype 2, but the 95% CI included 0. During the Active Phase, descriptive analyses by serotype showed different VE estimates ranging from 34.7% (serotype 2) to 72.4% (serotype 4). VE was 34.7% against serotype 2, but the 95%CI was greater than 0 as all VCD cases were included over this period and then improved the precision around the point estimate.

Other secondary objectives, VE against VCD due to at least 3 serotypes post-Dose 3 and during the Active Phase, VE against VCD post-Dose 1 (period excluding the 28 days post-Dose 1 vaccination) were also analyzed but are not presented in the synopsis.

Immunogenicity

Immunogenicity was evaluated in the immunogenicity and reactogenicity subset and analyzed by the measurement of dengue neutralizing Abs using the dengue plaque reduction neutralization test (PRNT50).

Immunogenicity results in the FASI are presented below.

Seropositivity Against at Least 1, 2, 3 or 4 Serotypes (FASI)

Baseline seropositivity rates (percentages of subjects with neutralizing Ab titers ≥ 10 (1/dil)) against at least 1 serotype were similar in both treatment groups.

At baseline, in the FASI, the percentage of subjects seropositive against at least 1, 2, 3 or 4 serotypes, were similar across the 2 treatment groups. Seropositivity at baseline against all 4 serotypes was 42.0% in the CYD Dengue Vaccine Group and 40.8% in the Control Group. In the CYD Dengue Vaccine Group, the percentages of subjects seropositive increased post-injection 2 and post-injection 3 (84.9% and 91.0%, respectively). From 1 to 5 years post-injection 3, the percentage of seropositive subjects remained high (72.1%, 65.4%, 72.8%, 73.9%, and 69.3%, respectively).

In the Control Group, the percentage of subjects seropositive remained stable overtime.

GMTs by Serotype (FASI)

Component (PRNT- [l/dil])	Timepoint	CYD Dengue Vaccine Group			Control Group		
		M	GMT	(95% CI)	M	GMT	(95% CI)
Serotype 1	Pre-Inj 1	1309	38.3	(33.8; 43.5)	655	42.1	(35.0; 50.6)
	Post- Inj 2	1317	153	(137; 170)	654	46.1	(38.2; 55.7)
	Post- Inj 3	1316	166	(150; 183)	657	46.6	(38.7; 56.1)
	Year 1 FU Post-Inj 3	1290	105	(92.8; 119)	634	57.2	(46.9; 69.8)
	Year 2 FU Post-Inj 3	1286	90.1	(79.6; 102)	649	62.4	(51.5; 75.6)
	Year 3 FU Post-Inj 3	1294	104	(92.2; 118)	649	80.3	(66.0; 97.6)
	Year 4 FU Post-Inj 3	1286	98.5	(87.7; 111)	644	80.9	(66.9; 97.8)
	Year 5 FU Post-Inj 3	1275	81.2	(72.5; 91.0)	640	77.6	(65.4; 92.2)
Serotype 2	Pre-Inj 1	1313	55.3	(48.7; 62.9)	654	62.1	(51.7; 74.7)
	Post- Inj 2	1316	360	(329; 394)	655	69.5	(57.7; 83.6)
	Post- Inj 3	1314	355	(327; 386)	657	68.5	(57.1; 82.2)
	Year 1 FU Post-Inj 3	1298	194	(175; 214)	640	78.1	(64.8; 94.0)
	Year 2 FU Post-Inj 3	1284	150	(135; 166)	649	77.9	(65.3; 92.8)
	Year 3 FU Post-Inj 3	1295	217	(195; 241)	649	118	(97.9; 142)
	Year 4 FU Post-Inj 3	1285	168	(151; 187)	645	113	(94.7; 135)
	Year 5 FU Post-Inj 3	1275	144	(130; 160)	640	102	(86.8; 120)
Serotype 3	Pre-Inj 1	1307	40.1	(35.6; 45.1)	650	40.7	(34.5; 48.0)
	Post- Inj 2	1313	203	(184; 223)	656	40.8	(34.6; 48.1)
	Post- Inj 3	1314	207	(189; 226)	657	42.5	(36.2; 49.9)
	Year 1 FU Post-Inj 3	1298	186	(168; 206)	639	62.1	(51.8; 74.6)
	Year 2 FU Post-Inj 3	1255	118	(106; 132)	637	55.8	(47.1; 66.1)
	Year 3 FU Post-Inj 3	1294	158	(141; 177)	649	86.1	(71.9; 103)
	Year 4 FU Post-Inj 3	1286	153	(138; 170)	645	87.0	(73.1; 103)
	Year 5 FU Post-Inj 3	1275	120	(108; 133)	640	76.2	(65.3; 89.0)
Serotype 4	Pre-Inj 1	1313	25.3	(22.9; 28.0)	653	26.2	(22.6; 30.3)
	Post- Inj 2	1318	151	(139; 163)	655	24.4	(21.3; 28.1)
	Post- Inj 3	1315	151	(141; 162)	657	26.0	(22.6; 29.8)
	Year 1 FU Post-Inj 3	1293	85.5	(78.5; 93.0)	621	26.0	(22.4; 30.3)
	Year 2 FU Post-Inj 3	1268	70.0	(64.1; 76.4)	640	30.4	(26.2; 35.2)
	Year 3 FU Post-Inj 3	1293	97.5	(89.4; 106)	645	48.2	(41.4; 56.2)
	Year 4 FU Post-Inj 3	1286	89.5	(82.3; 97.3)	643	46.7	(40.2; 54.1)
	Year 5 FU Post-Inj 3	1275	65.7	(60.3; 71.6)	640	40.1	(34.8; 46.1)

Overall, geometric means of titers (GMTs) at baseline were comparable across serotypes with a trend to higher GMTs for serotype 2. GMTs ranged from 25.3 (1/dil) for serotype 4 to 55.3 (1/dil) for serotype 2 in the CYD Dengue Vaccine Group and from 26.2 (1/dil) for serotype 4 to 62.1 (1/dil) for serotype 2 in the Control Group.

After 2 and 3 injections, GMTs increased as compared to the baseline. Similar levels of GMTs were observed for each serotype after the second and the third injection. The highest level of GMTs was observed for serotype 2. After the third injection, GMTs were 166 (1/dil), 355 (1/dil), 207 (1/dil), and 151 (1/dil) for serotypes 1, 2, 3, and 4, respectively.

One year post-injection 3, GMTs were higher as compared to baseline for all serotypes, with geometric mean of the individual titer ratios (GMTRs) (1 year post-injection 3/baseline) at 1.96 (1/dil) for serotype 1, 2.61 (1/dil) for serotype 2, 3.48 (1/dil) for serotype 3, and 2.40 (1/dil) for serotype 4. Different levels of decrease of GMTs depending on serotype were observed one year post-injection 3 as compared to post-injection 3 with higher decrease of GMTs for serotype 2 and similar GMTs for serotype 3. GMTs one year post-injection 3 ranged from 85.5 (1/dil) for serotype 4 to 194 (1/dil) for serotype 2.

Two years post-injection 3, GMTs remained higher as compared to baseline for all serotypes with GMTRs (2 years post-injection 3/baseline) at 1.66 for serotype 1, 1.99 for serotype 2, 2.17 for serotype 3, and 2.00 for serotype 4. Different levels of decrease of GMTs depending on serotype were observed 2 years post-injection 3 as compared to post-injection 3 with higher decrease of GMTs for serotype 2. GMTs 2 years post-injection 3 ranged from 70.0 (1/dil) for serotype 4 to 150 (1/dil) for serotype 2.

Three years post-injection 3, GMTs still remained higher than baseline levels for all serotypes. It is noteworthy that GMTs at year 3 post-injection 3 tended to be higher than the levels observed at year 2 post-injection 3 for all serotypes. From year 2 to year 3 post-injection, GMTs increased from 90.1 to 104 for serotype 1, from 150 to 217 for serotype 2, from 118 to 158 for serotype 3, and from 70.0 to 97.5 for serotype 4.

Four years post-injection 3, GMTs were still at similar values as compared to those observed 3 year post-injection 3: GMTs was 98.5 (1/dil) for serotype 1, 168 (1/dil) for serotype 2, 153 (1/dil) for serotype 3, and 89.5 (1/dil) for serotype 4; GMTRs (4 years post-injection 3/baseline) were at 1.82 for serotype 1, 2.23 for serotype 2, 2.79 for serotype 3, and 2.50 for serotype 4.

Five years post-injection 3, GMTs were at lower values as compared to those observed 4 year post-injection 3: GMTs was 81.2 (1/dil) for serotype 1, 144 (1/dil) for serotype 2, 120 (1/dil) for serotype 3, and 65.7 (1/dil) for serotype 4; GMTRs (5 years post-injection 3/baseline) were at 1.50 for serotype 1, 1.90 for serotype 2, 2.17 for serotype 3, and 1.83 for serotype 4.

In the Control Group, GMTs per serotype remained stable over time, except during year 3 post-injection 3. Between the second and third year post-injection 3 the GMTs increased for all serotypes: from 62.4 to 80.3 (1/dil) for serotype 1, from 77.9 to 118 (1/dil) for serotype 2, from 55.8 to 86.1 (1/dil) for serotype 3, and from 30.4 to 48.2 (1/dil) for serotype 4. Four years post-injection 3, GMTs were similar to those observed 3 years post-injection 3: 80.9 (1/dil) for serotype 1, 113 (1/dil) for serotype 2, 87.0 (1/dil) for serotype 3, and 46.7 (1/dil) for serotype 4. Five years post-injection 3, GMTs were slightly lower than those observed 4 years post-injection 3: 77.6 (1/dil) for serotype 1, 102 (1/dil) for serotype 2, 76.2 (1/dil) for serotype 3, and 40.1 (1/dil) for serotype 4.

Safety

All subjects were assessed for safety (SAEs) and reactogenicity solicited reaction and unsolicited non-serious AEs were evaluated on the immunogenicity and reactogenicity subset. A safety overview summarizing AEs and SAEs reported from D0 up to 48 months after the third injection (safety analysis set) and reactogenicity events reported within 28 days after any injection (subset analysis) is given hereafter:

Safety overview

	CYD Dengue Vaccine Group			Control Group		
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n**	**%**	**(95% CI)**
Safety Analysis Set (Active Phase)	**N=6848**			**N=3424**		
SAE*	355	5.2	(4.7; 5.7)	220	6.4	(5.6; 7.3)
Death	4	<0.1	(0.0; 0.1)	1	<0.1	(0.0; 0.2)
Safety Analysis Set (HP/SEP)	**N=6782**			**N=3387**		
SAE*	668	9.8	(9.2; 10.6)	372	11.0	(9.9; 12.1)
Death	6	<0.1	(0.0; 0.2)	3	<0.1	(0.0; 0.3)
Reactogenicity Subset	**N=1334**			**N=663**		
Immediate unsolicited non-serious AE	0	0	(0.0; 0.3)	0	0	(0.0; 0.6)
Solicited reactions	896	67.3	(64.7; 69.8)	423	63.8	(60.0; 67.5)
Solicited injection site reaction†	633	47.5	(44.8; 50.2)	285	43.0	(39.2; 46.9)
Solicited systemic reaction†	760	57.1	(54.3; 59.7)	367	55.4	(51.5; 59.2)
Unsolicited non-serious AE	489	36.7	(34.1; 39.3)	268	40.4	(36.7; 44.3)
Unsolicited non-serious AR	19	1.4	(0.9; 2.2)	6	0.9	(0.3; 2.0)
Unsolicited non-serious injection site AR	9	0.7	(0.3; 1.3)	2	0.3	(0.0; 1.1)
Unsolicited non-serious systemic AE	489	36.7	(34.1; 39.3)	268	40.4	(36.7; 44.3)
Unsolicited non-serious systemic AR	10	0.7	(0.4; 1.4)	4	0.6	(0.2; 1.5)

*This includes SAEs due to VCD

† Data missing for 2 subjects in the CYD Dengue Vaccine Group

Solicited Injection Site Reactions

After the first injection, no difference was observed between the 2 groups in terms of solicited injection site reactions. In both groups, injection site pain was the most frequently reported solicited reaction (30.5% in the CYD Dengue Vaccine Group and 29.6% in the Control Group). Most of solicited injection site reactions were of Grade 1. Almost all solicited injection site reactions occurred within 3 days after injection and resolved within 1 to 3 days.

Only one Grade 3 injection site reaction was reported: one subject in the CYD Dengue Vaccine Group experienced a pain recorded as Grade 3 for one day, after the first injection.

After the second injection, there was a trend of less injection site reactions reported (23.6% in the CYD Dengue Vaccine Group and 20.8% in the Control Group) compared with the first injection in both groups (32.4% in the CYD Dengue Vaccine Group and 31.5% in the Control Group). After the third injection, a similar incidence of injection site reactions was reported compared to after the second injection in both groups.

Solicited Systemic Reactions

After the first injection, no difference was observed between the 2 groups in terms of solicited systemic reactions. In both groups, headache and malaise were the most frequently reported solicited reaction (29.1% and 23.4%, respectively, in the CYD Dengue Vaccine Group and 25.3% and 22.3%, respectively, in the Control Group). Solicited systemic reactions were mostly reported as Grade 1. The majority occurred within 3 days after injection (except fever in the Control Group which occurred within 8 to 14 days) and resolved within 1 to 3 days.

Grade 3 solicited systemic reactions were reported in ≤ 1.4% of subjects and in similar frequency in both groups. Grade 3 fever was reported in 18 subjects (1.4%) and 7 subjects (1.1%), respectively, in the CYD Dengue Vaccine Group and the Control Group.

After the second injection, solicited systemic reactions tended to be less frequently reported (27.1% in the CYD Dengue Vaccine Group and 28.4% in the Control Group) compared with the first injection (40.4% in the CYD Dengue Vaccine Group and 37.3% in the Control Group). There was similar frequency of reporting of solicited systemic reactions after the second and after the third injection in both groups.

Unsolicited Non-serious AEs

After the first injection, the percentage of subject experiencing at least one unsolicited AEs was similar in the 2 groups: 20.4% in the CYD Dengue Vaccine Group and 25.5% in the Control Group. For both groups, the most frequently reported unsolicited non-serious AEs were in the system organ class (SOC) Infections and infestations (11.9% in the CYD Dengue Vaccine Group and 15.7% in the Control Group), Respiratory, thoracic and mediastinal disorders (4.7% in the CYD Dengue Vaccine Group and 6.2% in the Control Group), and Gastrointestinal disorders (3.1% in the CYD Dengue Vaccine Group and 4.1% in the Control Group). These AEs were mainly reported as Grade 1, after 15 days after the first injection and lasted 7 days or less. A total of 21 subjects reported at least one Grade 3 unsolicited non-serious AEs within 28 days (11 subjects [0.8%] in the CYD Dengue Vaccine Group and 10 subjects [1.5%] in the Control Group). The most common Grade 3 unsolicited non-serious AEs in the CYD Dengue Vaccine Group were in the SOC Infections and infestations.

After the second injection, there was a trend for less frequent unsolicited non-serious AEs (13.8% in the CYD Dengue Vaccine Group and 15.7% in the Control Group) as compared to the first injection (20.4% in the CYD Dengue Vaccine Group and 25.5% in the Control Group). There was similar frequency of reporting of unsolicited AEs after the second and after the third injection in both groups.

After any injection, 19 subjects (1.4%) in the CYD Dengue Vaccine Group and 6 subjects (0.9%) in the Control Group reported at least one unsolicited non-serious AE related to vaccination according to the Investigator (adverse reaction [AR]): the majority of the ARs were in the SOC General disorders and administration site conditions (11 subjects [0.8%] in the CYD Dengue Vaccine Group and 2 subjects [0.3%] in the Control Group), Skin and subcutaneous tissue disorders (3 subjects [0.2%] in the CYD Dengue Vaccine Group and 1 subject [0.2%] in the Control Group), and Infections and infestations (2 subjects [0.1%] in the CYD Dengue Vaccine Group and 1 subject [0.2%] in the Control Group). Related unsolicited AEs were mostly diseases or disorders commonly reported in subjects in this age range. Most were Grade 1 reactions. Only one Grade 3 unsolicited non-serious AR was reported: one subject reported a Grade 3 unsolicited non-serious AR (hypersensitivity) in the CYD Dengue Vaccine Group, after the first injection, that resolved within 2 days following health care contact and prescription of medication.

SAEs

Active Phase

One immediate SAE was reported as related to the study procedure by the Investigator in the CYD Dengue Vaccine Group, a suspect hypoglycemic malaise 6 minutes after the first injection.

Within 28 days after any injections, 87 subjects reported a total of 88 SAEs (0.8% in the CYD Dengue Vaccine Group and 1% in the Control Group respectively). Most SAEs were in the SOCs Infections and Infestations (26 subjects [0.4%] in the CYD Dengue Vaccine Group and 18 subjects [0.5%] in the Control Group), Injury, poisoning and procedural complications (11 subjects [0.2%] in the CYD Dengue Vaccine Group and 6 subjects [0.2%] in the Control Group), and Nervous system disorders (6 subjects [< 0.1%] in the CYD Dengue Vaccine Group and 5 subjects [0.1%] in the Control Group). Overall, there was no cluster of events within 28 days post any injection in term of nature or time to onset from injection.

A total of 575 subjects experienced 647 SAEs during the Active Phase of the trial. There were no differences between treatment groups: 355 subjects (5.2%) in the CYD Dengue Vaccine Group and 220 subjects (6.4%) in the Control Group. During the 6-month follow-up period, most SAEs were in the SOCs Infections and Infestations (161 subjects [2.4%] in the CYD Dengue Vaccine Group and 110 subjects [3.2%] in the Control Group), Injury, poisoning and procedural complications (58 subjects [0.8%] in the CYD Dengue Vaccine Group and 19 subjects [0.6%] in the Control Group) and Gastrointestinal disorders (26 subjects [0.4%] in the CYD Dengue Vaccine Group and 8 subjects [0.2%] in the Control Group).

Among the 647 SAEs reported, a total of 2 SAEs (< 0.1%) was assessed as related to treatment by the Investigator:

- Acute disseminated encephalomyelitis reported in an 8-year old male child in the CYD Dengue Vaccine Group 7 days after the first injection. The subject, without detectable vaccine virus in blood or cerebrospinal fluid, recovered 15 days later without clinical sequelae and there was no recurrence of event. The subject was not withdrawn from the study and was still followed up for safety purpose but no additional injections were given
- Allergic angioedema with swelling of face and generalized urticaria 18 days after the first injection reported in a subject in the Control Group.

Few neurological unrelated SAEs were reported within 28 days (6 subjects [< 0.1%] in the CYD Dengue Vaccine Group and 5 [0.1%] in the Control Group) and during the 6-month follow-up (20 subjects [0.3%] in the CYD Dengue Vaccine Group and 11 subjects [0.3%] in the Control Group).

No immediate hypersensitivity or allergic reactions, and no cases of viscerotropic or neurotropic disease, were reported.

LTFU

During Y3, 164 subjects (2.4%) and 89 subjects (2.6%) experienced at least one SAE in the CYD Dengue Vaccine Group and in the Control Group, respectively. This corresponds to 175 and 94 SAEs reported in the CYD Dengue Vaccine Group and in the Control Group, respectively. During Y4, 192 subjects (2.8%) and 113 subjects (3.3%) experienced at least one SAE in the CYD Dengue Vaccine Group and in the Control Group, respectively. This corresponds to 205 and 118 SAEs reported in the CYD Dengue Vaccine Group and in the Control Group, respectively. During Y5, 206 subjects (3.1%) and 121 subjects (3.6%) experienced at least one SAE in the CYD Dengue Vaccine Group and in the Control Group, respectively. This corresponds to 226 and 132 SAEs reported in the CYD Dengue Vaccine Group and in the Control Group, respectively. During Y6, 191 subjects (2.9%) and 105 subjects (3.2%) experienced at least one SAE in the CYD Dengue Vaccine Group and in the Control Group, respectively. This corresponds to 203 and 112 SAEs reported in the CYD Dengue Vaccine Group and in the Control Group, respectively. For Y3 to Y6, these events were all reported as unrelated to vaccination. The most common SAEs reported during the LTFU were from the SOC Infections and infestations (6.3% in the CYD Dengue Vaccine Group and 6.9% in the Control Group), Injury, poisoning and procedural complications (1.8% in the CYD Dengue Vaccine Group and 2.0% in the Control Group), and Gastrointestinal disorders (0.8% in the CYD Dengue Vaccine Group and 0.9% in the Control Group).

Deaths

Active Phase

Four deaths were reported in the CYD Dengue Vaccine Group, all of them were not related to vaccination (3 traffic accidents and one tracheal injury). One death was reported in the Control Group (subject diagnosed with acute lymphoblastic leukemia during the Active Phase, died during Y3).

LTFU One death was reported in the Control Group during Y3: encephalitis. During Y4, 4 deaths were reported: 3 in the CYD Dengue Vaccine Group (2 from head injury from a motorcycle accident, 1 from cardiogenic shock following a myocarditis) and 1 in the Control Group (acute pyelonephritis of left kidney). During Y5, 1 death was reported in the Control Group (ruptured aneurysm). No death was related to treatment or dengue disease. During Y6, 3 deaths were reported in the CYD Dengue Vaccine Group (eclampsia, drowning, and motorcycle accident). No death was related to treatment or dengue disease
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