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Sponsor: Sanofi Pasteur	Study Identifiers: U1111-1111-6073, NCT01187433,2014-001715-39
Drug substance: CYD Dengue Vaccine	Study code: CYD30
Title of the study: Immunogenicity and Safety of CYD Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Brazil	
Study center: One study center on Brazil	
Study period: Date first subject enrolled: 20/Aug/2010 Date last subject completed: 15/May/2012	
Phase of development: Phase II	
Objectives: Primary Objectives : 1) To describe the humoral immune response to dengue viruses before and after each vaccination with CYD dengue vaccine. 2) To evaluate the safety of each vaccination with CYD dengue vaccine.	
Methodology: CYD30 was a randomized, blind-observer, controlled, monocenter, Phase II trial in 150 healthy children and adolescents in Brazil. There were three injections (D0, D0 + 6 months, D0 + 12 months) and two groups of subjects: <ul style="list-style-type: none"> • CYD Dengue Vaccine Group (N=100) received CYD dengue vaccine as first, second, and third injections. • Control Group (N=50) received a placebo (NaCl 0.9%) as first, second and third injections. 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/patients: Planned: 150 Randomized: 150 Evaluated: Immunogenicity: 148 Safety: 150	
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 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 vaccination until at least 4 weeks after the last vaccination.	

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 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 (SC)

Control Product: Placebo (NaCl)

Form: Liquid

Composition: NaCl 0.9%

Route of administration: SC

Duration of participation: Expected duration of per subject's participation is 18 months.

Criteria for evaluation

Primary Endpoints

Immunogenicity

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

Safety

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

Statistical methods:

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

Two statistical analyses of safety and immunogenicity were performed on unblinded data (one after the third vaccination and one after the end of the follow-up period).

Summary:**Subject Disposition:**

A total of 150 subjects were enrolled in the study: 100 subjects in the CYD dengue vaccine group and 50 subjects in the Control group.

Fifteen subjects were withdrawn from the study: 11 (11.0%) in the CYD dengue vaccine group (non-compliance with protocol and voluntary withdrawal) and 4 (8.0%) in the Control group (non-compliance with protocol and voluntary withdrawal). 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.

All randomized subjects were included in the safety analysis sets and 98.7% of the subjects were included in the full analysis set (FAS). There were 148/150 (98.7%) subjects in the per protocol (PP) analysis set post-Inj 1, 130/150 (86.7%) subjects in the PP analysis set post-Inj 2, and 110/150 (73.3%) subjects in the PP analysis set post-Inj 3.

Demographics:

Overall, 54.7% (81/148) of subjects were female and 45.3% (67/148) of subjects were male in the FAS. The percentage of females (59.6% [59/99]) was higher than males (40.4% [40/99]) in the CYD dengue vaccine group whereas there was a higher percentage of males (55.1% [27/49]) than females (44.9% [22/49]) in the Control group. The mean age was similar between the treatment groups, with an overall mean age of 12.7 years (range 9.0 to 16.9 years) at enrollment. All subjects in the FAS were Hispanic.

Primary Objective: Immunogenicity**Seropositivity against each Dengue Virus Serotype**

In the CYD dengue vaccine group, the percentage of subjects who were seropositive at baseline for each dengue serotype was similar to that in the Control group, ranging from 47.5% (47/99) for serotype 4 to 65.7% (65/99) for serotype 2.

In the CYD dengue vaccine group, there was an increase in seropositivity rates post-Inj 1 and post-Inj 2 with a more pronounced increase post-Inj 1 for serotypes 3 and 4. At post-Inj 3, the net increase from baseline in the percentage of seropositive subjects was higher for serotype 4 (52.5%) as compared to the other serotypes which were similar: 37%, 33.2%, 37.4%, for serotypes 1, 2, and 3, respectively. At post-Inj 3 in the CYD dengue vaccine group, 96.6% (86/89) of subjects were seropositive for Abs to serotype 1, 98.9% (88/89) of subjects were seropositive for Abs to serotype 2, and 100% (89/89) were seropositive for Abs to serotypes 3 and 4.

In the Control group, the percentage of subjects who were seropositive at baseline ranged from 51.0% (25/49) for serotype 4 to 67.3% (33/49) for serotype 2. These percentages were relatively unchanged following each of the 3 injections except for serotype 4 which had, at post-Inj 3, a net increase from baseline of 22.9%. In the Control group at post-Inj 3, the percentage of subjects who were seropositive was 69.6% (32/46) for serotype 1, 73.9% (34/46) for serotypes 3 and 4, and 76.1% (35/46) for serotype 2.

By Baseline Flavivirus Status:**FV Immune at Baseline**

The majority of subjects in both treatment groups were FV immune at baseline: 80.8% (80/99) of subjects in the CYD dengue vaccine group and 83.7% (41/49) of subjects in the Control group.

In the CYD dengue vaccine group, the seropositivity rates at baseline for each serotype were similar to those observed in the Control group: 73.8% (59/80) for serotype 1; 81.3% (65/80) for serotype 2; 77.5% (62/80) for serotype 3; and 58.8% (47/80) 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. At post-Inj 3 in the CYD dengue vaccine group, the percentage of subjects who were seropositive was 98.6% (72/73) for serotype 1, and 100% (73/73) for serotypes 2, 3 and 4.

In the Control group, seropositivity rates were recorded at baseline and were 75.6% (31/41) for serotype 1, 80.5% (33/41) for serotype 2, 78.0% (32/41) for serotype 3, and 61.0% (25/41) for serotype 4. There were no appreciable changes in seropositivity for the dengue serotypes 1, 2 and 3 whereas at post-Inj 3 for serotype 4, the net increase from baseline was 23.2%. At post-Inj 3 in the Control group, the percentage of subjects who were seropositive was 81.6% (31/38), 89.5% (34/38), 86.8% (33/38), and 84.2% (32/38) for serotypes 1, 2, 3, and 4, respectively.

FV Non-Immune at Baseline

At baseline, 19.2% (19/99) of subjects in the CYD dengue vaccine group and 16.3% (8/49) of subjects in the Control group were FV non-immune.

In the CYD dengue vaccine group, seropositivity rates gradually increased from baseline for serotype 1 after each injection. For serotypes 2, 3, and 4, seropositivity rates increased mainly at post-Inj 1 and post-Inj 2. At post-Inj 3, the proportion of subjects in the CYD dengue vaccine group who were seropositive was 87.5% (14/16) for serotype 1, 93.8% (15/16) for serotype 2, and 100% (16/16) for serotypes 3 and 4.

In the Control group, seropositivity rates increased from baseline only at post-Inj 3 for all 4 serotypes. At post-Inj 3, the proportion of subjects in the Control group who were seropositive was 12.5% (1/8) for serotypes 1, 2 and 3, and 25% (2/8) for serotype 4.

Seropositivity against 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 68.7% (68/99), 62.6% (62/99), 56.6% (56/99), and 47.5% (47/99), 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 than for the subsequent injections. The percentage of subjects who were seropositive for at least 3 or all 4 serotypes increased more gradually after the first and second injections. No increase in seropositivity rates for at least 1, 2 or 3 serotypes was observed at post-Inj 3 and a marginal increase was observed for all 4 serotypes. At post-Inj 3, all subjects (100% [89/89]) were seropositive for at least 1 or 2 serotypes, 98.9% (88/89) were seropositive for at least 3 serotypes, and 96.6% (86/89) 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 71.4% (35/49), 67.3% (33/49), 61.2% (30/49), and 46.9% (23/49), respectively. There were no appreciable changes in these rates after each injection, except in subjects seropositive for all 4 serotypes where a higher increase was observed.

By Baseline Flavivirus Status:

FV Immune at Baseline

In the CYD dengue vaccine group, the percentage subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes was 85.0% (68/80), 77.5% (62/80), 70.0% (56/80), and 58.8% (47/80), 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 and reached 100% at post-Inj 2. At post-Inj 3, all subjects were seropositive for at least 3 serotypes, and the percentage of subjects who were seropositive for all 4 serotypes reached 98.6% (72/73).

In the Control group, the percentage of subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes was 85.4% (35/41), 80.5% (33/41), 73.2% (30/41), and 56.1% (23/41), respectively. There was a gradual increase in these rates after any of the two first injections which was more pronounced for at least all 4 serotypes. At post-Inj 3, the percentage of subjects in the Control group who were seropositive for at least 1, 2, 3, or all 4 serotypes was 89.5% (34/38), 89.5% (34/38), 84.2% (32/38), and 78.9% (30/38), respectively.

FV Non-Immune at Baseline

In the CYD dengue vaccine group, increases in seropositivity from baseline occurring post-Inj 1 were more pronounced for at least 1 serotype (94.7% [18/19]) and were more gradual for all 4 serotypes (10.5% [2/19], 75.0% [12/16], and 87.5% [14/16], respectively at post-Inj 1, 2, and 3). No increases for at least 1, 2, and 3 serotypes were observed at post-Inj 3. In the CYD dengue vaccine group, the percentage of subjects who were seropositive at post-Inj 3 was 100% (16/16) for at least 1 or 2 serotypes, 93.8% (15/16) for at least 3 serotypes, and 87.5% (14/16) for all 4 serotypes.

In the Control group, 2 subjects (25%) became seropositive for at least 1 serotype, and 1 subject (12.5%) for at least 2, 3 or all 4 serotypes at post-Inj 3.

GMTs

In the CYD dengue vaccine group, the baseline GMTs were 41.4, 67.0, 81.9, and 15.0 (1/dil) for serotypes 1, 2, 3, and 4, respectively. The GMTs for serotypes 1, 2, and 3 increased from baseline in the CYD dengue vaccine group at post-Inj 1 and at post-Inj 2. At post-Inj 3 GMTs remained elevated versus baseline but decreased slightly versus post-Inj 2. The GMTs for serotype 4 increased more gradually after each injection (with a marginal decrease at post-Inj 2). The highest GMTs were observed at post-Inj 3 for serotype 4 (432 [1/dil]), and at post-Inj 2 for serotype 1, 2 and 3 (436, 647, and 1031 [1/dil], respectively). The GMTs of post-Inj 2 (V07)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 7.26, 6.80, 8.57, and 15.4 for serotypes 1, 2, 3, and 4, respectively. The GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 4.92, 6.21, 6.26, and 20.2 for serotypes 1, 2, 3, and 4, respectively. At post-Inj 3 in the CYD dengue vaccine group, the GMTs for serotypes 1, 2, 3, and 4 were 267, 544, 741, and 432 (1/dil), respectively.

In the Control group, the baseline GMTs were 47.2, 68.3, 94.7, and 17.5 (1/dil) for serotype 1, 2, 3, and 4, respectively. The GMTs for all 4 serotypes remained similar or slightly increased from baseline to post-Inj 2.

When compared to the Control group, the GMTs of post-Inj 2 (V07)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 3.4-fold higher for serotype 1, 3.9-fold higher for serotype 2, 4.6-fold higher for serotype 3, and 12.1-fold higher for serotype 4. The GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 3.6-fold higher for serotype 1, 3.7-fold higher for serotype 2, 5.0-fold higher for serotype 3, and 14.4-fold higher for serotype 4.

By Baseline Flavivirus Status:

FV Immune at Baseline

In the CYD dengue vaccine group, the baseline GMTs were 68.5 (1/dil) for serotype 1, 124 (1/dil) for serotype 2, 159 (1/dil) for serotype 3, and 19.5 (1/dil) for serotype 4. The GMTs for all 4 serotypes were markedly increased from baseline at post-Inj 1. For serotypes 1, 2 and 3, the GMTs observed at post-Inj 2 (661, 978 and 1426 (1/dil), respectively) were marginally higher as compared to the GMTs observed at post-Inj 1 (549, 816 and 1263 (1/dil), respectively). At post-Inj 3, the GMTs for serotypes 1, 2, and 3 were marginally lower to those at post-Inj 2; for serotype 4, the GMT at post-Inj 3 was higher than the GMT at post-Inj 2. The GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in FV immune subjects in the CYD dengue vaccine group were 4.83 for serotype 1, 5.93 for serotype 2, 5.07 for serotype 3, and 19.1 for serotype 4. At post-Inj 3, the GMTs were 381, 835, 1031, and 485 (1/dil), for serotypes 1, 2, 3, and 4, respectively, in FV immune subjects in the CYD dengue vaccine group.

In the Control group, the baseline GMTs were 73.1 (1/dil) for serotype 1, 114 (1/dil) for serotype 2, 168 (1/dil) for serotype 3, and 22.4 (1/dil) for serotype 4. Marginal increases in the GMTs for all 4 serotypes were observed in the Control group, with highest values at post-Inj 2 for serotypes 1, 2, and 3. The GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in FV immune subjects in the Control group were 1.49 for serotype 1, 1.99 for serotype 2, 1.41 for serotype 3, and 1.62 for serotype 4. At post-Inj 3, the GMTs were 126, 242, 266, and 46.5 (1/dil), for serotypes 1, 2, 3, and 4, respectively, in the Control group.

When compared to subjects in the Control group, the GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 3.2-fold higher for serotype 1, 3.0-fold higher for serotype 2, 3.6-fold higher for serotype 3, and 11.8-fold higher for serotype 4.

FV Non-Immune at Baseline

In the CYD dengue vaccine group, the GMTs for serotypes 1, 2, 3, and 4 were markedly increased from baseline. For serotypes 1, 2, 3 and 4, the GMTs observed at post-Inj 2 (57.3, 86.2, 212 and 227 [1/dil], respectively) were higher as compared to the GMTs observed at post-Inj 1 (10.3, 10.2, 54.1 and 165 [1/dil], respectively). At post-Inj 3, the GMTs for all serotypes were similar or slightly decreased compared to those at post-Inj 2. The GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 5.34 for serotype 1, 7.67 for serotype 2, 16.3 for serotype 3, and 25.5 for serotype 4. At post-Inj 3 in the CYD dengue vaccine group, the GMTs were 53.4, 76.7, 163, and 255 (1/dil), respectively.

In the Control group, nominal increases in GMTs were observed at post-Inj 3 for all 4 serotypes. At post-Inj-3, the GMTs for serotypes 1, 2, 3, and 4 were 8.61, 7.37, 6.78, and 7.01 (1/dil), respectively.

When compared to the Control group, the GMTs of post-Inj 3 (V09)/Pre-Inj 1 (V01) in the CYD dengue vaccine group were 6.2-fold higher for serotype 1, 10.4-fold higher for serotype 2, 24.0-fold higher for serotype 3, and 36.4-fold higher for serotype 4.

Primary Objective: Safety**Solicited Injection Site Reactions:**After the First Injection

Solicited injection site reactions were reported by 28.3% (28/99) of subjects in the CYD dengue vaccine group and 30.6% (15/49) of subjects in the Control group.

Pain in both treatment groups after the first injection was the most frequently reported solicited injection site reaction. Injection site pain was reported with a similar frequency in the CYD dengue vaccine group (26.3% [26/99]) and the Control group (30.6% [15/49]).

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 pain was reported by only 1 subject in the Control group. No other Grade 3 injection site reactions were reported after the first injection.

By Baseline Flavivirus Status

Solicited injection site reactions in the CYD dengue vaccine group were reported by 30.9% (25/81) of FV immune subjects and 16.7% (3/18) of FV non-immune subjects. In the Control group, the rates were 29.3% (12/41) of FV immune subjects and 37.5% (3/8) of FV non-immune subjects.

Pain in both treatment groups after the first injection was the most frequently reported solicited injection site reaction by FV immune and FV non-immune subjects. Injection site pain in the CYD dengue vaccine group was reported by 28.4% (23/81) of FV-immune subjects and 16.7% (3/18) of FV non-immune subjects. In the Control group, injection site pain was reported by 29.3% (12/41) of FV immune subjects and 37.5% (3/8) of FV non-immune subjects.

After the Second Injection

Solicited injection site reactions were reported by 22.6% (21/93) of subjects in the CYD dengue vaccine group and 14.9% (7/47) 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 slightly higher percentage of subjects in the CYD dengue vaccine group (21.5% [20/93]) than in the Control group (14.9% [7/47]).

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 pain was reported by only 1 subject in the Control group. No other Grade 3 injection site reactions were reported after the second injection.

By Baseline Flavivirus Status

Solicited injection site reactions in the CYD dengue vaccine group were reported by 23.4% (18/77) of FV immune subjects and 18.8% (3/16) of FV non-immune subjects. In the Control group, the rates were 15.4% (6/39) of FV immune subjects and 12.5% (1/8) of FV non-immune subjects.

Pain in both treatment groups after the second injection was the most frequently reported solicited injection site reaction by FV immune and FV non-immune subjects. Injection site pain in the CYD dengue vaccine group was reported by 22.1% (17/77) of FV immune subjects and 18.8% (3/16) of FV non-immune subjects. In the Control group, injection site pain was reported by 15.4% (6/39) of FV immune subjects and 12.5% (1/8) of FV non-immune subjects.

After the Third Injection

Solicited injection site reactions were reported by 16.9% (15/89) of subjects in the CYD dengue vaccine group and 15.6% (7/45) of subjects in the Control group.

Similarly to the first and second injections, 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 similar frequency in the CYD dengue vaccine group (16.9% [15/89]) and in the Control group (15.6% [7/45]).

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 pain was reported by only 1 subject in the Control group. No other Grade 3 injection site reactions were reported after the third injection.

By Baseline Flavivirus Status

Solicited injection site reactions in the CYD dengue vaccine group were reported by 19.2% (14/73) of FV immune subjects and 6.3% (1/16) of FV non-immune subjects. In the Control group, the rates were 16.2% (6/37) of FV immune subjects and 12.5% (1/8) of FV non-immune subjects.

Pain in both treatment groups after the third injection was the most frequently reported solicited injection site reaction by FV immune and FV non-immune subjects. Injection site pain in the CYD dengue vaccine group was reported by 19.2% (14/73) of FV immune subjects and 6.3% (1/16) of FV non-immune subjects. In the Control group, injection site pain was reported by 16.2% (6/37) of FV immune subjects and 12.5% (1/8) of FV non-immune subjects.

Solicited Systemic Reactions:

After the First Injection

Solicited systemic reactions were reported by 61.6% (61/99) of subjects in the CYD dengue vaccine group and 53.1% (26/49) 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 48.5% (48/99) of subjects in the CYD dengue vaccine group and 40.8% (20/49) 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.

Overall, the majority of the solicited systemic reactions were Grade 1 in intensity. Grade 3 solicited systemic reactions were reported by 12.1% (12/99) of subjects in the CYD dengue vaccine group and included fever (3.1% [3/98]), headache (8.1% [8/99]), malaise (3.0% [3/99]), myalgia (2.0% [2/99]), and asthenia (4.0% [4/99]). Grade 3 solicited systemic reactions in the Control group were reported by 14.3% (7/49) of subjects and included fever (2.1% [1/48]), headache (10.2% [5/49]), malaise (2.0% [1/49]), myalgia (6.1% [3/49]), and asthenia (4.1% [2/49]).

By Baseline Flavivirus Status

Solicited systemic reactions in the CYD dengue vaccine group were reported by 60.5% (49/81) of FV immune subjects and 66.7% (12/18) of FV non-immune subjects. In the Control group, the rates were 51.2% (21/41) of FV immune subjects and 62.5% (5/8) of FV non-immune subjects.

Headache in both treatment groups after the first injection was the solicited systemic reaction reported most frequently by FV immune and FV non-immune subjects. Headache was reported by 46.9% (38/81) of FV immune subjects and 55.6% (10/18) of FV non-immune subjects in the CYD dengue vaccine group. In the Control group, headache was reported by 41.5% (17/41) of FV immune subjects and 37.5% (3/8) of FV non-immune subjects.

After the Second Injection

Solicited systemic reactions were reported with similar frequencies by subjects in the CYD dengue vaccine group (45.7% [43/94]) and the Control group (44.7% [21/47]) after the second injection, and at lower rates than observed after the first injection.

Headache in both treatment groups after the second injection was the most frequently reported solicited systemic reaction. Headache was reported by 28.7% (27/94) of subjects in the CYD dengue vaccine group and 34.0% (16/47) 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 3 solicited systemic reactions were reported by 11.7% (11/94) of subjects in the CYD dengue vaccine group and included fever (2.2% [2/92]), headache (5.3% [5/94]), malaise (6.4% [6/94]), myalgia and asthenia (both 3.2% [3/94]). Grade 3 solicited systemic reactions in the Control group were reported by 8.5% (4/47) of subjects and included headache (6.4% [3/47]), malaise and myalgia (both 4.3% [2/47]).

By Baseline Flavivirus Status

Solicited systemic reactions in the CYD dengue vaccine group were reported by 46.2% (36/78) of FV immune subjects and 43.8% (7/16) of FV non-immune subjects. In the Control group, the rates were 46.2% (18/39) of FV immune subjects and 37.5% (3/8) of FV non-immune subjects.

Headache in both treatment groups after the second injection was the solicited systemic reaction reported most frequently by FV immune and FV non-immune subjects. Headache was reported by 28.2% (22/78) of FV immune subjects and 31.3% (5/16) of FV non-immune subjects in the CYD dengue vaccine group. In the Control group, headache was reported by 35.9% (14/39) of FV immune subjects and 25.0% (2/8) of FV non-immune subjects.

After the Third Injection

Solicited systemic reactions were reported by 40.4% (36/89) of subjects in the CYD dengue vaccine group and 26.7% (12/45) of subjects in the Control group.

Headache in both treatment groups after the third injection was the most frequently reported solicited systemic reaction. Headache was reported by 27.0% (24/89) of subjects in the CYD dengue vaccine group and 20.0% (9/45) 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 3 solicited systemic reactions were reported by 11.2% (10/89) of subjects in the CYD dengue vaccine group and included fever (3.7% [3/82]), headache (5.6% [5/89]), malaise, myalgia and asthenia (all 2.2% [2/89]). Grade 3 solicited systemic reactions in the Control group were reported by 15.6% (7/45) of subjects and included fever (7.0% [3/43]) and headache (8.9% [4/45]).

By Baseline Flavivirus Status

Solicited systemic reactions in the CYD dengue vaccine group were reported by 42.5% (31/73) of FV immune subjects and 31.3% (5/16) of FV non-immune subjects. In the Control group, the rates were 29.7% (11/37) of FV immune subjects and 12.5% (1/8) of FV non-immune subjects.

Headache in both treatment groups after the third injection was the solicited systemic reaction reported most frequently by FV immune and FV non-immune subjects. Headache was reported by 27.4% (20/73) of FV immune subjects and 25.0% (4/16) of FV non-immune subjects in the CYD dengue vaccine group. In the Control group, headache was reported by 21.6% (8/37) of FV immune subjects and 12.5% (1/8) of FV non-immune subjects.

Immediate Unsolicited AEs:

No immediate unsolicited AEs or ARs were reported during the study

Unsolicited AEs:

After the First Injection

Unsolicited AEs were reported by 56% (56/100) of subjects in the CYD dengue vaccine group and 46% (23/50) of subjects in the Control group.

The most frequently reported unsolicited AEs were in the SOC of infections and infestations: 21.0% (21/100) of subjects in the CYD dengue vaccine group and 14.0% (7/50) of subjects in the Control group. Nasopharyngitis was the most frequently reported unsolicited AE in the SOC of infections and infestations, reported by 7.0% (7/100) of subjects in the CYD dengue vaccine group and 8.0% (4/50) of subjects in the Control group.

Grade 3 unsolicited non-serious AEs within 28 days after the first injection were reported by 9.0% (9/100) of subjects in the CYD dengue vaccine group and 8.0% (4/50) of subjects in the Control group.

After the Second Injection

Unsolicited AEs were reported by 54.3% (51/94) of subjects in the CYD dengue vaccine group and 55.3% (26/47) in the Control group.

The most frequently reported unsolicited AEs were in the SOC of infections and infestations for the CYD dengue vaccine group, reported by 19.1% (18/94) of subjects and in the SOC of gastrointestinal disorders for the Control group, reported by 19.1% (9/47) of subjects. In the CYD dengue vaccine group, upper respiratory tract infection was the most frequently reported unsolicited AE in the SOC of infections and infestations, reported by 7.4% (7/94) of subjects. In the Control group, abdominal pain was the most frequently reported unsolicited AE in the SOC gastrointestinal disorders, reported by 6.4% (3/47) of subjects.

Grade 3 unsolicited non-serious AEs within 28 days after the second injection were reported by 8.5% (8/94) of subjects in the CYD dengue vaccine group and 14.9% (7/47) of subjects in the Control group.

After the Third Injection

Unsolicited AEs were reported by 35.6% (32/90) of subjects in the CYD dengue vaccine group and 30.4% (14/46) in the Control group.

The most frequently reported unsolicited AEs were in the SOC of infections and infestations: 22.2% (20/90) of subjects in the CYD dengue vaccine group and 10.9% (5/46) of subjects in the Control group. In the CYD dengue vaccine group, upper respiratory tract infection was the most frequently reported unsolicited AE in the SOC of infections and infestations, reported by 7.8% (7/90) of subjects. In the Control group, nasopharyngitis and rhinitis were the most frequently reported unsolicited AEs in the SOC of infections and infestations, both reported by 4.3% (2/46) of subjects.

Grade 3 unsolicited non-serious AEs within 28 days after the third injection were reported by 8.9% (8/90) of subjects in the CYD dengue vaccine group and 6.5% (3/46) of subjects in the Control group.

Unsolicited ARs:

Unsolicited ARs within 28 days after any injection were reported by 3.0% (3/100) of subjects in the CYD dengue vaccine group and no subjects in the Control group. One unsolicited AR with Grade 3 intensity (myalgia) was reported within 28 days after any injection. This event occurred in a subject in the CYD dengue vaccine group 20 days after the first injection, and lasted 2 days.

Deaths and SAEs:

There were no deaths during the study. SAEs were reported by 5.0% (5/100) of subjects in the CYD dengue vaccine group and by 6.0% (3/50) of subjects in the Control group. None of the SAEs were considered related to the injection by the Investigator and, except for one subject who recovered with sequelae, all subjects recovered.

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