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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur **Drug substance:** CYD Dengue Vaccine	**Study Identifiers:** U1111-1127-6970, NCT00842530, 2014-001710-25 **Study code:** CYD23
Title of the study: Efficacy and Safety of Dengue Vaccine in Healthy Children Aged 4 to 11 Years in Thailand	
Study center: One study center in Thailand	
Study period: Date first subject enrolled: 05/Feb/2019 Date last subject completed: 22/Mar/2012	
Phase of development: Phase IIb	

Objectives:

Primary Objective:

To assess the efficacy of dengue vaccine after three injections in preventing symptomatic VC* dengue cases, regardless of the severity, due to any of the four serotypes in children aged 4 to 11 years at the time of inclusion.

* According to WHO Guidelines for the evaluation of dengue vaccines in populations exposed to natural infection. TDR/IVR/DEN/01

Secondary Objectives:

ALL SUBJECTS:

Efficacy (in all subjects)

1) To assess the efficacy of dengue vaccine after three injections in children aged 4 to 11 years at the time of inclusion in:
   - Preventing severe VC dengue cases due to any of the four serotypes.
   - Preventing symptomatic dengue cases, either VC or probable based on serological criteria, due to any of the four serotypes.
2) To assess the efficacy of dengue vaccine after at least two injections in children aged 4 to 11 years at the time of inclusion in:
   - Preventing symptomatic, VC dengue cases due to any of the four serotypes.
   - Preventing severe VC dengue cases due to any of the four serotypes.
   - Preventing symptomatic dengue cases, either VC or probable based on serological criteria, due to any of the four serotypes.

   For the secondary efficacy objectives, dengue cases were taken into account if they occurred more than 28 days after vaccination.
3) To evaluate the relationship between post-Injection 3 neutralizing antibody (Ab) level and the subsequent occurrence of symptomatic dengue cases in children aged 4 to 11 years at the time of inclusion.

Safety (in all subjects)

To evaluate the occurrence of SAEs in all subjects throughout the trial period.

SUBSETS OF SUBJECTS:

Immunogenicity (in the first 300 subjects)

To describe the humoral immune response to each dengue serotype before and after each dengue vaccination in a subgroup of children aged 4 to 11 years at the time of inclusion.

Reactogenicity (in 1050 subjects)

To evaluate the reactogenicity of dengue vaccine in terms of injection site and systemic reactogenicity after each injection in a subgroup of children aged 4 to 11 years at the time of inclusion.

Vaccine viremia (in the first 100 subjects)

To detect vaccine viremia 8 and 15 days after the first and second injections in a subgroup of children aged 4 to 11 years at the time of inclusion.

Methodology:

CYD23 was a randomized, observer-blind, controlled, monocenter, Phase IIb trial in 4002 subjects aged 4-11 years in Thailand. There were 3 injections (at 0,6 and 12 months) and 2 groups of subjects:

- CYD dengue vaccine group: 2668 subjects received CYD dengue vaccine (100 subjects in Cohort 1 and 2568 in Cohort 2)
- Control group: 1334 subjects received either:
  - 1 injection of rabies vaccine and 2 injections of placebo (50 subjects in Cohort 1), or
  - 3 injections of placebo (1284 subjects in Cohort 2)

Two-step approach for enrollment:

- Step 1: The first 150 subjects (Cohort 1) received their first injection (100 received the dengue vaccine and 50 received the rabies vaccine) and were followed for safety up to 14 days,
- An Independent Data Monitoring Committee (IDMC) reviewed Day (D) 14 safety data,
- The IDMC and Sponsor's recommendation to proceed with the inclusion of Cohort 2 and with the second injection of Cohort 1 was submitted to the Ethics Committee (EC) for consideration, along with the safety data from the first cohort,
- Step 2: Once approval had been obtained from the EC, Cohort 2 (n=3852) was enrolled.

The IDMC was also involved in the regular review of safety and efficacy data, which could have impacted the follow-up of the subjects and the remaining injections. Any fatal outcome or related SAE were promptly reviewed by the IDMC.

Follow-up of dengue cases:

The active detection of dengue cases (i.e., the Active Phase) started from the first injection until all subjects had been followed for at least 13 months after the third injection, on the condition that at least 27 cases of virologically-confirmed (VC) dengue had been detected and included in the per-protocol analysis set for Efficacy (PPSE). If 27 cases had not been detected, the active detection period would have been extended until this number had been reached. Beyond this time point, the detection of hospitalized dengue cases up to 5 years after the last injection in addition to fatal and related SAEs is done through CYD57 (for the subjects who consented to participate in CYD57 study), although cases occurring up to the hold of CYD23 study are also described in the present CSR.

Number of subjects:

Planned: 4002
Enrolled: 4002
Randomized: 4002

Evaluated:

Full Analysis Set for Efficacy: 3839
Per-Protocol Analysis Set Efficacy: 3673
Full Analysis Set for Immunogenicity: 296
Safety: 3997

Diagnosis and criteria for inclusion:

1) Aged 4 to 11 years on the day of inclusion.
2) Subject in good health, based on medical history and physical examination.
3) Provision of assent form signed by the subject (for subjects ≥ 7 years old) and informed consent form signed by the parent or another legally acceptable representative.
4) Subject and parent/legally acceptable representative able to attend all scheduled visits and to comply with all trial procedures.
5) Subject attending one of the schools involved in the trial.
6) For a female subject of child-bearing potential (girls post-menarche), avoid becoming pregnant (use of an effective method of contraception or abstinence) for at least 4 weeks prior to first vaccination, until at least 4 weeks after the last vaccination.

Study treatments

Investigational product: CYD Dengue Vaccine (Phase II lot)

Form: Powder and solvent for suspension for injection.

Composition: Each 0.5-mL reconstituted dose of tetravalent dengue vaccine contains:

5 ± 1 $\log_{10}$ cell-culture infectious dose 50% 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% containing human serum albumin 2.5%

Route of administration: Subcutaneous

Control Product 1: Rabies vaccine (Verorab®)

Form: Powder and solvent for suspension for injection

Composition: Each 0.5 mL of reconstituted dose contains:

Freeze dried (powder)

Component	Quantity (per reconstituted 0.5 mL dose)	Function
Inactivated rabies virus (Wistar rabies PM/WI 38 1503-3M strain)	≥ 2.5 IU[a]	Active substance
Maltose	52.5 mg	Lyo-excipient
Human albumin	2.5 mg	excipient
BME medium[b]	qs	excipient
Water for injections	*qs*	*excipient*

a Potency measured using NIH test in mice

b BME: Basal Medium Eagle: mixture of mineral salts, vitamins, and amino-acids including L-Phenylalanine

No preservative or adjuvant was added.

Solvent

Solvent was a sterile solution of 0.4% sodium chloride in water for injection

Component	Quantity (per reconstituted 0,5mL dose)
Sodium chloride	2 mg
Water for injection	qs 0.5 mL

Route of administration: SC

Control Product 2 (Investigational): Placebo (sodium chloride)

Form : Liquid

Composition: NaCl 0.9%

Route: SC

Duration of participation: The planned duration of each subject's participation in the trial was initially approximately 4 years.

Criteria for evaluation:

Primary Endpoints:

Symptomatic VC dengue case defined as:

- Acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), and
- VC by reverse transcriptase-polymerase chain reaction (RT-PCR) or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay (ELISA) Antigen (Ag) test, and
- Occurring >28 days after the third injection

Secondary Endpoints:

ALL SUBJECTS:

Efficacy – definition of severe dengue cases

VC dengue cases were classified as severe if they corresponded to:

- Dengue hemorrhagic fever (DHF) grade I, II, III, and IV according to the 1999 WHO definition:

  Clinical Manifestations

  a) Fever: acute onset, high and continuous, lasting 2 to 7 days.
  b) Any of the following hemorrhagic manifestations (including at least a positive tourniquet test): petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and hematemesis and/or melena.

  Laboratory Findings

  c) Thrombocytopenia (platelet count=100 000/mm3 or less).
  d) Plasma leakage as shown by hemoconcentration (hematocrit increased by 20% or more) or pleural effusion (seen on chest X-ray) and/or hypoalbuminemia.

  The first two clinical criteria, plus thrombocytopenia and signs of plasma leakage were sufficient to establish a clinical diagnosis of DHF. Pleural effusion (seen on chest X-ray) and/or hypoalbuminemia provide supporting evidence of plasma leakage.

  DHF was graded as follows:
  Grade I: Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test.
  Grade II: Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the form of skin and/or other hemorrhages.
  Grade III: Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness.
  Grade IV: Profound shock with undetectable blood pressure and pulse.

Or if any of the following manifestations were present:

1) Thrombocytopenia: platelet count ≤ 50 000/mm^3
2) Any hemorrhage that needs blood transfusion
3) Objective evidence of capillary permeability documented by one or several of the following:
   a) Increase in hematocrit by ≥ 20% compared to normal for age, or ([Maximum hematocrit - minimum hematocrit]/min]*100% ≥ 20%
   b) Pleural or abdominal (ascites) effusion (diagnosed either by clinical signs or radiography or other imaging method)
   c) Hypoproteinemia
4) Signs of circulatory failure manifested by:
   a) Narrow pulse pressure < 20 mm Hg, or hypotension for age (as defined by systolic pressure < 80 mm Hg in children < 5 years and systolic pressure < 90 mm Hg in children ≥ 5 years), and
   b) Rapid and weak pulse, and
   c) Signs of poor capillary perfusion (cold and clammy extremities, delayed capillary refill).
5) Visceral manifestations such as:
   a) Neurological symptoms (convulsions or change in level of consciousness)
   b) Hepatic failure or elevation of hepatic enzyme (> 5-fold normal level)
   c) Metabolic (hypoglycemia) or electrolyte (hyponatremia, hypocalcemia) disturbances or volume overload (acute pulmonary edema or congestive heart failure)
   d) Other visceral manifestations such as cardiomyopathy, acute renal failure, acute respiratory failure, cholecystitis

Efficacy – Definition of probable cases based on serological criteria

Suspected dengue cases were considered as probable based on serological criteria if the presence of IgM was observed in the acute or in the convalescent sample and/or a 4-fold increase in IgG was observed between the acute and convalescent samples.

Relationship between neutralizing Ab levels and subsequent occurrence of dengue cases *(in subjects with VC dengue and the first 300 subjects)*

- Neutralizing Ab levels against each of the four parental dengue virus serotype strains of Sanofi Pasteur's dengue vaccine constructs (and potentially against Thai circulating strains) were measured in samples taken 28 days after the third injection in subjects having developed VC dengue after the third vaccination and in the samples from the first 300 subjects (dengue neutralization assay).

Safety

Occurrence of SAEs in all subjects as follows:

- Up to 6 months after the last injection: all SAEs,
- From 6 months after the last injection until the end of trial: only related SAEs and fatal (even if unrelated) SAEs.

SUBSETS OF SUBJECTS:

Immunogenicity (in the first 300 subjects)

- Neutralizing Ab levels against each of the four parental dengue virus strains of Sanofi Pasteur's dengue vaccine constructs (and potentially against Thai circulating strains) were measured in sera collected from the first 300 vaccinated subjects before and 28 days after each injection (dengue neutralization assay), and 1 year after the third injection, and will be measured 2, and 3 years after the third injection.

Reactogenicity

- In 1050 subjects (clinical reactogenicity):
  - Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, severity, action taken, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination.
  - Occurrence, time to onset, number of days of occurrence, action taken, and severity of solicited, i.e., pre-listed in the subject's diary and electronic case report form (eCRF), injection site reactions occurring up to 7 days after each vaccination.
  - Occurrence, time to onset, number of days of occurrence, action taken, and severity of solicited systemic reactions occurring up to 14 days after each vaccination.
  - Occurrence, nature (MedDRA preferred term), time to onset, duration, severity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each vaccination.

- In the first 100 subjects (biological safety):
  - Occurrence and timing of out-of-normal-range biological test results before and 8 and 15 days after the first and the second injections in the first 100 vaccinated subjects.

Vaccine viremia (in the first 100 subjects)

Occurrence and level of dengue vaccine viruses in sera collected 8 and 15 days after the first and after the second injection in the first 100 vaccinated subjects (quantitative RT-PCR).

Statistical methods:

Statistical analyses

Two statistical analyses were performed for this trial:

- A preliminary blinded safety analysis based on post-Injection 1 and post-Injection 2 was performed by an independent contract research organization
- A second analysis was performed to assess the efficacy after the complete schedule had been received (assessment of the primary objective), immunogenicity, and safety. It included all efficacy, immunogenicity, and safety data collected during the efficacy period (Active Phase) up to at least 13 months after the third injection of the last subject.

Analysis for the primary endpoints

The following hypotheses were tested using an alpha of 2.5%

H0: VE ≤ 0%

H1: VE > 0%

Where VE =100*(1-P_{VX}/P_{CO})

with P_{VX}: Density incidence (DI) in the Dengue group
with P_{CO}: DI in the Control group

DI was defined as the ratio of the number of cases occurring during the follow-up period to the population at risk

The statistical methodology was based on the use of the two-sided 95% CI of the VE. The CI was calculated using the Exact method described by Breslow & Day, 1987.

VE in preventing symptomatic VC dengue would be demonstrated if the lower bound of the 95% CI was greater than 0.

The PP analysis set was used for the main (primary) analysis.

Analyses for the secondary endpoints

The main efficacy parameters were described with 95% CI using the Exact method and the VE post-Injection 2 would be demonstrated as significant if the lower bound of the 95% CI was greater than 0.

The main immunogenicity parameters were described with 95% CI using the normal approximate method (Geometric Mean titer [GMT] and Geometric Mean of the individual Titers Ratio) or the exact binomial distribution described using the Clopper Pearson method.

The main safety parameters, were described with 95% CI using the exact binomial distribution described using the Clopper Pearson method.

Safety evaluation

The subset of 700 subjects in the vaccine group gives a probability of 95% of observing an event with a true incidence of 0.43% (rule of three) (Hanley and Lippman-Hand, 1983).

Summary:

Trial Population

A total of 4014 subjects were screened from which 4002 were enrolled and randomized (2669 subjects in the dengue group and 1333 subjects in the control group); 150 subjects were enrolled and randomized in Cohort 1 (100 subjects in the dengue group and 50 subjects in the control group) and 3852 subjects in Cohort 2 (2569 subjects in the dengue group and 1283 subjects in the control group).

The vast majority of subjects (95.7% of all subjects) present at V01 completed the Active Phase of the study.

Approximately 96% subjects were included in the FASE and approximately 92% were included in the PPSE. Failure to receive 3 injections and injection received outside the protocol-defined time windows were the most common reasons for exclusion from the PPSE.

Demographic Characteristics

Overall, there were slightly more female (51.8%) than male subjects (48.2%) and the mean age was 8.17 years. All demographic characteristics were similar in both treatment groups in the biological, immunological and reactogenicity subsets.

Efficacy

Primary Objective

VE Against VC Dengue After 3 Injections - PPSE

Dengue (N=2452)		Group	Control (N=1221)		Group	VE	
Person-years at risk	Cases	n Occurrences	Person-years at risk	Cases	Occurrences	%	(95% CI)
2522	45	45	1251	32	33	30.2	(-13.4; 56.6)

Cases: number of subjects with at least 1 VC dengue episode.
n Occurrences: number of VC dengue episodes in the considered period.
The VE of the CYD dengue vaccine was considered as significant if the lower bound of its 95% CI was greater than 0.

After 3 injections of CYD dengue vaccine, the overall VE estimate was 30.2% (95% CI: -13.4, 56.6); the level of significance was not reached (the lower bound of its 95% CIs was not greater than 0).

A total of 78 VC dengue episodes was observed in 77 subjects after the completion of the 3 injections. Although this was more than the original estimate of 27 VC dengue cases, both the higher than estimated attack rate of dengue and a VE estimate that was lower than the 70% assumption resulted in the observed vaccine efficacy that did not reach statistical significance.

Secondary Objectives

VE Against Severe VC Dengue

Considering both WHO 1999 and IDMC severity assessments, a total of 5 severe VC dengue cases were identified during the Active Phase. Three were severe according to both WHO 1999 and IDMC severity assessments (1 in the dengue group and 2 in the control group), 1 was severe only according to the WHO 1999 criteria (in the dengue group) and 1 was severe only according to the IDMC assessment (in the dengue group). Moreover, there were no increases in the classic clinical signs of dengue such as bleeding, plasma leakage, or thrombocytopenia in vaccinees compared to controls. In conclusion, these results showed no increase of severe VC dengue in vaccinees as compared to controls.

VE Against VC Dengue After at Least 2 Injections - OES#2

Dengue (N=2584)		Group	Control (N=1300)		Group	VE	
Person-years at risk	Cases	n Occurrences	Person-years at risk	Cases	Occurrences	%	(95% CI)
3824	61	61	1905	47	49	35.3	(3.3; 56.5)

Cases: number of subjects with at least 1 VC dengue episode.
n Occurrences: number of VC dengue episodes in the considered period.
The VE of the CYD dengue vaccine was considered as significant if the lower bound of its 95% CI was greater than 0.

The estimate of VE after 2 injections was similar to that after 3 injections; however, it involved a higher number of cases than seen in the PPSE, enabling greater precision, with narrower CIs, and reached significance as the lower bound of the 95% CI was greater than 0.

VE Against VC Dengue After at Least 1 Injection - OES#1

Dengue (N=2666)		Group	Control (N=1331)		Group	Vaccine Efficacy	
Person-years at risk	Cases	n Occurrences	Person-years at risk	Cases	Occurrences	%	(95% CI)
5089	75	75	2532	56	60	33.4	(4.1; 53.5)

Cases: number of subjects with at least 1 VC dengue episode.
n Occurrences: number of VC dengue episodes in the considered period.

The estimate of VE after at least 1 injection was similar to that seen after at least 2 injections and in the PPSE. As for the estimate after at least 2 injections, the VE after at least 1 injection involved a higher number of cases than seen in the PPSE, enabling greater precision, with narrower CIs. Consequently, the lower bound of the 95% CI was greater than 0.

Incidence of VC Dengue According to Serotype - OES#1

	Dengue Group (N=2666)		Control Group (N=1331)		Relative Risk	
Strain	Person-years at risk	Cases	Person-years at risk	Cases	RR	(95% CI)
Serotype 1	5343	14	2666	18	0.388	(0.179, 0.826)
Serotype 2	5312	52	2662	27	0.965	(0.595, 1.60)
Serotype 3	5348	4	2667	11	0.181	(0.042, 0.612)
Serotype 4	5353	1	2679	5	0.100	(0.002, 0.894)
Not Identified*	5351	5	2681	1	2.51	(0.280, 118)

Cases: number of subjects with one virologically-confirmed dengue episode during the Active Phase.
* VC dengue cases confirmed only by NS1 method were classified in the Not Identified category.

From 28 days post-Injection 1 to the end of the Active Phase, the incidence of VC dengue due to serotype 2 was similar between treatment groups. VE (VE=[1–Relative Risk] X 100) against serotype 2 was correspondingly low (3.5%). For the other serotypes, the incidence of VC dengue cases was lower in vaccinees than in controls. Their respective VEs were 61.2% against serotype 1, 81.9% against serotype 3, and 90.0% against serotype 4.

Incidence of Hospitalized Dengue Cases - OES#1

	Dengue Group (N=2666)			Control Group (N=1331)			Relative Risk	
Time Period	M	Cases	n Occurrences	M	Cases	Occurrences	RR	(95% CI)
First year: D0 to Injection 3	2666	8	8	1331	7	7	0.571	(0.181, 1.85)
Second year: Injection 3 to the end of the Active Phase	2557	24	24	1282	23	23	0.523	(0.283, 0.970)

Cases: number of subjects with at least 1 VC dengue episode.
n Occurrences: number of VC dengue episodes in the considered period.

The risk of hospitalized VC dengue was lower in the dengue group both during the vaccination schedule and for the year following the third dose. Few cases of hospitalized dengue were observed during the first year, leading to large CIs. The number of hospitalized cases was approximately 3 times higher during the second year, enabling a more precise estimate of RR.

Duration of Clinical Syndrome and Hospitalization

Independently from the number of cases observed in each group, there were no differences between vaccinees and controls with regard to the rate of hospitalization or the duration of fever, clinical syndrome or hospitalization. This demonstrates that breakthrough dengue infection in vaccinees was not clinically more severe than that observed in control subjects. There is no evidence of any enhanced disease in vaccinees infected with dengue.

Immunogenicity

Immunogenicity was analyzed by the measurement of dengue neutralizing Abs using the plaque reduction neutralization test. All results are presented on the FASI.

GMTs

		Dengue Group (N=197)			Control Group (N= 99)		
Strain	**Time point**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
Serotype 1	**Pre-Inj 1**	197	42.8	(30.7; 59.6)	99	26.6	(17.6; 40.2)
	Post-Inj 3	188	155	(116; 207)	96	27.8	(18.3; 42.2)
	1-Year Follow-Up Post-Inj 3	187	120	(87.0; 166)	94	35.8	(23.1; 55.4)
Serotype 2	**Pre-Inj 1**	197	56.8	(40.3; 80.1)	98	43.7	(27.8; 68.7)
	Post-Inj 3	188	358	(283; 453)	96	52.2	(32.3; 84.4)
	1-Year Follow-Up Post-Inj 3	187	158	(117; 213)	94	46.1	(29.4; 72.4)
Serotype 3	**Pre-Inj 1**	197	31.5	(24.2; 41.0)	99	28.7	(19.3; 42.6)
	Post-Inj 3	188	351	(289; 428)	96	46.2	(29.9; 71.4)
	1-Year Follow-Up Post-Inj 3	187	125	(97.2; 161)	94	35.1	(23.0; 53.6)
Serotype 4	**Pre-Inj 1**	197	28.1	(21.7; 36.4)	99	23.2	(15.6; 34.6)
	Post-Inj 3	188	151	(128; 178)	96	22.1	(15.3; 32.0)
	1-Year Follow-Up Post-Inj 3	187	152	(120; 192)	94	45.9	(30.4; 69.3)

M: number of subjects with available data for the relevant endpoint.

Overall, baseline GMTs were similar across serotypes for both treatment groups: baseline GMTs ranged from 28.1 (1/dil) to 56.8 (1/dil) in the dengue group and from 23.2 (1/dil) to 43.7 (1/dil) in the control group. Increases in GMTs were observed after the first and second injections. With the exception of serotype 3, the third injection was not associated with further increases in GMTs; after the first, second, and third injection, GMTs were respectively
94.4 (1/dil), 184 (1/dil), and 155 (1/dil) for serotype1
195 (1/dil), 351 (1/dil), and 358 (1/dil) for serotype 2
112 (1/dil), 218 (1/dil), and 351 (1/dil) for serotype 3
138 (1/dil), 183 (1/dil), and 151 (1/dil) for serotype 4

One year after the third injection of CYD dengue vaccine, GMTs for each serotype decreased as compared to post-Injection 3, but remained higher compared to baseline; GMTs ranged from 120 (1/dil) to 158 (1/dil) 1 year after the third injection.

Baseline seropositivity rates against each serotype were similar across serotypes for both treatment groups (ranged from 54.8% to 60.4% in the dengue group and from 45.5% to 58.2% in the control group). Seropositivity rates against each serotype increased after the first and second injections of CYD dengue vaccine, and were > 90% 28 days after the second injection. One year after the third injection of CYD dengue vaccine, the seropositivity rates remained > 85% against each serotype.

The fact that a substantial immune response was already observed after the second injection may be related to the high percentage of subjects immune at baseline. Indeed, almost all subjects dengue immune at baseline were seropositive against each dengue virus serotype after the second injection, whereas this was not the case for dengue non-immune subjects.

Baseline seropositivity rates against at least 1, 2, 3 or all 4 serotypes were similar in both treatment groups and were in dengue versus control group approximately 70% versus 69%, 58% versus 55%, 56% versus 49%, and 46% versus 35%, respectively. Seropositivity rates against all 4 serotypes increased to > 90% after the second injection and remained high after the third injection. One year after the third injection of CYD dengue vaccine, the seropositivity rates remained > 80% against all 4 serotypes.

Safety

Solicited Injection Site Reactions
After the first injection, the frequency of each injection site reaction was similar between treatment groups. In both treatment groups, pain was the most frequently reported injection site reaction (33.5% in the dengue group and 30.9% in the control group), followed, to a lesser extent, by erythema (13.3% in the dengue group and 16.3% in the control group) and swelling (9.0% in the dengue group and 9.2% in the control group). After the second and third injections, the percentages of subjects with pain, erythema or swelling were similar to those observed after the first injection.

Grade 3 solicited reactions were infrequent in both treatment groups (4.8% in the dengue group and 7.7% in the control group) and were mostly reported after the first injection.

In both treatment groups, almost all injection site reactions occurred within 3 days after injection and resolved within 1 to 3 days.

Solicited Systemic Reactions

The proportion of subjects with solicited systemic reactions after the first injection was similar in both treatment groups, with the exception of myalgia that tended to be more frequent in the dengue group. Headache was the most frequently reported solicited systemic reaction (39.6% in the dengue group and 35.2% in the control group). Malaise, myalgia and asthenia were reported to a lesser extent (approximately 25-30%, each) and fever was the least reported (13.8% in the dengue group and 14.7% in the control group). After the second and third injections, the percentages of subjects with headache, myalgia, malaise, or asthenia were similar to those observed after the first injection.

Grade 3 systemic reactions were infrequent in both treatment groups (4.6% in the dengue group and 7.4% in the control group) and were mostly reported after the first injection. In both treatment groups, almost all solicited systemic reactions occurred within 3 days after injection and resolved within 1 to 3 days.

Unsolicited AEs

After the first injection, the percentage of subjects who experienced at least one unsolicited AE was similar in both groups (22.7% of subjects in the dengue group and 25.7% in the control group). These percentages were similar after the second injection (24.8% in the dengue group and 24.6% in the control group) and were slightly lower after the third injection (16.6% in the dengue group and 19.8% in the control group).

For both treatment groups, the most frequently reported unsolicited AEs were in the SOC “infections and infestations” (across injections, the frequencies ranged from 10.2% to 16.1% in the dengue group and from 10.4% to 17.1% in the control group). The most frequently reported PT was “upper respiratory tract infection” (across injections, the frequencies ranged from 2.9% to 6.9% in the dengue group and from 3.8% to 6.1% in the control group), followed by “pharyngitis” (across injections, the frequencies ranged from 2.4% to 3.9% in the dengue group and from 2.4% to 4.6% in the control group).

After any injection, a maximum of 15 subjects (2.2%) in the dengue group and 14 of subjects (4.0%) in the control group reported Grade 3 unsolicited non-serious AEs. These were most often bronchitis, abdominal pain, common cold, nausea, pharyngitis, or gastritis for both treatment groups. None of these AEs were considered as related to treatment.

After any injection, 10 subjects (1.4%) reported an unsolicited non-serious AR in the dengue group (nausea, vomiting, and injection site hemorrhage). In the control group, only 1 subject (0.3%) reported a non-serious unsolicited AR (injection site hemorrhage after the second injection).

Deaths

Five deaths were reported, 4 occurred in the control group and 1 in the dengue group. None of them was considered as related to treatment: the causes of death were drowning, road accidents, head injury, and T-cell lymphoma.

SAEs

A total of 586 SAEs were reported during the study (584 occurred during the Active Phase). The percentages of subjects reporting SAEs during the Active Phase were similar between treatment groups; 11.8% of subjects in the dengue group and 13.2% of subjects in the control group reported SAEs.

Among the 586 SAEs reported, only 1 SAE (in the control group) was assessed as related to treatment by the Investigator: a female subject with a diagnosis of acute febrile illness. She recovered on the day of admission and was discharged on the next day.

Laboratory Parameters

There were no relevant changes in hematology or biochemistry parameters and there were no clinically significant biological abnormalities, as assessed by the Investigator, after injection of either CYD dengue vaccine or placebo/rabies vaccine.

Viremia

Among the 16 subjects with at least one detectable or quantifiable YF RT-PCR results, none had quantifiable levels of vaccine viral RNA (i.e., serotype-specific CYD RT-PCR ≥ LLOQ). Few cases of detectable vaccine viral RNA (i.e., ≥ LLOD but < LLOQ) were found. Most of these were Serotype 4, observed 8 days after injection (9 subjects after the first injection and 1 subject after the second injection). One case of detectable viral RNA was observed 8 days after the first injection for serotype 3. Serotypes 1 and 2 were not detected.

Pregnancies

A total of 5 pregnancies (4 in the dengue group and 1 in the control group) were reported from the beginning to the Passive Phase up to the end of the study. No pregnancy complications were reported. One of these pregnancies was a twin pregnancy and the two premature newborns reported an SAE. Both are reported by the Investigator as unrelated to the study vaccine

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