These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** U1111-1116-4986, IND 11219, NCT01374516, 2014-001716-19 **Study code:** CYD15
Title of the study: Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 years in Latin America	
Study center(s): This was a multi-center trial conducted at 22 sites across Brazil, Colombia, Honduras, Mexico, and Puerto Rico (approximately 1 to 9 sites in each country).	
Study period: Date first subject/patient enrolled: 08/Jun/2011 Date last subject/patient completed: 05/Mar/2018	
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 four serotypes in children and adolescents aged 9 to 16 years at the time of inclusion.

Secondary objectives:

ALL SUBJECTS (N=20 875):

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:
   a. due to any of the 4 serotypes
   b. due to at least 3 serotypes
   c. 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:
   a. due to any of the 4 serotypes
   b. due to at least 3 serotypes
   c. 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 and throughout the trial (from D0 until the end of the trial).

SUBSET OF SUBJECTS (N=2000):

Immunogenicity

6) To describe the 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:

This was a randomized, observer-blind, placebo-controlled, multi-center, Phase III trial in 5 countries, involving 20 875 subjects.

Children and adolescents aged 9 to 16 years were randomized in a 2 to 1 ratio to receive 3 injections (at 0, 6, and 12-months) of either products:

- **CYD Dengue Vaccine** : N=13 917 (CYD Dengue Vaccine Group)
- **Placebo** (NaCl 0.9%): N=6958 (Control Group)

A licensed non-dengue vaccine appropriate for the age group was offered to the participants at least 6 months after the last dose. This active non-dengue vaccine was intended to offer benefit to the subjects.

Immunogenicity and reactogenicity were assessed in a subset of 2000 subjects (1334 in the CYD Dengue Vaccine Group and 666 in the Control Group). This subset of subjects was evaluated to enable the generation of country-specific data on reactogenicity, immunogenicity post-immunization and overtime, as well as baseline dengue and yellow fever (YF) antibody (Ab) levels. The targeted number of subjects enrolled into the immunogenicity and reactogenicity subset was defined at a country level. The recruitment in the subset, initially planned to be performed within the first 2 months, was extended in some countries. Between 150 and 900 subjects were targeted to be enrolled in each participating country.

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 severity. Additionally, any related serious adverse event (SAE) or death was promptly reviewed by the IDMC.

Detection of dengue cases

Suspicion of dengue was based on the presence of an acute febrile episode, defined as ≥ 38°C for two days. 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 was <38°C.

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

Active Phase

For each subject, the Active Phase of dengue case detection began after the first injection (Dose 1) and was expected to continue until 13 months after the third injection (Dose 3). It was assumed that 12 months of surveillance should result in the detection of a sufficient number of virologically-confirmed dengue (VCD) cases to allow for an assessment of efficacy. The continuation of the Active Phase for 13 months post-injection 3 is 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, SMS and home visits; the method of contact could differ at each site). The purpose of this contact was to remind parents to take their child to the trial center or health care center in the event of 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 a febrile illness and requiring hospitalization were screened for dengue. In this phase, there was a minimum frequency of one contact every 3 months and surveillance of identified non-study healthcare sites was performed. For subjects who did not consent to participate in the Surveillance Expansion Period (SEP), this phase continued until the end of the trial.

Surveillance Expansion Period

Subjects who consented to take part into the SEP (at the Surveillance Expansion visit [Vse]) were actively followed for dengue case detection similarly to the Active Phase. Thus, surveillance was designed to maximize the detection of symptomatic VCD (hospitalized or not) in order to describe CYD dengue vaccine efficacy and safety in preventing symptomatic dengue.

To ease the reading of this report, the 4 years of the Hospital Phase or SEP are referred to as the long-term follow-up period (LTFU). Furthermore, each year of this LTFU will be identified in relation with the beginning of the study. Thus, Year 3 of the study (Y3) will stand for Year 1 of Hospital Phase (Y1 of Hospital Phase [HP]). Likewise, Y4 will stand for Y2 of HP/SEP, Y5 for Y3 of HP/SEP, and Y6 for Y4 of HP/SEP.

Management of suspected dengue cases

In addition to the tests performed as part of the local standard of care, two 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 Hospital Phase. Subjects who consented to participate in the SEP had only one blood sample (acute sample) taken:

1) The first blood sample (acute 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 Day (D) 0 until Vse, but it was not performed after the Vse. Acute samples were used for the virological confirmation of dengue cases.
2) The second blood sample (convalescent blood sample) is taken, from D0 until Vse, during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample). Testing includes 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 to be 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 to be performed during the acute phase before the first blood sample was taken. However, if a subject presented with other clinical signs of hemorrhage, the tourniquet test was not mandatory.

Number of subjects:	Planned: 20875 Randomized: 20869 Treated: 20854
Evaluated:	
	Efficacy: 20854 Immunogenicity: 1944 Safety: 20854

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 9 to 16 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 to 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 injections at 0, 6, and 12 months

Investigational medicinal product: Placebo (NaCl)

Formulation: Solution of NaCl 0.9%

Route of administration: SC

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

Duration of participation:

The planned duration of participation in the trial (first visit to last visit) for a subject was approximately 72 months (~ 6 years), except for prematurely discontinued subjects:

The duration of the Active Phase for each subject was expected to be 25 months.

The duration of the Hospital Phase was originally expected to be from the end of the Active Phase until the end of the study; however the SEP was implemented in May 2015, before the end of the Hospital Phase. Therefore, for subjects declining participation in the SEP, the duration of the Hospital Phase was expected to be 47 months. For subjects who consented, the duration of the SEP was from the moment of consent until the end of the study.

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 cases of symptomatic dengue that were virologically-confirmed in a 12-month period were 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=20,875):

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 28 days post-vaccination) was performed.

Safety

- Occurrence of SAEs, including serious AESIs, in all subjects was 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 Surveillance Expansion Period and during the trial.

SUBSET OF SUBJECTS (N=2000):

Immunogenicity

Neutralizing Ab level against each of the four parental dengue virus strains of CYD dengue vaccine constructs (and potentially against recently isolated strains) were 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 levels were measured on samples obtained at Vse, whenever it occured.

In addition, baseline neutralizing Abs against YF 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 VE after the complete schedule of vaccinations 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 confirmed on the modified Full Analysis Set for Efficacy (mFASE).

Additional descriptive statistical analyses were also performed after completion of each year of the LTFU period or when data become available, with a final analysis performed at the end of the study.

Analysis for the Primary Objective

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

H0: VE ≤ 25%

H1: VE > 25%

ppsiCI of the VE. The CIs were 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 VCD case occurring more than 28 days after the third dose have been considered as cases for this mFASE analysis during the Active Phase. Additional stratified analyses were conducted to take into account the different sites and/or countries and/or other covariates.

Analyses for the Secondary and Other Objectives

The main efficacy, safety, and immunogenicity parameters, as well as parameters about the occurrence of virologically-confirmed Zika cases, are 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 is 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

Tables crossing Dengue and Zika cases were computed.

Reactogenicity and Immunogenicity Evaluations

A subset of 2000 subjects (1334 in the CYD Dengue Vaccine Group and 666 in the Control Group) was included in the reactogenicity and immunogenicity analysis.

Reactogenicity:

Reactogenicity analysis described both solicited and unsolicited events. 1333 subjects in the CYD Dengue Vaccine Group give 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 have a range <5.5%.

Immunogenicity:

The same subset as for reactogenicity was used for the immunogenicity evaluation, except for the Zika antibody titers 1 month post-dose 3, for which the analysis was performed on 400 subjects. Immunogenicity parameters are described with 95% CI.

Summary:

Subjects Disposition

A total of 20 869 subjects; ie, 13 920 subjects in the CYD Dengue Vaccine Group and 6949 subjects in the Control Group, were randomized in the study between 08 June 2011 and 16 March 2012. The planned number of subjects in the overall population, n=20 875, was not achieved as 6 subjects were randomized several times (2 or 3 times).

Among enrolled subjects, a total of 2000 subjects ie, 1334 subjects in the CYD Dengue Vaccine Group and 666 subjects in the Control Group, were additionally randomized in the subset for immunogenicity and reactogenicity evaluation.

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=13920)		Control Group (N=6949)		All Subjects (N=20869)	
	Overall population n	Subset n	Overall population n	Subset n	Overall population n	Subset n
All	13920	1334	6949	666	20869	2000
Brazil	2370	202	1178	98	3548	300
Colombia	6497	613	3246	308	9743	921
Honduras	1866	200	933	100	2799	300
Mexico	2312	219	1152	108	3464	327
Puerto Rico	875	100	440	52	1315	152

n: number of subjects fulfilling the item listed

Approximately half of the subjects were included in Colombia (9743 subjects out of 20 869). This higher percentage of subjects was recruited in Colombia because this was the country with a history of more sustained circulation of the 4 serotypes in the years prior to the onset of the study.

Overall, 19 933 (95.5%) randomized subjects (13 290 [95.5%] in the CYD Dengue Vaccine Group and 6643 [95.6%] in the Control Group) completed the vaccination period (from D0 to 28 days after the third injection). Main reasons for vaccination discontinuation were voluntary withdrawal not due to an AE (3.0%) or non-compliance with protocol (1.0%), observed in similar proportions in the 2 treatment groups. Only 0.1% of the subjects discontinued vaccination due to the occurrence of an AE or a SAE.

Analysis Sets

The PPSE was the set used for the evaluation of the primary objective. It accounted for 90.2% of the randomized subjects. Overall, there were 18 834 in the PPSE: 12 573 subjects from the CYD Dengue Vaccine Group and 6261 subjects from the Control Group.

The FASE was the set of the subjects who received at least one injection. It accounted for 99.9% of the randomized subjects. Overall, there were 20 854 in the FASE: 13 914 subjects in the CYD Dengue Vaccine Group and 6940 subjects in the Control Group.

The mFASE was the set of the subjects who received 3 injections as per randomization including those with protocol deviations. It accounted for 95.5% of the randomized subjects. Overall, there were 19 931 subjects in the mFASE: 13 288 subjects in the CYD Dengue Vaccine Group and 6643 subjects in the Control Group.

The Safety Analysis Set (SafAS) was the set of the subjects who received at least one injection and were analyzed according to the treatment they actually received. It accounted for 100.0% of the subjects who received at least 1 injection (except the 2 subjects with serious non-compliance to GCPs). Overall, there were 20 854 subjects in the SafAS: 13 915 in the CYD Dengue Vaccine Group and 6939 in the Control Group.

The Full Analysis Set For Immunogenicity (FASI) was the set of the subjects who received at least 1 injection and had a blood sample with a result available after this injection. It accounted for 97.2% of the subjects randomized in the Immunogenicity and reactogenicity subset. Overall, there were 1944 subjects in the FASI: 1301 in the CYD Dengue Vaccine Group and 643 in the Control Group.

The Full Analysis Set for Antibody Persistence (FASAb) was defined as the subjects of the immunogenicity subset who received at least one injection. It accounted for 99.9% of the subjects randomized in the Immunogenicity and reactogenicity subset. Overall, there were 1997 subjects in the FASAb: 1333 in the CYD Dengue Vaccine Group and 664 in the Control Group.

The Reactogenicity Analysis Set was the set of the subjects included in the SafAS and who were part of the subset for the evaluation of reactogenicity. It accounted for 100% of the subjects randomized to the immunogenicity and reactogenicity subset (except 3 subjects not injected at D0:1 in the CYD Dengue Vaccine Group and 2 in the Control Group). Overall, there were 1997 subjects in the Reactogenicity Analysis Set: 1333 in the CYD Dengue Vaccine Group, and 664 in the Control Group.

FASE, mFASE, FASI, FASAb, SafAS, and Reactogenicity Analysis Set were used for the evaluation of the secondary and other objectives.

Demographic and Baseline Characteristics

Overall, there were 9482 female (50.3%) and 9352 male subjects (49.7%) included in the PPSE; the mean age at enrollment was 12.4 years. The ethnic origin of the subjects was American Indian (16.2%), Caucasian (8.0%), Black (3.1%) but most of subjects reported being Hispanic of mixed ethnic origins, classified as “Other” (72.6%). Demographic characteristics were very similar in the 2 treatment groups.

Overall, 79.4% of the subjects of the FASI were dengue-seropositive at baseline. Percentages were similar in both treatment groups. Baseline dengue-seropositivity rates varied by country and were higher in Colombia (92.2%) and Honduras (85.7%) compared to the other countries such as Mexico (53.1%) and Puerto Rico (56.2%). Similar observations were done for Flavivirus- and YF- seropositivity rates at baseline.

Dengue and YF seropositivity rates were similar in both age groups, although slightly higher in the older age group (74.9% and 77.1% for dengue and YF respectively in the 9-11 years age group vs. 83.8% and 82.3% for dengue and YF respectively in the 12-16 years age group).

The demographic characteristics were comparable across the different populations of analyses.

Efficacy

Overall, 10 053 febrile episodes were reported during the Active Phase, with a similar percentage in both groups; 89.2% of these febrile episodes had an acute sample collected within the first 5 days of fever onset and less than 1.5% did not have any acute and/or convalescent blood sample collected. Among these febrile episodes, 670 (281 in the CYD Dengue Vaccine Group and 389 in the Control Group in SafAS), were virologically-confirmed as being dengue episodes. Of these, 6 subjects presented with 2 consecutive VCD episodes occurring more than 14 days apart. In addition, 2 subjects were detected with a dengue episode that did not meet case definition for symptomatic VCD (fever lasted less than 2 days) and were excluded from the efficacy analysis. Therefore, a total of 662 symptomatic VCD cases (subjects with at least 1 VCD episode) due to any serotype were reported during the Active Phase in the FASE and 397 symptomatic VCD cases due to any serotype were reported from 28 days post-injection 3 to the end of the Active Phase in the PPSE.

The dengue density incidence based on symptomatic VCD observed in the Control Group during the Active Phase was 2.9 cases per 100 person-years at risk. This incidence was 3.8 cases per 100 person-years at risk from 28 days post-injection 3 to the end of the Active Phase.

Primary Objective

The table below presents the VE against symptomatic VCD due to any serotype after 3 injections in the PPSE. This primary analysis considered symptomatic VCD cases collected from 28 days after the third dose of vaccine to the end of the Active Phase (ie, up to 13 months after the third vaccination).

Vaccine efficacy against symptomatic VCD post-injection 3 due to any of the 4 serotypes - PPSE

	CYD Dengue Vaccine Group (N=12574)				Control Group (N=6261)				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	176	11792	1.5 (1.3; 1.7)	176	221	5809	3.8 (3.3; 4.3)	221	60.8	(52.0; 68.0)

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue 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 are 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 presented in the tables are the sum of individual units of time for which the participants contributed to the analyses. Incidence density was calculated as the number of cases divided by the cumulative person-years at risk

n Episodes: number of virologically-confirmed dengue 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%.

The overall primary estimate of VE against symptomatic VCD from 28 days post-injection 3 to the end of the Active Period due to any serotype was 60.8% (95% CI: 52.0; 68.0), and the primary objective was met with a lower bound of 95% CI above 25%.

Secondary Objectives

VE from 28 days post-dose 3 to the end of the Active Phase (in mFASE):

The VE estimates by serotype 28 days post-injection 3 to the end of the Active Phase were 50.3% (95% CI: 29.1; 65.2) for serotype 1, 42.3% (95% CI: 14.0; 61.1) for serotype 2, 74.0% (95% CI: 61.9; 82.4) for serotype 3 and 77.7% (95% CI: 60.2; 88.0) for serotype 4.

The VE estimate for symptomatic VCD due to any serotype in the mFASE was 61.3% (95% CI: 52.8; 68.2). This result was consistent with that observed in the PPSE.

VE during the Active Phase (after at least 1 dose - FASE):

The VE estimate against symptomatic VCD during the Active Phase due to any serotype was 64.7% (95% CI: 58.7; 69.8). The VE estimates by serotype were 54.8% (95% CI: 40.2; 65.9) for serotype 1, 50.2% (95% CI: 31.8; 63.6), 74.2% (95% CI: 63.9; 81.7) for serotype 3 and 80.9% (95% CI: 70.9; 87.7) for serotype 4.

Results from 28 days post-injection 1 to the end of the Active Phase were consistent with those observed during the Active Phase.

Cases of sequential infections (at least 2 VCD episodes occurring more than 14 days apart) were reported in a total of 6 subjects during the Active Phase, 3 in each treatment group. Co-infections (2 serotypes identified during the same VCD episode) were also reported during the Active Phase. A total of 14 cases: 6 in the CYD Dengue Vaccine Group and 8 in the Control Group were observed. Most of them (12 out of 14) occurred post-injection 3.

Immunogenicity

At baseline, the percentage of subjects presenting seropositivity (neutralizing Ab titers ≥ 10 [1/dil]) against each serotype was similar between the 2 treatment groups. Percentages of seropositivity ranged from 68.2% (serotype 4) to 76.5% (serotype 3) in the CYD Dengue Vaccine Group, and from 65.0% (serotype 4) to 73.8% (serotype 2) in the Control Group.

A summary of the geometric mean of titers (GMTs) for each serotype is presented below at baseline, after injection 2, injection 3 and one, two, three, and four years after injection 3, for the subjects included in the subset (FASI).

Summary of GMTs of dengue antibodies against each serotype with the parental dengue virus strains - FASI/FASAB

		CYD Dengue Vaccine Group (N=1301)			Control Group (N=643)		
Component	**Timepoint**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
Serotype 1 (PRNT- [l/dil])	**Pre-Inj 1 (V01)**	1297	128	(112; 145)	641	119	(98.7; 142)
	Post- Inj 2 (V04)	1296	458	(406; 517)	638	128	(106; 154)
	Post- Inj 3 (V06)	1291	395	(353; 441)	640	121	(101; 145)
	1-Year FU Post-Inj 3 (V07)	1261	266	(234; 302)	629	146	(121; 176)
	2-Year Follow-Up Post-Inj 3 (V09)	1222	209	(185; 237)	612	142	(118; 171)
	3-Year Follow-Up Post-Inj 3 (V10)	1177	259	(229; 293)	577	177	(147; 214)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	397	(347; 455)	529	283	(227; 353)
	5-Year Follow-Up Post-Inj 3 (V12)	1038	284	(252; 321)	508	210	(172; 255)
Serotype 2 (PRNT- [l/dil])	**Pre-Inj 1 (V01)**	1299	138	(123; 156)	640	115	(97.2; 136)
	Post- Inj 2 (V04)	1297	622	(566; 684)	639	124	(104; 148)
	Post- Inj 3 (V06)	1291	574	(528; 624)	640	129	(109; 152)
	1-Year FU Post-Inj 3 (V07)	1264	371	(336; 409)	629	145	(122; 173)
	2-Year Follow-Up Post-Inj 3 (V09)	1223	339	(307; 374)	612	173	(146; 206)
	3-Year Follow-Up Post-Inj 3 (V10)	1176	342	(311; 376)	577	187	(157; 222)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	387	(346; 432)	528	241	(199; 292)
	5-Year Follow-Up Post-Inj 3 (V12)	1038	297	(269; 328)	508	201	(168; 242)
Serotype 3 (PRNT- [l/dil])	**Pre-Inj 1 (V01)**	1300	121	(108; 136)	639	114	(95.9; 136)
	Post- Inj 2 (V04)	1297	556	(506; 610)	639	117	(98.3; 139)
	Post- Inj 3 (V06)	1291	508	(465; 555)	640	124	(105; 147)
	1-Year FU Post-Inj 3 (V07)	1265	292	(263; 325)	629	137	(114; 165)
	2-Year Follow-Up Post-Inj 3 (V09)	1219	303	(274; 334)	610	170	(142; 203)
	3-Year Follow-Up Post-Inj 3 (V10)	1175	326	(295; 362)	577	186	(156; 223)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	371	(331; 416)	529	237	(193; 290)
	5-Year Follow-Up Post-Inj 3 (V12)	1038	346	(313; 383)	508	224	(185; 271)
Serotype 4 (PRNT- [l/dil])	**Pre-Inj 1 (V01)**	1297	43.6	(39.6; 48.0)	640	39.0	(33.9; 44.7)
	Post- Inj 2 (V04)	1295	261	(242; 281)	637	40.9	(35.5; 47.0)
	Post- Inj 3 (V06)	1291	241	(226; 258)	640	44.3	(38.6; 50.8)
	1-Year FU Post-Inj 3 (V07)	1265	174	(161; 188)	625	51.5	(44.3; 59.8)
	2-Year Follow-Up Post-Inj 3 (V09)	1223	138	(128; 149)	612	56.5	(48.8; 65.5)
	3-Year Follow-Up Post-Inj 3 (V10)	1175	173	(160; 185)	577	76.5	(66.1; 88.6)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	190	(173; 208)	529	101	(85.1; 119)
	5-Year Follow-Up Post-Inj 3 (V12)	1038	144	(134; 156)	508	73.6	(63.4; 85.5)

M: number of subjects available for the endpoint
Overall, GMTs at baseline were comparable across the 2 treatment groups for each serotype. GMTs were lower for serotype 4 in both groups.

In the CYD Dengue Vaccine Group

After injection 2, GMTs increased as compared to baseline and remained stable after injection 3. Indeed, comparable levels of GMTs were observed for each serotype after the second and the third injections with a slight trend to decrease from post-injection 2 to post-injection 3 for all serotypes. The highest level of GMTs was observed for serotype 2 and the lowest for serotype 4.

One year post-injection 3, the levels of GMTs (1/dil) were above baseline values for all 4 serotypes, although they decreased from those post-injection 3.

Since one year after injection 3, the levels of GMTs were stable for all serotypes and remained above baseline. GMTR 3-Year Post-injection 3/Pre-injection 1 ranged from 1.65 for serotype 1 to 3.18 for serotype 4.

Four years after injection 3, the levels of GMTs tended to increase from previous follow-up years for all 4 serotypes, and reached the same level as post-injection 3 for serotype 1. GMTs (1/dil) were 397, 387, 371, and 190 for serotypes 1, 2, 3, and 4, respectively. GMTR 4-Year Post-Injection 3/Pre-injection 1 ranged from 2.41 for serotype 1 to 3.56 for serotype 4.

Five years after injection 3, the levels of GMTs tended to decrease as compared to four years after injection 3. GMTs (1/dil) were 284, 297, 346, and 144 for serotypes 1, 2, 3, and 4, respectively. GMTR 5-Year post-injection 3/pre-injection 1 ranged from 1.80 for serotype 1 to 2.69 for serotype 4.

In Control Group

In the Control Group, the GMTs per serotype tended to remain stable after any placebo injection, and stable from year to year between the third injection and the third year post-injection 3.

Four years after injection 3, the levels of GMTs tended to increase from previous follow-up years for all 4 serotypes, and were 283, 241, 237, and 101 for serotypes 1, 2, 3, and 4, respectively.

Five years after injection 3, the levels of GMTs tended to decrease as compared to four years after injection 3 and were 210, 201, 224, and 73.6 for serotypes 1, 2, 3, and 4, respectively.

Safety

All subjects were assessed for safety (SAEs) and a subset of subjects (reactogenicity subset) was assessed for solicited reactions and unsolicited non-serious AEs/ARs.
An overview of the safety and reactogenicity during the Active Phase and the LTFU is given in the table below:

Safety overview after any injection - SafAS

Subjects experiencing at least one:	CYD Dengue Vaccine Group (N=13915) n/M	%	(95% CI)	Control Group (N=6939) n/M	%	(95% CI)
REACTOGENICITY SUBSET						
Within 28 days after any vaccine injections						
Immediate unsolicited non-serious AE	3/1333	0.2	(0.0; 0.7)	1/664	0.2	(0.0; 0.8)
Immediate unsolicited non-serious AR	1/1333	<0.1	(0.0; 0.4)	1/664	0.2	(0.0; 0.8)
Solicited reaction	994/1328	74.8	(72.4; 77.2)	495/659	75.1	(71.6; 78.4)
Solicited injection site reaction	675/1328	50.8	(48.1; 53.6)	279/658	42.4	(38.6; 46.3)
Solicited systemic reaction	909/1328	68.4	(65.9; 70.9)	458/659	69.5	(65.8; 73.0)
Unsolicited non-serious AE	595/1333	44.6	(41.9; 47.4)	292/664	44.0	(40.2; 47.8)
Unsolicited non-serious AR	16/1333	1.2	(0.7; 1.9)	5/664	0.8	(0.2; 1.7)
Unsolicited non-serious injection site AR	9/1333	0.7	(0.3; 1.3)	3/664	0.5	(0.1; 1.3)
Unsolicited non-serious systemic AE	592/1333	44.4	(41.7; 47.1)	290/664	43.7	(39.9; 47.5)
Unsolicited non-serious systemic AR	7/1333	0.5	(0.2; 1.1)	2/664	0.3	(0.0; 1.1)
ALL SUBJECTS						
Within 28 days after any vaccine injections						
AE leading to discontinuation*	0/13915	0.0	(0.0; 0.0)	0/6939	0.0	(0.0; 0.1)
Immediate SAE	0/13915	0.0	(0.0; 0.0)	0/6939	0.0	(0.0; 0.1)
SAE	82/13915	0.6	(0.5; 0.7)	42/6939	0.6	(0.4; 0.8)
Death	0/13915	0.0	(0.0; 0.0)	0/6939	0.0	(0.0; 0.1)
During the Active Phase						
AE leading to discontinuation*	10/13915	<0.1	(0.0; 0.1)	9/6939	0.1	(0.1; 0.2)
SAE	571/13915	4.1	(3.8; 4.4)	311/6939	4.5	(4.0; 5.0)
Death	6/13915	<0.1	(0.0; 0.1)	6/6939	<0.1	(0.0; 0.2)
During the Hospital Phase/SEP						
AE leading to discontinuation*	38/13296	0.3	(0.2; 0.4)	23/6644	0.3	(0.2; 0.5)
SAE	1297/13296	9.8	(9.3; 10.3)	650/6644	9.8	(9.1; 10.5)
Death	36/13296	0.3	(0.2; 0.4)	21/6644	0.3	(0.2; 0.5)
During the entire study						
AE leading to discontinuation*	48/13915	0.3	(0.3; 0.5)	32/6939	0.5	(0.3; 0.7)
SAE	1765/13915	12.7	(12.1; 13.2)	911/6939	13.1	(12.3; 13.9)
Death	42/13915	0.3	(0.2; 0.4)	27/6939	0.4	(0.3; 0.6)

n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint

* Identified in the termination form (at V06/V07/V10/V11/V12) as SAE or other AE.

The safety profile was similar in CYD dengue vaccine recipients and placebo recipients

Solicited Reactions

Overall, 74.8% of subjects in the CYD Dengue Vaccine Group and 75.1% in the Control Group experienced at least 1 solicited reaction after any injection.

Injection site reactions within 7 days of any injections were reported in 50.8% of subjects in the CYD Dengue Vaccine Group and 42.4% in the Control Group and Grade 3 injection site reactions were reported in 2.0% of subjects in the CYD Dengue Vaccine Group and 1.4% in the Control Group. Pain was the injection site reaction most frequently reported after any injection in the 2 groups (48.9% in the CYD Dengue Vaccine Group and 41.0% in the Control Group). Erythema and swelling were less frequently reported (less than 10% in the 2 groups). Injection site reactions tended to decrease after the second injections and remained stable after the third injection in both groups. Most injection site reactions started within 3 days of each injection and were present for 3 days or less during the solicited period.

The proportion of Grade 3 injection site reactions did not increase with the number of injections.

Systemic reactions within 14 days of any injection were reported in 68.4% of subjects in the CYD Dengue Vaccine Group and 69.5% in the Control Group and Grade 3 systemic reactions were reported in 13.9% of subjects in the CYD Dengue Vaccine Group and 11.4% of subjects in the Control Group. Headache was the systemic reaction the most frequently reported after any injection in the 2 groups (54.7% in the CYD Dengue Vaccine Group and 57.5% in the Control Group). Malaise, myalgia and asthenia were also commonly reported (between 37.3% and 43.4% in the 2 groups) and fever was the least reported (16.7% in the CYD Dengue Vaccine Group and 18.8 % in the Control Group). All systemic reactions except fever tended to decrease after the second injection and remained stable after the third one. The proportion of fever remained stable after each injection in the 2 treatment groups. Most systemic reactions started within 3 days of each injection, except for fever that could start any time within 14 days of any injection. Most of these reactions were present for 3 days or less during the solicited period.

Immediate unsolicited AEs and reactions

A few immediate unsolicited AEs (0.2%) were reported within 30 minutes of vaccination in the 2 treatment groups ie, in 3 subjects in the CYD Dengue Vaccine Group and 1 subject in the Control Group. All occurred after injection 1 and none led to subject's hospitalization. Among these, only two (ie, Grade 3 asthmatic crisis and Grade 3 urticaria in one subject from the CYD Dengue Vaccine Group) were reported as related to vaccination by the Investigator and led to subject's discontinuation from further injections but he completed the Active Phase. Both immediate AEs required a health care contact and a medication. They resolved respectively 2 and 3 days after onset and were considered as AESI.

Unsolicited non-serious AEs and ARs

Unsolicited non-serious AEs were reported in 44.6% of subjects in the CYD Dengue Vaccine Group and 44.0% in the Control Group within 28 days after any injection. They were mostly common diseases or disorders of the childhood or adolescence, belonging to the following System Organ Classes (SOCs): "Infections and infestations" (25.8% in the CYD Dengue Vaccine Group and 26.4% in the Control Group), "Gastrointestinal disorders" (12.2% in the CYD Dengue Vaccine Group and 12.0% in the Control Group), "Respiratory, thoracic and mediastinal disorders", (8.7% in the CYD Dengue Vaccine Group and 8.4% in the Control Group) or "System nervous disorders", (7.9% in the CYD Dengue Vaccine Group and 6.8% in the Control Group). AEs from the other SOCs accounted for less than 5% in both groups.

Unsolicited non-serious AEs were mostly of Grade 1 or Grade 2 intensity. At least one Grade 3 unsolicited non-serious systemic AE was reported in 5.3% of subjects in the CYD Dengue Vaccine Group and in 3.9% of subjects in the Control Group. Most of these Grade 3 unsolicited non-serious AEs started after15 days or more post any injection and resolved within 7 days or less. The frequency of reported unsolicited non-serious AEs was stable in the 2 treatment groups over the doses. Similarly, the frequency of AEs reported in each most representative SOC tended to be stable over the doses in both groups.

Few unsolicited non-serious AEs reported within 28 days after any injection were related to vaccination by the Investigator ie, in 1.2% of subjects in the CYD Dengue Vaccine Group and in 0.8% in the Control Group. Unsolicited non-serious ARs reported at the injection site were pain, haematoma, pruritus and anesthesia in the CYD Dengue Vaccine Group and pain and induration in the Control Group. Unsolicited non-serious systemic ARs reported were malaise, abdominal pain, vomiting, dyspnea, generalized erythema, vertigo, asthma crisis and urticaria in the CYD Dengue Vaccine Group and pruritus and lymphadenitis in the Control Group. Unsolicited non-serious ARs started within 3 days of any injection and mostly resolved within 3 days or less.
No Grade 3 unsolicited non-serious injection site ARs were reported after any injection and Grade 3 unsolicited non-serious systemic ARs were reported in 2 subjects in the CYD Dengue Vaccine Group: Grade 3 asthma crisis and Grade 3 urticaria that occurred immediately after the first injection (see paragraph *immediate unsolicited AEs and reactions above)* and Grade 3 malaise that started 20 days after injection 1, resolved spontaneously the same day and did not lead to study discontinuation.

SAEs

SAEs Within the Active Phase:

A total of 882 subjects reported at least 1 SAE during the Active Phase: 571 (4.1%) in the CYD Dengue Vaccine Group and 311 (4.5%) in the Control Group. Most SAEs reported during the Active Phase were diseases or injuries commonly reported in the childhood and adolescence which belonged to the SOCs: “Infections and Infestations” (295 subjects [2.1%] in the CYD Dengue Vaccine Group and 188 subjects [2.7%] in the Control Group), “Injury, poisoning and procedural complications” (103 subjects [0.7%] in the CYD Dengue Vaccine Group and 35 subjects [0.5%] in the Control Group). SAEs from the other SOCs accounted for less than 0.5% in both groups.

SAEs Within 28 days after any injection:

A total of 124 subjects: 82 (0.6%) in the CYD Dengue Vaccine Group and 42 (0.6%) in the Control Group, reported a total of 129 SAEs within 28 days of any injection: 85 in the CYD Dengue Vaccine Group and 44 in the Control Group.

In the CYD Dengue Vaccine Group, a total of 75 out of 85 events (88.2%) met seriousness criterion “hospitalization or prolongation of hospitalization”, 12 (14.1%) were “important medical event”, 2 (2.4%) were “life threatening” 1 met the criterion “persistent or significant disability”, and 1 met the criterion “congenital abnormality or birth defect”. Some SAEs could have several seriousness criteria (eg “hospitalization or prolongation of hospitalization” and “other important medical event”). The outcome of the SAEs was “recovered” for 80 out of 85 SAEs, “recovered with sequelae” for 3 SAEs and “ongoing” after 28 days for 2 SAEs. Similar results were observed in the Control Group.

In both groups, most SAEs reported within 28 days after any injection were diseases or injuries commonly reported in the childhood and adolescence which belonged to the following SOCs: “Infections and Infestations” (37 subjects [0.3%] in the CYD Dengue Vaccine Group and 16 subjects [0.2%] in the Control Group), “Injury, poisoning and procedural complications” (15 subjects [0.1%] in the CYD Dengue Vaccine Group and 4 subjects [<0.1%] in the Control Group), as well as “Gastrointestinal disorders” (eg abdominal pain, inguinal hernia) and “Nervous system disorders” (eg convulsion, epilepsy) , “Respiratory, thoracic and mediastinal disorders” (eg asthma) and “Skin and subcutaneous tissue disorders” eg urticaria) reported in <0.1% of subjects in each SOC, in the two groups.

No pattern (cluster) of events was found within 28 days after vaccination.

A total of 4 SAEs (<0.1%) were assessed as related to the vaccine by the Investigator and the Sponsor during the Active Phase: 3 in the CYD Dengue Vaccine Group and 1 in the Control Group (Table 7.7). One additional case in the CYD Dengue Vaccine Group was assessed as related only by the Sponsor, although assessed as not related by Investigator. All 5 subjects were discontinued from further injections but followed for safety and dengue surveillance, as per protocol:

In the CYD Dengue Vaccine Group, acute polyneuropathy, asthma attack and allergic urticaria were reported. These related SAEs occurred between few hours to 3 days post-injection 1 or injection 2. Of these 3 SAEs, only acute polyneuropathy required hospitalization. One additional SAE was assessed as related to vaccination by the Sponsor but not the Investigator. Unspecified seizures were reported 18 hours after injection. This case required hospitalization and resolved the same day.

In the Control Group, visual impairment was reported 21 hours post -injection 1. Subject was hospitalized and recovered 3 days after SAE onset.

SAEs occurred from D0 to the end of the 6-Month Follow-up period:

During the period from D0 to the end of the 6-month follow-up period, 646 subjects, 414 (3.0%) in the CYD Dengue Vaccine Group and 232 (3.3%) in the Control Group, reported a total of 711 SAEs (453 in the CYD Dengue Vaccine Group and 258 in the Control Group respectively).

In the CYD Dengue Vaccine Group, a total of 403 out of 453 events (89.0%) met seriousness criterion “hospitalization or prolongation of hospitalization”, 53 (11.7%) were “other important medical event”, 10 (2.2%) were “life threatening”, 2 met the criterion “persistent or significant disability”, 2 met the criterion “death” , and 1 met the criterion “congenital abnormality or birth defect”. Some SAEs could have several seriousness criteria (eg, “hospitalization or prolongation of hospitalization” and “other important medical event”). Similar results were observed in the Control Group.

Among the 711 SAEs reported from D0 up to 6-month follow-up period after the third injection, no other SAEs than the 4 reported within 28 days after the first and the second injections were assessed as related to treatment by the Investigator.

SAEs occurred beyond the 6-Month Follow-up period up to the end of Y6:

During the period from the 6 months follow-up up to the end of Y6, 2153 subjects, 1432 (10.3%) in the CYD Dengue Vaccine Group and 721 (10.4%) in the Control Group, reported a total of 2713 SAEs (1792 in the CYD Dengue Vaccine Group and 921 in the Control Group, respectively).

In the CYD Dengue Vaccine Group, a total of 1523 out of 1792 events (85.0%) met seriousness criterion "hospitalization or prolongation of hospitalization", 358 (20.0%) were "other important medical event", 56 (3.1%) were "life threatening", 40 (2.2%) met the criterion "death", and 6 (<0.1%) met the criterion "persistent or significant disability". Some SAEs could have several seriousness criteria (eg, "hospitalization or prolongation of hospitalization" and "other important medical event"). Similar results were observed in the Control Group.

Among the 3424 SAEs reported from D0 up to 60 months after the third injection, no other SAEs than the 4 reported within 28 days after the first and the second injections were assessed as related to treatment by the Investigator.

Deaths

Active Phase

There were 12 deaths reported during the Active Phase, 6 in each treatment group. Most deaths were accidental or the consequence of injuries. Subjects in CYD Dengue Vaccine Group died due to accidental asphyxia, poisoning deliberate, renal failure due to vasculitis, spinal cord injuries, acute respiratory failure and multiple injuries. Subjects in Control Group died due to drowning, lupus nephritis, broncho-aspiration, road traffic accident, head injury and osteosarcoma metastactic. None of deaths was assessed as related to product by the Investigator or the Sponsor.

LTFU

There were 57 deaths reported during the LTFU, 36 in the CYD Dengue Vaccine Group and 21 in the Control Group. Most deaths were accidental or the consequence of injuries. Subjects in CYD Dengue Vaccine Group died due to car accident, homicide, multiple crushing injuries after being run over by a tractor-trailer, injuries by firearm or white weapon, intoxication, sudden death, fall, suicide, homicide, autoimmune encephalitis, acute pulmonary edema linked to lupus, and acute respiratory failure due to epilepsy. Subjects in the Control Group died due to gunshot wounds, homicide, septic shock secondary to compression of chest, car accidents, panencephalitis, osteosarcoma, drowning, suicide, and intracranial hemorrhage. None of deaths was assessed as related to product by the Investigator or the Sponsor.

AESIs

Non-serious hypersensitivity/allergic reactions within 7 days after any injection

Seven subjects experienced at least one non-serious hypersensitivity/allergic reaction AESI within 7 days of any injection ie, 4 in the CYD Dengue Vaccine Group (2 subjects experienced dyspnea, 1 subject developed generalized erythema, and 1subject experienced asthmatic crisis and urticaria) and 3 in the Control Group (asthma [2 episodes], and pruritus). Most were of Grade 1 intensity except asthmatic crisis and urticaria that were of Grade 3 (see paragraph *Immediate unsolicited AEs and reactions* above). They did not lead to discontinuation from further injections except asthmatic crisis and urticaria. In addition to asthmatic crisis and urticaria, one of the 2 episodes of dyspnea, generalized erythema in the CYD Dengue Vaccine Group, and pruritus in the Control Group were assessed as related to study product.

Serious hypersensitivity/allergic reactions within 7 days after any injection

Five subjects experienced at least one serious AESI hypersensitivity/allergic reaction within 7 days of any injection: 4 in the CYD Dengue Vaccine Group (2 subjects had asthma, 1 subject had asthmatic crisis and 1subject developed urticaria) and 1 in the Control Group (asthma). In the CYD Dengue Vaccine Group, one case of asthma and the case of urticaria occurred within 24 hours of the vaccine injection (post-injection 1 and post-injection 2, respectively).

These 2 SAEs did not require hospitalization but subjects were discontinued from the following injections. Both SAEs were assessed as related to vaccination by both the Investigator and the Sponsor. The second case of asthma and asthmatic crisis in the CYD Dengue Vaccine Group and the case of asthma in the Control Group required hospitalization. These 3 SAEs occurred post-injection 1 or injection 2 and none of them were assessed as related to the study product or led to discontinuation from further injections. All serious AESIs resolved.

Serious associated viscerotropic disease (AVD) and serious associated neurotropic disease (AND)

No event of viscerotropic or neurotropic disease was observed.

Serious Dengue disease

During the Active Phase, serious dengue disease events were reported in 41 subjects in the CYD Dengue Vaccine Group and 48 subjects in the Control Group; 14 out of 41 (34.1%) in the CYD Dengue Vaccine Group and 40 out of 48 (83.3%) in the Control Group were virologically-confirmed.

During the LTFU, serious dengue disease were reported in 60 subjects (0.5%) in the CYD Dengue Vaccine Group and 47 subjects (0.7%) in the Control Group.

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