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Sponsor: Sanofi Pasteur	Study Identifiers: U1111-1111-5511, IND 11219, NCT00993447, 2014-001707-53
Drug substance(s): CYD Dengue Vaccine	Study code: CYD13
Title of the study: Immunogenicity and Safety of Sanofi Pasteur's CYD Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Latin America	
Study center(s): This was a multicenter, multinational trial involving 4 investigators in 4 countries.	
Study period: Date first subject/patient enrolled: 09/Oct/2009 Date last subject/patient completed: 29/Aug/2011	
Phase of development: Phase II	
Objectives: Primary Objectives: 1) To describe the humoral immune response to each dengue serotype before and after each injection with Sanofi Pasteur's CYD dengue vaccine. 2) To evaluate the safety of each injection with Sanofi Pasteur's CYD dengue vaccine.	
Methodology: Randomized, observer-blind (first and second injections), single-blind (third injection), controlled, multicenter, multinational, Phase II trial in 600 healthy children and adolescents in Colombia, Honduras, Mexico, and Puerto Rico. There were to be 3 injections (D0, D0+6 months, D0+12 months) and 2 groups of subjects: <ul style="list-style-type: none"> • Dengue Vaccine Group was to receive the 5555 formulation of Sanofi Pasteur's CYD dengue vaccine as first, second, and third injections. • Control Group was to receive a placebo (NaCl) as first and second injections and ADACEL vaccine as third injection. An Independent Data Monitoring Committee (IDMC) was involved in the regular review of safety data. Any fatal outcome, serious adverse events (SAEs), virologically-confirmed, and suspected dengue cases were to be reviewed by the IDMC.	
Number of subjects:	Planned: 600 Randomized: 600 Treated: 600
Evaluated:	Immunogenicity: 600 Safety: 600

Diagnosis and criteria for inclusion:

- 1) Aged 9 to 16 years on the day of inclusion
- 2) Subject in good health, based on medical history and physical examination
- 3) Provision of assent form/informed consent form signed by the subject and by the parent(s) or another legally acceptable representative
- 4) Subject and parent(s)/legally acceptable representative(s) able to attend all scheduled visits and to comply with all trial procedures
- 5) For a female subject of child-bearing potential, avoid becoming pregnant (use of an effective method of contraception or abstinence) for at least 4 weeks prior to first injection until at least 4 weeks after the last injection

Study treatments

Investigational Product: CYD Dengue Vaccine

Form: Powder and solvent for suspension for injection

Composition: Each 0.5 mL dose of reconstituted vaccine contains:

$5 \pm 1 \log_{10}$ cell culture infectious dose 50% (CCID50) of each chimeric dengue serotype 1, 2, 3, and 4 (5555 formulation)

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 (SC)

Dose regimen: Three injections were administered: at D0, D0 + 6 months, and D0 + 12 months

Control Product: Placebo

Form: Liquid

Composition: NaCl 0.9%

Route of administration: SC

Control Product #2: ADACEL, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Form: Injectable suspension

Composition: Each dose of ADACEL vaccine (0.5 mL) contains the following active ingredients:

Acellular Pertussis

Detoxified Pertussis Toxin (PT)	2.5 µg
Filamentous Hemagglutinin (FHA)	5 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg
Tetanus Toxoid (T)	5 Lf
Diphtheria Toxoid (d)	2 Lf

Other ingredients per dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, $\leq 5 \mu\text{g}$ residual formaldehyde, $< 50 \text{ ng}$ residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative).

Route of administration: Intramuscular (IM)

Duration of participation: 18 months

Criteria for evaluation:

Primary Endpoints:

Immunogenicity:

- Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were to be measured in sera collected from all subjects before and 28 days after each injection (dengue plaque reduction neutralization test [PRNT]).

Safety:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, whether it leads to discontinuation or not, and relationship to injection of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each injection.
- Occurrence, time to onset, number of days of occurrence, intensity, whether it leads to discontinuation or not, and action taken of solicited (pre-listed in the subject's diary card (DC) and electronic case report form [eCRF]) injection site reactions occurring up to 7 days after each injection.
- Occurrence, time to onset, number of days of occurrence, intensity, whether it leads to discontinuation or not, and action taken of solicited systemic reactions occurring up to 14 days after each injection.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, whether it leads to discontinuation or not, action taken and relationship to injection (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each injection.
- Occurrence of SAEs throughout the trial.

Statistical methods:

All main analyses were descriptive. For the main parameters, 95% CIs of point estimates were calculated using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.

Two planned statistical analyses of safety and immunogenicity were to be performed on unblinded data: 1 after the third injection and 1 after the end of the follow-up period.

Summary:

Population Characteristics:

Subject Disposition:

A total of 600 subjects were screened and enrolled in the study: 401 subjects in the CYD dengue vaccine group and 199 subjects in the Control group.

The percentage of subjects who were withdrawn from the study was similar in both treatment groups, and there were no notable differences between treatment groups in the reasons for withdrawal from the study. A total of 90.7% (544/600) of subjects completed the study. The most common reason for not completing the study was voluntary withdrawal not for an AE. One subject in the CYD dengue vaccine group discontinued due to an AE (hepatitis A).

All randomized subjects were included in the full analysis and the safety analysis sets. There were 570/600 (95.0%) subjects in the PP analysis set post-Inj 1, 527/600 (87.8%) subjects in the PP analysis set post-Inj 2, and 498/600 (83.0%) subjects in the PP analysis set post-Inj 3.

Demographics:

Overall, 52.0% (312/600) of subjects were females and 48.0% (288/600) of subjects were males in the FAS. The percentages of females (50.9% [204/401]) and males (49.1% [197/401]) were balanced in the CYD dengue vaccine group whereas there was a higher percentage of females (54.3% [108/199]) than males (45.7% [91/199]) in the Control group. The mean age was similar between the treatment groups, with an overall mean age of 12.6 years (range 9.0 to 17.0 years) at enrollment. All of the subjects in the study were Hispanic.

Immunogenicity:

Primary Objective: Humoral Immune Response to Each Dengue Serotype Before and After Each Injection

Seropositivity

In the CYD dengue vaccine group, the percentage of subjects who were seropositive at baseline for each serotype was slightly lower than in the Control group, and ranged from 62.6% (251/401) for serotype 4 to 69.6% (279/401) for serotype 3.

In the CYD dengue vaccine group, there was an increase in seropositivity rates after each injection with a more pronounced increase post-Inj 1 for serotypes 2, 3, and 4 and a more gradual increase after each dose for serotype 1. At post-Inj 3, the net increases from baseline in the percentage of subjects who were seropositive were similar for all serotypes. At post-Inj 3 in the CYD dengue vaccine group, 98.9% (360/364) of subjects were seropositive for Abs to serotypes 2 and 4, 100% (364/364) of subjects were seropositive for Abs to serotype 3, and 94.2% (343/364) were seropositive for Abs to serotype 1.

In the Control group, the percentage of subjects who were seropositive at baseline ranged from 67.8% (135/199) for serotypes 1 and 4, to 73.9% (147/199) for serotype 2. These percentages were relatively unchanged following each of the 3 injections.

By Baseline Flavivirus Status

FV-Immune at Baseline

The majority of subjects in both treatment groups were FV-immune at baseline: 78.8% (316/401) of subjects in the CYD dengue vaccine group and 80.4% (160/199) of subjects in the Control group.

In the CYD dengue vaccine group, the seropositivity rates at baseline were similar to, but slightly lower than, those observed in the Control group: 81.3% (257/316) for serotype 1; 88.0% (278/316) for serotype 2; 88.3% (279/316) for serotype 3; and 79.4% (251/316) for serotype 4. For each of the serotypes, a more pronounced increase in seropositivity was observed at post-Inj 1, with additional increases at post-Inj 2 and post-Inj 3. At post-Inj 3 in the CYD dengue vaccine group, the percentage of subjects who were seropositive was 97.6% (280/287) for serotype 1, 99.7% (286/287) for serotype 2, and 100% (287/287) for serotypes 3 and 4.

In the Control group, seropositivity rates were recorded at baseline and were 84.4% (135/160) for serotype 1, 91.9% (147/160) for serotype 2, 90.6% (145/160) for serotype 3, and 84.4% (135/160) for serotype 4. There were no appreciable changes in seropositivity for the 4 dengue serotypes in the Control group after any injection.

FV-Naïve at Baseline

At baseline, 21.2% (85/401) of subjects in the CYD dengue vaccine group and 19.1% (38/199) of subjects in the Control group were FV-naïve.

In the CYD dengue vaccine group, seropositivity rates gradually increased from baseline for all 4 serotypes after each injection. At post-Inj 1 and post-Inj 2 the seropositivity rates were higher for serotypes 2, 3 and 4 compared to serotype 1. At post-Inj 3, the proportion of subjects in the CYD dengue vaccine group who were seropositive was 81.8% (63/77), 96.1% (74/77), 100% (77/77), and 94.8% (73/77) for serotypes 1, 2, 3, and 4, respectively.

In the Control group, seropositivity rates increased from baseline for all 4 serotypes. At post-Inj 3, the proportion of subjects in the Control group who were seropositive was 19.4% (7/36) for serotypes 1 and 2, 16.7% (6/36) for serotype 3, and 5.6% (2/36) for serotype 4.

Seropositivity for at Least 1, 2, 3 or 4 Dengue Virus Serotypes

In the CYD dengue vaccine group, the percentages of subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes were 75.1% (301/401), 69.1% (277/401), 64.6% (259/401), and 56.9% (228/401), respectively. The increases in the percentages of subjects who were seropositive for at least 1 or at least 2 serotypes were more pronounced at post-Inj 1 whereas the percentage of subjects who were seropositive for at least 3 or all 4 serotypes increased more gradually after each injection. At post-Inj 3, all subjects (100% [364/364]) were seropositive for at least 1 or 2 serotypes, 98.6% (359/364) were seropositive for at least 3 serotypes, and 93.4% (340/364) were seropositive for all 4 serotypes.

In the Control group, the percentage of subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes was 77.9% (155/199), 72.9% (145/199), 69.8% (139/199), and 61.8% (123/199), respectively. There were no appreciable changes in these rates after each injection.

By Baseline Flavivirus Status

FV-Immune at Baseline

In the CYD dengue vaccine group, the percentage of subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes was 95.3% (301/316), 87.7% (277/316), 82.0% (259/316), and 72.2% (228/316), respectively. The increases in the percentage of subjects who were seropositive for at least 1, 2, 3, or all 4 serotypes were more pronounced at post-Inj 1. At post-Inj 3, all but 1 subject (99.7% [286/287]) were seropositive for at least 3 serotypes, and the percentage of subjects who were seropositive for all 4 serotypes reached 97.6% (280/287).

In the Control group, the percentage of subjects who were seropositive at baseline for at least 1, at least 2, at least 3, or all 4 serotypes was 96.9% (155/160), 90.6% (145/160), 86.9% (139/160), and 76.9% (123/160), respectively. There were no notable changes in these rates after any of the 3 injections.

FV-Naïve at Baseline

In the CYD dengue vaccine group, the largest increases from baseline in seropositivity occurred at post-Inj 1 for at least 1 serotype (95.2% [80/84]) and at post-Inj 3 for all 4 serotypes (77.9% [60/77]). In the CYD dengue vaccine group, the percentage of subjects who were seropositive at post-Inj 3 was 100% (77/77) for at least 1 or 2 serotypes, 94.8% (73/77) for at least 3 serotypes, and 77.9% (60/77) for all 4 serotypes.

In the Control group, an increase in seropositivity for at least 1 serotype occurred at post-Inj 1, when 16.2% (6/37) of subjects were seropositive. At post-Inj 3, the percentage subjects who were seropositive had increased and was 25.0% (9/36) for at least 1 serotype, 16.7% (6/36) for at least 2 serotypes, 13.9% (5/36) at least 3 serotypes, and 5.6% (2/36) for all 4 serotypes.

Dengue Neutralizing Antibody Levels

In the CYD dengue vaccine group, the baseline geometric mean titers (GMTs) were similar to those observed in the Control group for all 4 serotypes: 74.2, 92.6, 85.0, and 37.2 for serotypes 1, 2, 3, and 4, respectively. The GMTs for all 4 serotypes increased from baseline in the CYD dengue vaccine group. The highest GMTs were observed at post-Inj 3 for serotypes 1 and 3, at post-Inj 2 for serotype 2, and at post-Inj 1 for serotype 4.

In the Control group, the baseline GMTs were 81.9 for serotype 1, 100 for serotype 2, 88.8 for serotype 3, and 40.1 for serotype 4. The GMTs for all 4 serotypes increased from baseline to post-Inj 3.

When compared to the Control group, the GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 3.1-fold higher for serotype 1, 3.4-fold higher for serotype 2, 4.6-fold higher for serotype 3, and 6.3-fold higher for serotype 4.

By Baseline Flavivirus Status

FV-Immune at Baseline

In the CYD dengue vaccine group, the baseline GMTs were 153 for serotype 1, 203 for serotype 2, 182 for serotype 3, and 63.8 for serotype 4. The GMTs for all 4 serotypes were markedly increased at post-Inj 1. For serotypes 1 and 3, the GMTs observed at post-Inj 2 (607 and 782, respectively) and post-Inj 3 (580 and 827, respectively) were comparable to those observed at post-Inj 1 (604 and 863, respectively) whereas the GMTs for serotypes 2 and 4 at post-Inj 2 (888 and 395, respectively) and post-Inj 3 (741 and 341, respectively) were lower compared to the GMTs observed at post-Inj 1 (1001 and 549, respectively). At post-Inj 3, the GMTs were 580, 741, 827, and 341, for serotypes 1, 2, 3, and 4, respectively.

In the Control group, the baseline GMTs were 162 for serotype 1, 207 for serotype 2, 179 for serotype 3, and 66.5 for serotype 4. Marginal increases in the GMTs for all 4 serotypes were observed in the Control group. At post-Inj 3, the GMTs were 205, 266, 248, and 72.5, for serotypes 1, 2, 3, and 4, respectively, in the Control group.

When compared to subjects in the Control group, the GMs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 2.8-fold higher for serotype 1, 2.5-fold higher for serotype 2, 3.0-fold higher for serotype 3, and 4.6-fold higher for serotype 4.

FV-Naïve at Baseline

In the CYD dengue vaccine group, the GMTs for serotypes 1, 2, 3, and 4 were markedly increased from baseline. A gradual increase in GMTs was observed for serotypes 1, 2, and 3 with the highest GMTs observed at post-Inj 3. For serotype 4; however, the highest GMT was observed at post-Inj 1. At post-Inj 3 in the CYD dengue vaccine group, the GMTs were 34.6, 101, 174, and 119, respectively.

In the Control group, nominal increases in GMTs were observed for all 4 serotypes. At post Inj-3, the GMTs for serotypes 1, 2, 3, and 4 were 8.36, 9.45, 7.53, and 5.63, respectively, in the Control group.

When compared to the Control group, the GMs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 4.1-fold higher for serotype 1, 10.7-fold higher for serotype 2, 23.1-fold higher for serotype 3, and 21.1-fold higher for serotype 4.

Safety:

Solicited Injection Site Reactions:

After the First Injection

At least 1 solicited injection site reaction after the first injection was reported by 31.6% (124/392) of subjects in the CYD dengue vaccine group and 27.6% (54/196) of subjects in the Control group.

Pain was the most frequently reported solicited injection site reaction in both treatment groups after the first injection. Injection site pain was reported with a similar frequency in the CYD dengue vaccine group (30.9% [121/392]) and the Control group (27.6% [54/196]).

The majority of all of the solicited injection site reactions began 0 to 3 days after the first injection, and resolved within 3 days of occurrence.

The majority of solicited injection site reactions were Grade 1 in intensity. Grade 3 injection site reactions were reported by 1.8% (7/392) of subjects in the CYD dengue vaccine group and 1.0% (2/196) of subjects in the Control group.

By Baseline Flavivirus Status

At least 1 solicited injection site reaction after the first injection in the CYD dengue vaccine group was reported by 29.9% (92/308) of FV-immune subjects and 38.1% (32/84) of FV-naïve subjects reported, and in the Control group, by 27.4% (43/157) of FV-immune subjects and 28.9% (11/38) of FV-naïve subjects.

Pain in both treatment groups after the first injection was the most frequently reported solicited injection site reaction by FV-immune and FV-naïve subjects. In the CYD dengue vaccine group, injection site pain was reported by 29.5% (91/308) of FV-immune subjects and 35.7% (30/84) of FV-naïve subjects. In the Control group, injection site pain was reported by 27.4% (43/157) of FV-immune subjects and 28.9% (11/38) of FV-naïve subjects.

After the Second Injection

Solicited injection site reactions after the second injection were reported by 27.3% (102/373) of subjects in the CYD dengue vaccine group and by 17.8% (33/185) of subjects in the Control group.

Pain in both treatment groups after the second injection was the most frequently reported solicited injection site reaction. Injection site pain was reported by a larger percentage of subjects in the CYD dengue vaccine group (27.1% [101/373]) than in the Control group (16.8% [31/185]).

Most of the solicited injection site reactions began 0 to 3 days after the second injection and resolved within 3 days.

Most of the solicited injection site reactions were Grade 1 in intensity. Grade 3 injection site reactions were reported by 2.1% (8/373) of subjects in the CYD dengue vaccine group and no subjects in the Control group.

By Baseline Flavivirus Status

At least 1 solicited injection site reaction after the second injection was reported by 23.4% (69/295) of FV-immune subjects and 42.3% (33/78) of FV-naïve subjects, and in the Control group, by 16.9% (25/148) of FV-immune subjects and 19.4% (7/36) of

FV-naïve subjects.

Pain in both treatment groups after the second injection was the most frequently reported solicited injection site reaction by FV-immune and FV-naïve subjects.

After the Third Injection

Injection site reactions after the third injection were reported by 24.7% (90/364) of subjects in the CYD dengue vaccine group and 67.2% (121/180) of subjects in the Control group.

Pain in both treatment groups after the third injection was the most frequently reported solicited injection site reaction. Injection site pain was reported with a higher frequency in the Control group (65.6% [118/180]) when ADACEL was administered compared to the CYD dengue vaccine group (24.2% [88/364]).

The majority of the solicited injection site reaction began 0 to 3 days after the third injection and resolved within 3 days.

The majority of the solicited injection site reactions were Grade 1 in intensity. Grade 3 injection site reactions after the third injection were reported by 0.5% (2/364) of subjects in the CYD dengue vaccine group and 3.3% (6/180) of subjects in the Control group.

By Baseline Flavivirus Status

At least 1 solicited injection site reaction in the CYD dengue vaccine group after the third injection was reported by 23.7% (68/287) of FV-immune subjects and 28.6% (22/77) of FV-naïve subjects and by 66.4% (95/143) of FV-immune subjects and 69.4% (25/36) of FV-naïve subjects in the Control group.

Pain in both treatment groups after the third injection was the most frequently reported solicited injection site reaction in FV-immune and FV-naïve subjects. Injection site pain in the CYD dengue vaccine group was reported by 23.0% (66/287) of FV-immune subjects and 28.6% (22/77) of FV-naïve subjects. In the Control group, injection site pain was reported by 65.0% (93/143) of FV-immune subjects and 66.7% (24/36) of FV-naïve subjects.

Most of the solicited injection site reactions were Grade 1 in intensity. Grade 3 pain in the CYD dengue vaccine group was reported by 0.3% (1/287) of FV-immune subjects and 1.3% (1/77) of FV-naïve subjects. In the Control group, Grade 3 pain, erythema, and swelling were reported by 2.8% (4/143), 0.7% (1/143), and 0.7% (1/143), respectively, of FV-immune subjects; Grade 3 pain was reported by 2.8% (1/36) of FV-naïve subjects.

Solicited Systemic Reactions:

After the First Injection

Solicited systemic reactions after the first injection were reported by 57.9% (227/392) in the CYD dengue vaccine group and by 54.3% (107/197) of subjects in the Control group.

Headache in both treatment groups after the first injection was the solicited systemic reaction reported most frequently. Headache was reported by 44.2% (173/391) of subjects in the CYD dengue vaccine group and 40.6% (80/197) of subjects in the Control group.

The majority of the solicited systemic reactions began 0 to 3 days after the first injection and resolved within 3 days.

The majority of the solicited systemic reactions were Grade 1 in intensity. Grade 3 solicited systemic reactions were reported by 11.2% (44/392) of subjects in the CYD dengue vaccine group and included fever (2.8% [11/392]), headache (6.6% [26/391]), malaise (3.6% [14/390]), myalgia (3.8% [15/390]), and asthenia (1.8% [7/390]). Grade 3 solicited systemic reactions in the Control group were reported by 4.6% (9/197) of subjects (see Section 9, Table 9.37) and included headache (2.5% [5/197]), myalgia (1.5% [3/197]), and asthenia (1.0% [2/197]).

By Baseline Flavivirus Status

At least 1 solicited systemic reaction after the first injection was reported by 56.8% (175/308) of FV-immune subjects and 61.9% (52/84) of FV-naïve subjects in the CYD dengue vaccine group, and in the Control group, by 52.5% (83/158) of FV-immune subjects and 63.2% (24/38) of FV-naïve subjects.

Headache in both treatment groups after the first injection was the solicited systemic reaction reported most frequently by FV

immune and FV-naïve subjects. Headache was reported by 43.3% (133/307) of FV-immune subjects and 47.6% (40/84) of FV-naïve subjects in the CYD dengue vaccine group. In the Control group, headache was reported by 41.1% (65/158) of FV-immune subjects and 39.5% (15/38) of FV-naïve subjects.

After the Second Injection

Solicited systemic reactions were reported with similar frequencies by subjects in the CYD dengue vaccine group (45.8% [171/373]) and the Control group (44.3% [82/185]) after the second injection, and at slightly lower rates than observed after the first injection.

Headache in both treatment groups after the second injection was the solicited systemic reaction reported most frequently by subjects. Headache was reported by 35.1% (131/373) of subjects in the CYD dengue vaccine group and 37.3% (69/185) of subjects in the Control group.

The majority of the solicited systemic reactions began 0 to 3 days after the second injection and resolved within 3 days.

The majority of the solicited systemic reactions were Grade 1 in intensity. Grade 2 fever and headache were reported by a higher percentage of subjects in the Control group than in the CYD dengue vaccine group. Grade 3 solicited systemic reactions were reported by 5.4% (20/373) of subjects in the CYD dengue vaccine group and included fever (0.5% [2/371]), headache (3.8% [14/373]), malaise (1.6% [6/373]), myalgia (2.1% [8/373]), and asthenia (1.3% [5/373]). Grade 3 solicited systemic reactions in the Control group were reported by 3.8% (7/185) of subjects (see Section 9, Table 9.38) and included headache (2.2% [4/185]), malaise (2.2% [4/185]), myalgia (1.6% [3/185]), and asthenia (0.5% [1/185]).

By Baseline Flavivirus Status

At least 1 solicited systemic reaction after the second injection was reported by 47.1% (139/295) of FV-immune subjects and 41.0% (32/78) of FV-naïve subjects in the CYD dengue vaccine group, and in the Control group, by 43.9% (65/148) of FV-immune subjects and 44.4% (16/36) of FV-naïve subjects.

Headache in both treatment groups after the second injection was the solicited systemic reaction reported most frequently by FV-immune and FV-naïve subjects.

After the Third Injection

Solicited systemic reactions were reported by a smaller percentage of subjects in the CYD dengue vaccine group (39.3% [143/364]) compared to the Control group (49.4% [89/180]).

Headache in both treatment groups after the third injection was the solicited systemic reaction reported most frequently. Headache was reported by 29.1% (106/364) of subjects in the CYD dengue vaccine group and 34.4% (62/180) of subjects in the Control group.

The majority of the solicited systemic reactions began 0 to 3 days after the second injection and resolved within 3 days.

The majority of the solicited systemic reactions were Grade 1 in intensity; of note, Grade 2 asthenia in the Control group was reported more frequently than Grade 1 asthenia. Overall, Grade 3 systemic reactions were reported by a smaller proportion of subjects in the CYD dengue vaccine group (3.3% [12/364]) compared to the Control group (5.0% [9/180]). Grade 3 fever (1.7% [3/180]), malaise (2.2% [4/180]), myalgia (2.8% [5/180]), and asthenia (1.1% [2/180]) were reported by a higher percentage of subjects in the Control group than in the CYD dengue vaccine group (0.0%, 0.5% [2/364], 0.8% [3/364], and 0.5% [2/364], respectively). Grade 3 events of headache were reported by 2.7% (10/364) of subjects in the CYD dengue vaccine group compared to 2.2% (4/180) of subjects the Control group.

By Baseline Flavivirus Status

At least 1 solicited systemic reaction after the third injection was reported by 39.7% (114/287) of FV-immune subjects and 37.7% (29/77) of FV-naïve subjects in the CYD dengue vaccine group, and in the Control group, by 47.6% (68/143) of FV-immune subjects and 55.6% (20/36) of FV-naïve subjects.

Headache in both treatment groups was the solicited systemic reaction reported most frequently by FV-immune and FV-naïve subjects.

Immediate Unsolicited AEs:

One immediate unsolicited AE (dizziness) was reported by a subject in the Control group after the first injection. The event resolved on the same day with no action taken, and was considered not related to the injection by the Investigator. No subjects reported immediate unsolicited AEs after the second or third injections.

Unsolicited AEs:After the First Injection

Unsolicited AEs within 28 days after the first injection were reported by 42.1% (169/401) of subjects in the CYD dengue vaccine group and 42.2% (84/199) of subjects in the Control group.

The most frequently reported unsolicited AEs were reported by 18.5% (74/401) of subjects in the CYD dengue vaccine group and 15.6% (31/199) of subjects in the Control group in the System Organ Class (SOC) of infections and infestations; nasopharyngitis in this SOC was reported by 10.2% (41/401) of subjects in the CYD dengue vaccine group and 7.0% (14/199) of subjects in the Control group.

Grade 3 unsolicited non-serious AEs within 28 days after the first injection were reported by 5.7% (23/401) of subjects in the CYD dengue vaccine group and 5.0% (10/199) of subjects in the Control group.

After the Second Injection

Unsolicited AEs within 28 days after the second injection were reported with a similar frequency in both treatment groups: 36.2% (135/373) of subjects in the CYD dengue vaccine group and 35.1% (65/185) in the Control group.

The most frequently reported unsolicited AEs were reported by 20.4% (76/373) of subjects in the CYD dengue vaccine group and 22.2% (41/185) of subjects in the Control group in the SOC of infections and infestations; nasopharyngitis in this SOC was reported by 12.3% (46/373) of subjects in the CYD dengue vaccine group and 13.5% (25/185) of subjects in the Control group.

Grade 3 unsolicited non-serious AEs within 28 days after the second injection were reported by 5.1% (19/373) of subjects in the CYD dengue vaccine group and 3.8% (7/185) of subjects in the Control group.

After the Third Injection

Unsolicited AEs within 28 days after the third injection were reported by 26.9% (98/364) of subjects in the CYD dengue vaccine group and 22.2% (40/180) of subjects in the Control group.

The most frequently reported unsolicited AEs were reported by 11.5% (42/364) of subjects in the CYD dengue vaccine group and 12.8% (23/180) of subjects in the Control group in the SOC of infections and infestations; nasopharyngitis in this SOC was reported by 9.1% (33/364) of subjects in the CYD dengue vaccine group and 11.1% (20/180) of subjects in the Control group.

Grade 3 unsolicited non-serious AEs within 28 days after the third injection were reported by 2.5% (9/364) of subjects in the CYD dengue vaccine group and 2.2% (4/180) of subjects in the Control group.

Unsolicited ARs:

Unsolicited non-serious ARs within 28 days after any injection were reported by 5.0% (20/401) of subjects in the CYD dengue vaccine group and 4.0% (8/199) of subjects in the Control group. The most frequently reported unsolicited ARs were, with 3.2% (13/401) of subjects in the CYD dengue vaccine group and 2.0% (4/199) of subjects in the Control group reporting at least 1 unsolicited AR. The unsolicited ARs reported with the greatest frequency were in the SOC of general disorders and administration site conditions, and included injection site pruritus, injection site bruising, and injection site pain.

One unsolicited AR with Grade 3 intensity (cough) was reported within 28 days after any injection. This event occurred in a subject (102-00066) in the CYD dengue vaccine group 1 day after the first injection, and resolved in 1 to 3 days.

Discontinuation due to AEs:

One subject in the CYD dengue vaccine group was discontinued from the study for an AE (hepatitis A) 2 days after receiving the first injection. The event was assessed by the Investigator as not related to the injection.



Deaths and SAEs:

There were no deaths during the study. SAEs were reported by 2.5% (10/401) of subjects in the CYD dengue vaccine group and 7.5% (15/199) of subjects in the Control group. None of the SAEs reported were considered related to injection by the Investigator, and all of the subjects recovered.

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