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Sponsor: Sanofi Pasteur	Study Identifiers: U1111-1114-7646, NCT01134263
Drug substance: CYD Dengue Vaccine	Study code: CYD17
Title of the study: Lot-to-Lot Consistency and Bridging Study of a Tetravalent Dengue Vaccine in Healthy Adults in Australia	
Study center(s): 8 study centers in Australia	
Study period: Date first subject enrolled: 05/Oct/2009 Date last subject completed: 12/Jun/2012	
Phase of development: Phase III	
Objectives: Primary Objective: Lot Consistency To demonstrate that three different Phase III lots of CYD dengue vaccine induce an equivalent immune response in terms of post-Dose 3 geometric mean titers (GMTs) against the four parental serotypes. Secondary Objectives: Immunogenicity To demonstrate that data from one Phase II lot and pooled data from Phase III lots of CYD dengue vaccine show an equivalent immune response in terms of post-Dose 3 GMTs against the four parental serotypes. Safety To describe the safety of the CYD dengue vaccine in all subjects after each dose.	
Methodology: This was a multi-center, observer-blind, randomized, placebo-controlled, Phase III study of 4 lots of CYD dengue vaccine in 715 healthy adult subjects aged 18 to 60 years in Australia. Each subject was to receive a 3-dose primary series of injections (at month 0, 6, and 12), followed by a 6-month safety follow-up. A total of 715 healthy adults were randomized to receive one of the 4 lots of CYD dengue vaccine or placebo: CYD dengue vaccine – Phase III Lot 1. CYD dengue vaccine – Phase III Lot 2. CYD dengue vaccine – Phase III Lot 3. CYD dengue vaccine – Phase II Lot. Placebo (NaCl 0.9%). All subjects were to receive 3 doses and provided a blood sample at baseline (pre-injection) for flavivirus (FV) status and immunogenicity assessment, and a blood sample 28 days after the third dose. Reactogenicity data were collected in all subjects after each dose. Serious adverse events (SAEs) including serious adverse events of special interest (AESIs) were collected throughout the study.	

<p>Number of subjects</p> <p>Planned: 715 Randomized: 712</p> <p>Evaluated</p> <p>Full analysis set: 712 Per protocol analysis set: 547 Safety analysis set: 712</p>
<p>Diagnosis and criteria for inclusion:</p> <p>An individual had to meet <i>all</i> of the following criteria to be considered for trial enrollment:</p> <ol style="list-style-type: none"> 1) Aged 18 to 60 years on the day of inclusion 2) Informed consent form had been signed and dated 3) Able to attend all scheduled visits and to comply with all trial procedures 4) For a woman of childbearing potential, use of an effective method of contraception, or abstinence from at least 4 weeks prior to the first vaccination until at least 4 weeks after the last vaccination (i.e., for 14 months)
<p>Study treatments</p> <p>Investigational product: CYD dengue vaccine (Phase III lots)</p> <p>Form: Powder and solvent for suspension for injection</p> <p>Composition: Each 0.5 mL dose of reconstituted vaccine contains:</p> <p style="padding-left: 40px;">$5 \pm 1 \log_{10}$ cell-culture infectious dose 50% (CCID50) of each live, attenuated, dengue serotype 1, 2, 3, 4 virus</p> <p style="padding-left: 40px;">Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminoethane, and urea</p> <p>Route of administration: Subcutaneous (SC)</p>
<p>Investigational Product: CYD dengue vaccine (Phase II lot)</p> <p>Form: Powder and solvent for suspension for injection</p> <p>Composition: Each 0.5 mL dose of reconstituted vaccine contains:</p> <p style="padding-left: 40px;">$5 \pm 1 \log_{10}$ CCID50 of each live, attenuated, dengue serotype 1, 2, 3, 4 virus</p> <p style="padding-left: 40px;">Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminoethane, and urea</p> <p>Route of administration: SC</p>
<p>Control Product: Placebo (NaCl)</p> <p>Form: Solution for injection</p> <p>Composition: NaCl 0.9%</p> <p>Route of administration: SC</p>
<p>Duration of treatment/participation: The duration of each subject's participation in the trial was approximately 18 months</p>

Criteria for evaluation:

Primary Endpoint:

Neutralizing antibody (Ab) levels against each of the four dengue virus serotypes contained in the CYD dengue vaccine were measured in sera collected from all subjects 28 days after the third dose (dengue neutralization assay).

Secondary Endpoints:

Immunogenicity

Neutralizing Ab levels against each of the four dengue virus serotypes contained in the CYD dengue vaccine were measured in sera collected from all subjects 28 days after the third dose (dengue neutralization assay).

Safety

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

Occurrence, time to onset, number of days of occurrence, action taken, and intensity, of solicited (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 dose.

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

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

Occurrence of SAEs, including serious AESIs, throughout the trial period.

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

Statistical methods:

An equivalence testing approach was used to compare GMTs 28 days after the third injection, between each pair of Phase III lots for each serotype "s" on the following individual hypotheses:

$$H_0^{i,j,s} : \text{GMT}_i^s / \text{GMT}_j^s \leq \frac{1}{\delta} \text{ or } \geq \delta \Leftrightarrow \left| \log_{10}(\text{GMT}_i^s) - \log_{10}(\text{GMT}_j^s) \right| \geq \log_{10}(\delta)$$

$$H_1^{i,j,s} : \frac{1}{\delta} < \text{GMT}_i^s / \text{GMT}_j^s < \delta \Leftrightarrow \left| \log_{10}(\text{GMT}_i^s) - \log_{10}(\text{GMT}_j^s) \right| < \log_{10}(\delta)$$

with:

H, hypothesis

i, j in {1,2,3}= number of lot, $i \neq j$

s, serotypes in {1, 2, 3, 4}

δ equivalence limit was set at 2; i.e., 0.301 ($=\log_{10}[2]$), for each serotype "s"

For a serotype, the equivalence among the three lots was demonstrated if all individual null hypotheses were rejected (i.e., if the equivalence was demonstrated for each pair of lots; i.e., 3 individual tests).

Equivalence among the three lots was demonstrated if the equivalence was demonstrated for all serotypes.

The overall hypotheses were:

H_0 Overall: equivalence between the three lots was not demonstrated for at least one serotype

H_1 Overall: equivalence between the three lots was demonstrated for all serotypes

The statistical methodology was based on the use of the two-sided 95% CI of the differences of the means of the \log_{10} transformed post-injection titers between pairs of lots. The CI for differences was calculated using normal approximation of log-transformed titers.

Equivalence among the three lots was demonstrated if, for each pair of lots and each serotype, the lower limit of the 95% CI was > -0.301 and the upper limit was < 0.301 .

The Per-Protocol Analysis Set was used for the main analysis.

Once lot-to-lot consistency had been established, the immunogenicity of the Phase III lots (pooled data) were compared to that of the Phase II lot using an equivalence testing approach.

The statistical methodology was based on the use of the two-sided 95% CI of the difference of the \log_{10} transformation of post-injection GMTs between the compared CYD dengue vaccine groups. The CI for the differences was calculated using normal approximation of log-transformed titers.

Two statistical analyses were performed on unblinded data (after the third injection, and after the end of the follow-up period).

Safety results are descriptive and are presented with 95% CIs by using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.

Summary:

Trial Population

A total of 715 subjects were randomized: 164 subjects in the Phase III Lot 1 group, 163 subjects in the Phase III Lot 2 group, 163 subjects in the Phase III Lot 3 group, 168 subjects in the Phase II lot group and 57 subjects in the placebo group. A total of 712 subjects were vaccinated at Visit (V) 01 and were therefore included in the Full Analysis Set (FAS).

In total, 86.2% of subjects (614/712) in the FAS completed the study up to 28 days after the third injection. The drop-out rate was 13.8% (98/712) during the vaccination period and overall, the percentages of early withdrawals were evenly distributed across study groups.

The most frequent reason for early withdrawal was voluntary withdrawal (5.9% of subjects [42/712]). The percentages of subjects were roughly the same in each group; most of the voluntary withdrawals occurred following V01. The next most frequent reasons for early withdrawal were non-compliance with the protocol (3.2% of subjects [23/712]) and lost to follow-up (2.2% of subjects [16/712]).

Only a few subjects discontinued the trial due to an AE (1.5% of subjects [11/712]) or an SAE (0.8% of subjects [6/712]). The number of subjects who did not complete the study due to an AE or an SAE was distributed evenly across groups.

In total, 94.7% (674/712) of subjects (including those subjects who had an early withdrawal) were contacted 6 months after the last injection.

Demographic Characteristics

Overall, there were slightly more females (54.9%) than males (45.1%) in the FAS. Overall, the same trend was observed for the Safety Analysis Set, the PP Analysis Set

Overall, the mean age was 39.0 years and was similar across treatment groups. The same trend was observed for the Safety Analysis Set and PP Analysis Set.

Primary Objective:

Lot-to-Lot Consistency

The lot-to-lot consistency between 3 Phase III lots was analyzed by calculating the difference of log₁₀ GMT between each pair of lots for the four dengue virus serotypes.

Equivalence of the GMTs 28 days after the third injection was statistically demonstrated in the PP Analysis Set for each pair of lots for each serotype (11/12 comparisons) except for serotype 2 (Lot 1-Lot 2) where the upper limit of the 95% CI was 0.340; i.e., higher than the pre-defined limit of 0.301 (Table S1).

Table S1: Difference of log₁₀GMT of antibodies against parental dengue virus serotypes among three Phase III lots 28 days after the third injection - Per Protocol Analysis Set

Components	Difference of Log ₁₀ GMT					
	Lot 1 – Lot 2		Lot 2 – Lot 3		Lot 3 – Lot 1	
	Diff	(95% CI)	Diff	(95% CI)	Diff	(95% CI)
Serotype 1	0.055	(-0.067;0.178)	0.024	(-0.102;0.151)	-0.080	(-0.204;0.045)
Serotype 2	0.174	(0.009;0.340)	-0.120	(-0.297;0.056)	-0.054	(-0.225;0.117)
Serotype 3	0.058	(-0.068;0.184)	-0.042	(-0.167;0.082)	-0.016	(-0.144;0.113)
Serotype 4	0.144	(-0.006;0.295)	-0.060	(-0.207;0.088)	-0.085	(-0.242;0.073)

Note: Lot consistency for each pair of lots was demonstrated if for each pair of lots and each serotype, the lower limit of the 95% CI was > -0.301 and the upper limit was < 0.301.

Only 1 statistical comparison out of 12 was not achieved but was considered as not clinically significant based on the similarity between Phase III lots for all serotypes, including serotype 2 and since the GMTs for serotype 2 observed in each Phase III lot (65.9 [1/dil], 44.1 [1/dil] and 58.1 [1/dil], respectively) were consistently higher than the GMT observed in the Phase II lot (25.7 [1/dil]).

Table S2: GMT of antibodies against parental dengue virus serotypes among three Phase III lots 28 days after the third injection - Per Protocol Analysis Set

Components	Phase III Lot								
	Lot 1 (N=129)			Lot 2 (N=123)			Lot 3 (N=124)		
	M	GMT	(95% CI)	M	GMT	(95% CI)	M	GMT	(95% CI)
Serotype 1	129	20.6	(16.9;25.1)	123	18.1	(14.8;22.2)	124	17.1	(13.9;21.2)
Serotype 2	129	65.9	(50.6;85.7)	123	44.1	(33.3;58.3)	124	58.1	(43.2;78.2)
Serotype 3	129	74.2	(60.1;91.7)	123	65	(53.2;79.3)	124	71.6	(58.2;88.2)
Serotype 4	129	131.8	(101.4;171.3)	123	94.6	(75.3;118.7)	124	108.5	(84.2;139.7)

M: Number of subjects available for the endpoint.

A similar trend was observed for the FAS (i.e., for all subjects who received at least one dose of CYD dengue vaccine, including subjects who had a positive dengue Ab status at baseline): equivalence of the GMTs 28 days after the third injection was demonstrated for each pair of lots for each serotype, except for serotype 2 (Lot 1-Lot 2).

The standard deviation 0.54 used for the power calculation and sample size estimation was the most conservative point estimate observed for all serotypes based on results observed in study CYD12 (a Phase II, double-blind, randomized, descriptive, multicenter study in 250 adult subjects in the US) where neutralizing Ab response was measured by a microneutralization assay. The standard deviations observed in CYD17 were higher than 0.54, particularly for the serotype 2, and were due in part to the higher intrinsic variability of the neutralizing Ab assay used in CYD17, which used the Plaque Reduction Neutralization Test (PRNT) (not the microneutralization assay originally used in CYD12).

Overall, although 1 comparison out of 12 was not statistically achieved, the Phase III lots may be considered as not clinically different as:

- For serotype 1, 3 and 4, the GMTs 28 days after the third injection were statistically equivalent across the 3 Phase III lot groups.
- For serotype 2, although equivalence was not shown between 2 lots (Table S1), the GMTs observed (65.9 [1/dil], 44.1 [1/dil] and 58.1 [1/dil], respectively) were consistently higher than the GMT observed in the Phase II lot (25.7 [1/dil]) and were consistent with those observed in study CYD12 (54.8 [1/dil]) which used the Phase II lot and was also conducted in a non-endemic area using the same vaccination schedule.

Secondary Objectives:

Bridging

The protocol stated that if equivalence of the three Phase III lots was shown, an equivalence testing approach was to be used to test if the Phase III investigational vaccine (pooled data from the three lots) was equivalent to a Phase II lot in terms of GMT 28 days after the third vaccination. As lot-to-lot consistency was not fully statistically demonstrated for all 12 comparisons, the bridging could not be formally tested as per the original protocol design. Nevertheless, considering the marginal difference observed in only one lot to lot comparison, pooled Phase III lots GMTs were calculated and compared to the Phase II lot GMTs. The level of GMTs 28 days after the third injection for serotypes 1, 3 and 4 was similar in the pooled Phase III lots (18.6 [1/dil], 70.2 [1/dil] and 110.9 [1/dil], respectively) compared to the Phase II lot (15.1 [1/dil], 83.6 [1/dil] and 115.4 [1/dil], respectively). For serotype 2, the level of GMT was higher in each individual Phase III lot (65.9 [1/dil], 44.1 [1/dil] and 58.1 [1/dil]) compared to the Phase II lot (25.7 [1/dil]).

Similar trends were observed in the FAS as in the PP Analysis Set for serotypes 1, 2 and 4; however, for serotype 3, the level of GMTs was lower for the pooled Phase III lots (69.3 [1/dil]) than the Phase II lot (93.4 [1/dil]).

Humoral Immunogenicity

The immunogenicity section for the secondary objective present results from the FAS. Similar results were observed for the PP Analysis Set.

GMTs

At baseline, the GMTs obtained using the dengue PRNT assay ranged from 5.0 (1/dil) to 5.65 (1/dil) for all serotypes and all lot groups.

Overall, GMTs 28 days after the third injection for all serotypes in all lot groups were significantly higher compared to baseline (Table S2). In the Phase II lot group, the GMTs after the third injection for each of the 4 serotypes (1, 2, 3 and 4) were 16.1 (1/dil), 29.3 (1/dil), 93.4 (1/dil) and 121 (1/dil), respectively.

The immune profile was consistent across lots, with higher GMTs 28 days after the third injection for all serotypes.

Seropositivity Against Each Parental Dengue Serotype

At baseline, a total of 93.1% (663/712) of subjects were dengue non-immune (i.e., dengue neutralizing Abs < 10 [1/dil] as determined by dengue neutralizing assay).

Overall, seropositivity rates 28 days after the third injection for all serotypes in all lot groups, increased compared to baseline and were as follows:

- In the Phase III Lot 1 group, seropositivity rates after the third injection for each of the 4 serotypes (1, 2, 3 and 4) were 71.4%, 86.4%, 91.4% and 92.1%, respectively.
- In the Phase III Lot 2 group, seropositivity rates after the third injection for each of the 4 serotypes (1, 2, 3 and 4) were 62.2%, 77.6%, 93.0% and 91.6%, respectively.
- In the Phase III Lot 3 group, seropositivity after the third injection for each of the 4 serotypes (1, 2, 3 and 4) were 59.0%, 82.8%, 94.8% and 91.0%, respectively.
- In the pooled Phase III lots group, seropositivity rates after the third injection for each of the 4 serotypes (1, 2, 3 and 4) were 64.3%, 82.3%, 93.0% and 91.6%, respectively.
- In the Phase II lot group, seropositivity rates after the third injection for each of the 4 serotypes (1, 2, 3 and 4) were 56.4%, 73.8%, 98.0% and 92.6%, respectively.

Regardless of the lot, there were similar seropositivity rates for each serotype 28 days after the third injection. Moreover, the immune profile was consistent across lots, with seropositivity rates highest for serotypes 4, 3 and 2 compared to serotype 1.

Seropositivity Against At Least 1, 2, 3 or all 4 Serotypes

Across CYD dengue vaccine groups, the percentage of subjects seropositive against at least 1, 2, 3, or 4 serotypes was as follows:

- Seropositivity rates against at least 1 dengue virus serotype ranged across lots from 4.3% to 10.2% at baseline and from 99.3% to 100% 28 days after the third injection.
- Seropositivity rates against at least 2 dengue virus serotypes ranged across lots from 0.6% to 1.8% at baseline and from 92.3% to 96.0% 28 days after the third injection.
- Seropositivity rates against at least 3 dengue virus serotypes ranged across lots from 0.6% to 1.8% at baseline and from 78.3% to 85.0% 28 days after the third injection.
- Seropositivity rates against at least 4 dengue virus serotypes ranged across lots from 0.0% to 1.8% at baseline and from 45.6% to 62.9% 28 days after the third injection.

Overall, the seropositivity rates against at least 1, 2, 3 and 4 serotypes 28 days after the third injection largely increased from baseline in all lot groups. Moreover, there were similar seropositivity rates between the lots for at least 1, 2, 3 and 4 serotypes 28 days after the third injection.

Safety

Based on the safety overview, the safety profile was similar after each dose in the Phase III lots and in the Phase II lot. Therefore, the descriptive comparison of the safety parameters between CYD dengue vaccine lots and placebo are summarized as follows:

- Descriptive comparison of the range for the Phase III lots and the Phase II lot.
- Descriptive comparison of the CYD dengue vaccine groups (all lots pooled) and the placebo group.

Overall the frequency of solicited and unsolicited reactions in each treatment group was similar. Solicited systemic reactions were reported in a slightly lower percentage of subjects after the third injection than after the second injection and the first injection. The nature, and severity of AEs were similar between treatment groups. Overall, SAEs corresponded to common medical conditions. Two subjects experienced SAEs which were assessed as related to study vaccine by the Investigator.

Immediate Reactions

A total of 3 subjects (2 subjects in the Phase III Lot 2 group and 1 subject in the Phase II lot group) had at least one immediate unsolicited adverse reaction (AR) after the first injection (i.e., within the 30-minute observation period). Subjects reported pruritus, dysgeusia and dizziness, respectively, all of which were of Grade 1 intensity, lasted 1 day and resolved spontaneously. One subject in the Phase III Lot 1 group had one immediate unsolicited AR (Grade 1 erythema to the face) after the second injection. This event lasted 1 day and resolved spontaneously. No subjects had immediate unsolicited ARs after the third injection. No immediate reactions occurred after subsequent injections.

Solicited Reactions

The percentage of subjects experiencing at least one solicited reaction (including both solicited injection site and solicited systemic reactions) was similar across CYD dengue vaccine groups: 79.6% (129/162) of subjects in the Phase III Lot 1 group, 78.1% (125/160) of subjects in the Phase III Lot 2 group, 83.6% (133/159) of subjects in the Phase III Lot 3 group, and 84.1% (138/164) of subjects in the Phase II lot group; and overall, was higher than in the placebo group (66.7% [38/57] of subjects).

After any injection, the percentage of subjects experiencing at least one Grade 3 solicited reaction was similar across groups and tended to be higher than the placebo group; most Grade 3 solicited reactions were systemic reactions.

After the first injection

Across the CYD dengue vaccine groups, pain was the most frequently reported injection site reaction followed by erythema and swelling. The rates of pain and erythema were similar in the Phase III lot groups (ranging from 22.2% [36/162] to 28.3% [45/159] and 1.9% [3/162] to 6.9% [11/159] of subjects, respectively) and were similar compared to the Phase II lot group (21.3% [35/164] and 4.9% [8/164] of subjects, respectively). Swelling was reported by 0.0% (0/159) to 0.6% (1/160) of subjects in the Phase III lot groups and by 1.2% (2/164) of subjects in the Phase II lot group. The rates of pain were higher in the pooled CYD dengue vaccine groups (23.6% [152/645] of subjects) as compared to the placebo group (8.8% [5/57] of subjects). Erythema and swelling were not reported in the placebo group.

For all groups, most of the solicited injection site reactions were of Grade 1 intensity, appeared within 3 days after vaccination and the number of days of occurrence ranged from 1 to 3 days. There were no Grade 3 solicited injection site reactions after the first injection.

The rate of headache tended to be similar in the Phase III lot groups (ranging from 41.9% [67/160] to 51.6% [82/159] of subjects) and similar to the Phase II lot group (50.6% [83/164] of subjects). The rate of malaise in the Phase III lot groups ranged from 25.6% (41/160) to 42.8% (68/159) of subjects; the rate of malaise in the Phase II lot group (39.6% [65/164] of subjects) was within this range. The rates of asthenia and myalgia were similar in the Phase III lot groups (ranging from 17.3% [28/162] to 23.3% [37/159] and 28.4% [46/162] to 31.4% [50/159] of subjects, respectively) and were lower in the Phase III lot groups than in the Phase II lot group (29.9% [49/164] and 40.9% [67/164] of subjects, respectively). The rates of headache, malaise and asthenia were similar in the pooled CYD dengue vaccine groups (47.4% [306/645], 33.6% [217/645] and 22.5% [145/645] of subjects, respectively) and the placebo group (42.1% [24/57], 33.3% [19/57] and 22.8% [13/57] of subjects, respectively). The rates of myalgia were higher in the pooled CYD dengue vaccine groups (33.0% [213/645] of subjects) than in the placebo group (22.8% [13/57] of subjects).

Fever was reported by 0.6% (1/162) to 1.9% (3/159) of subjects in the Phase III lot groups and by 2.4% (4/164) of subjects in the Phase II lot group. Fever was not reported in the placebo group.

For all groups, most of the solicited systemic reactions were of Grade 1 intensity, appeared within 3 days of injection (except for fever, where most subjects reported between Day 8 and Day 14 after injection) and the number of days of occurrence ranged from 1 to 3 days.

Few subjects experienced at least one Grade 3 event:

- 3.1% (5/162) to 6.9% (11/160) of subjects in the Phase III lots group, 4.3% (7/164) of subjects in the Phase II lot group and 5.3% (3/57) of subjects in the placebo group experienced Grade 3 headache.
- 3.1% (5/162) to 3.8% (6/160) of subjects in the Phase III lots group, 4.9% (8/164) of subjects in the Phase II lot group and 1.8% (1/57) of subjects in the placebo group experienced Grade 3 malaise.
- 1.9% (3/162) to 3.1% (5/160) of subjects in the Phase III lots group, 3.7% (6/164) of subjects in the Phase II lot group and 1.8% (1/57) of subjects in the placebo group experienced Grade 3 asthenia.
- 1.2% (2/162) to 3.1% (5/160) of subjects in the Phase III lots group, 6.1% (10/164) of subjects in the Phase II lot group and 1.8% (1/57) of subjects in the placebo group experienced Grade 3 myalgia.

No subject experienced Grade 3 fever after the first injection.

After the second injection

As for the first injection, across the CYD dengue vaccine groups, pain was the most frequently reported injection site reaction followed by erythema and swelling. The rates of injection site reactions after the second injection were similar to the rates reported after the first injection for all lots. The rates of pain, erythema and swelling were similar in the Phase III lot groups (ranging from 26.5% [40/151] to 32.9% [46/140], 3.3% [5/151] to 9.5% [14/148] and 0.0% [0/140] to 2.7% [4/148] of subjects, respectively) and were similar compared to the Phase II lot group (30.3% [46/152], 7.2% [11/152] and 0.7% [1/152] of subjects, respectively). The rates of pain were higher in the pooled CYD dengue vaccine groups (30.5% [180/591] of subjects) as compared to the placebo group (9.6% [5/52] of subjects). Erythema and swelling were not reported in the placebo group.

For all groups, most of the solicited injection site reactions were of Grade 1 intensity, appeared within 3 days after vaccination and the number of days of occurrence ranged from 1 to 3 days. One subject (Subject 004-00031) in the Phase III Lot 2 group experienced Grade 3 injection site pain, on Day 2 after the second injection, which resolved spontaneously within 7 days.

After the third injection

As for the first and second injections, across the CYD dengue vaccine groups, pain was the most frequently reported injection site reaction followed by erythema and swelling. The rates of injection site reactions after the third injection are similar for all lots compared to the rates reported after the first and second injections. The rates of pain, erythema and swelling were similar across the Phase III lot groups (ranging from 23.0% [31/135] to 27.1% [38/140], 5.6% [8/143] to 8.9% [12/135] and 1.4% [2/143] to 2.9% [4/140] of subjects, respectively) and were similar compared to the Phase II lot group (27.5% [41/149], 8.7% [13/149] and 2.0% [3/149], respectively). The rates of pain were higher in the pooled CYD dengue vaccine groups (26.1% [148/567] of subjects) as compared to the placebo group (10.2% [5/49] of subjects), the rates of swelling were similar in the pooled CYD dengue vaccine groups (1.9% [11/567] of subjects) and the placebo group (2.0% [1/49] of subjects) and erythema was not reported in the placebo group.

As for the first injection, across the CYD dengue vaccine groups, headache, malaise and myalgia were the most frequently reported systemic reactions. The rates of headache and malaise decreased after the second injection for all lots compared to the rates reported after the first injection. The rates of headache, malaise and myalgia were similar across the Phase III lot groups (ranging from 37.1% [52/140] to 39.9% [59/148], 26.0% [39/150] to 30.0% [42/140] and 17.3% [26/150] to 22.9% [32/140] of subjects, respectively). The rates of headache and myalgia were similar in the Phase III lot groups and the Phase II lot group (37.3% [57/153] and 20.4% [31/152] of subjects, respectively) and the rates of malaise tended to be higher in the Phase III lots than in the Phase II lot group (22.4% [34/152] of subjects). The rates of asthenia were similar across the Phase III lots (ranging from 13.3% [20/150] to 13.6% [19/140] of subjects, respectively) and tended to be lower in the Phase III lots than in the Phase II lot group (17.1% [26/152] of subjects). The rates of headache tended to be higher in the pooled CYD dengue vaccine groups (38.1% [225/591] of subjects) than in the placebo group (32.7% [17/52] of subjects). The rates of malaise, myalgia and asthenia were similar in the pooled CYD dengue vaccine groups (26.8% [158/590], 20.0% [118/590] and 14.4% [85/590] of subjects, respectively) and the placebo group (26.9% [14/52], 23.1% [12/52] and 15.4% [8/52] of subjects, respectively).

Fever was reported by 1.4% (2/148) to 2.9% (4/140) of subjects in the Phase III lot groups and by 1.3% (2/152) of subjects in the Phase II lot group. Fever was not reported in the placebo group.

For all groups, most of the solicited systemic reactions were of Grade 1 intensity, appeared within 3 days of injection and the number of days of occurrence ranged from 1 to 3 days.

Few subjects experienced at least one Grade 3 solicited systemic reaction:

2.7% (4/148) to 3.6% (5/140) of subjects in the Phase III lots group, 4.6% (7/153) of subjects in the Phase II lot group experienced Grade 3 headache; none in the placebo group.

2.0% (3/148) to 6.4% (9/140) of subjects in the Phase III lots group, 2.0% (3/152) of subjects in the Phase II lot group and 3.8% (2/52) of subjects in the placebo group experienced Grade 3 malaise.

0.7% (1/148) to 4.3% (6/140) of subjects in the Phase III lots group, 0.0% (0/152) of subjects in the Phase II lot group and 3.8% (2/52) of subjects in the placebo group experienced Grade 3 myalgia.

0.0% (0/148) to 3.6% (5/140) of subjects in the Phase III lots group, 2.0% (3/152) of subjects in the Phase II lot group experienced Grade 3 asthenia; none in the placebo group.

One subject in the Phase III Lot 3 group experienced a Grade 3 fever on the day of the second injection, which resolved spontaneously within 14 days.

For all groups, most of the solicited injection site reactions were of Grade 1 intensity, appeared within 3 days after vaccination and the number of days of occurrence ranged from 1 to 3 days. Two subjects experienced Grade 3 solicited injection site reactions: one subject in the Phase III Lot 1 group experienced injection site pain on Day 0, Day 1 and Day 2 after the third injection, which resolved spontaneously within 7 days and one subject in the Phase III Lot 3 group experienced injection site pain on Day 1 after the third injection, which resolved spontaneously within 7 days.

As for the first and second injections, across the CYD dengue vaccine groups, headache, malaise and myalgia were the most frequently reported systemic reactions. The rates of solicited systemic reactions after the third injection decreased for all lots compared to the rates reported after the first and second injections. The rates of headache, malaise and myalgia were similar in the Phase III lot groups (ranging from 25.7% [36/140] to 38.5% [52/135], 17.1% [24/140] to 25.9% [35/135] and 17.1% [24/140] to 20.0% [27/135] of subjects, respectively) and similar to the Phase II lot group (30.9% [46/149], 18.1% [27/149] and 17.4% [26/149] of subjects, respectively). The rates of asthenia were similar in the Phase III lot groups (ranging from 12.1% [17/140] to 14.7% [21/143] of subjects) and similar to the Phase II lot group (10.1% [15/149] of subjects). The rates of malaise and asthenia were similar in the pooled CYD dengue vaccine groups (21.5% [122/567] and 12.3% [70/567] of subjects, respectively) and the placebo group (20.4% [10/49] and 10.2% [5/49] of subjects, respectively). The rates of headache and myalgia tended to be higher in the pooled CYD dengue vaccine groups (31.4% [178/567] and 18.5% [105/567] of subjects, respectively) than in the placebo group (24.5% [12/49] and 10.2% [5/49] of subjects, respectively).

Fever was reported by 1.4% (2/140) to 2.1% (3/143) of subjects in the Phase III lot groups and was not reported in the Phase II lot group. Rates of fever were similar in the CYD dengue vaccine groups and the placebo group (2.0% [1/49] of subjects).

Solicited systemic reactions were reported in a slightly lower percentage of subjects after the third injection than after the second injection and the first injection.

For all groups, most of the solicited systemic reactions were of Grade 1 intensity, appeared within 3 days of injection (except for fever which was reported at a similar rate throughout the 14-day post-injection period) and the number of days of occurrence ranged from 1 to 3 days.

Few subjects experienced at least one Grade 3 solicited systemic reaction:

2.1% (3/140) to 4.4% (6/135) of subjects in the Phase III lots group, 1.3% (2/149) of subjects in the Phase II lot group and 2.0% (1/49) of subjects in the placebo group experienced Grade 3 malaise.

1.4% (2/140) to 5.6% (8/143) of subjects in the Phase III lots group, 1.3% (2/149) of subjects in the Phase II lot group and 2.0% (1/49) of subjects in the placebo group experienced Grade 3 headache.

0.7% (1/140) to 2.2% (3/135) of subjects in the Phase III lots group, 2.0% (3/149) of subjects in the Phase II lot group experienced Grade 3 myalgia; none in the placebo group.

0.7% (1/140) to 3.0% (4/135) of subjects in the Phase III lots group, 0.7% (1/149) of subjects in the Phase II lot group and 2.0% (1/49) of subjects in the placebo group experienced Grade 3 asthenia.

No subject experienced Grade 3 fever after the third injection.

Unsolicited AEs and ARs

The percentage of subjects experiencing at least one unsolicited AE was similar across CYD dengue vaccine groups: 62.0% (101/163) of subjects in the Phase III Lot 1 group, 57.1% (92/161) of subjects the Phase III Lot 2 group, 65.9% (108/164) of subjects in the Phase III Lot 3 group and 65.3% (109/167) of subjects in the Phase II lot group; and overall, was similar to the placebo group (54.4% [31/57] of subjects).

The percentage of subjects experiencing at least one unsolicited AR was similar across CYD dengue vaccine groups: 18.4% (30/163) of subjects in the Phase III Lot 1 group, 14.3% (23/161) of subjects in the Phase III Lot 2 group,

22.6% (37/164) of subjects in the Phase III Lot 3 group and 23.4% (39/167) of subjects in the Phase II lot group; and overall, was similar to the placebo group (17.5% [10/57] of subjects).

Most unsolicited AEs were of Grade 1 or Grade 2 intensity, appeared within 7 days after injection, and the number of days of occurrence ranged from 1 to 3 days.

AEs Leading to Discontinuation

Eleven subjects had an AE leading to discontinuation: 1 subject in the Phase III Lot 1 group (influenza), 2 subjects in the Phase III Lot 2 group (erythematous rash and migraine), 5 subjects in the Phase III Lot 3 group (neutropenia, exacerbation of Barmah Forest virus, puncture site hematoma, fatigue and upper respiratory tract infection) and 3 subjects in the Phase II lot group (renal colic, gastrointestinal infection or disease and periorbital infection). Four of these AEs (erythematous rash, migraine, upper respiratory tract infection and periorbital infection) were assessed by the Investigator as related to the trial product.

SAEs

A total of 34 subjects reported 44 SAEs during the overall study, including 10 subjects who reported 11 SAEs occurring within 28 days after any injection.

A total of 18 subjects experienced at least one SAE after the first injection: 4 subjects in the Phase III Lot 1 group, 6 subjects in the Phase III Lot 2 group, 3 subjects in the Phase III Lot 3 group, 4 subjects in the Phase II lot group and 1 subject in the placebo group. One of these subjects, in the Phase III lot 3 group experienced 1 SAE (headache), which occurred 10 days after the first injection, and which was assessed as related to study vaccine both by the Investigator and the Sponsor.

A total of 12 subjects experienced at least one SAE after the second injection: 2 subjects in the Phase III Lot 1 group, 4 subjects in the Phase III Lot 2 group, 2 subjects in the Phase III Lot 3 group, and 4 subjects in the Phase II lot group. Of these subjects, one of the subject in the Phase II lot group experienced 1 SAE (polymyalgia rheumatica - possible), which occurred about one month after the second injection, and was assessed as related to study vaccine by the Investigator, and not related to study vaccine by the Sponsor.

A total of 6 subjects experienced at least one SAE after the third injection: 4 subjects in the Phase III Lot 1 group, 1 subject in the Phase III Lot 2 group, and 1 subject in the Phase II lot group. None was assessed as related to study vaccine by the Investigator nor the Sponsor.

Most of the SAEs reported after any injection corresponded to common medical conditions.

Six subjects were withdrawn from the study due to SAEs: One in the Phase II lot group (polymyalgia rheumatica - possible), One in the Phase III Lot 3 group (headache), Subject in the Phase III Lot 1 group (diabetic ketoacidosis), One in the Phase III Lot 1 group (hypergammaglobulinaemia benign monoclonal), One in the Phase III Lot 2 group (anxiety) and One in the placebo group (prostate cancer).

Four SAEs were ongoing at the end of the trial: polymyalgia rheumatica - possible for Subject in the Phase II lot group, type II diabetes mellitus for one in the Phase III lot 1 group, stress cardiomyopathy for one subject in the Phase III Lot 1 group and tendonitis for one in the Phase III Lot 2 group.

AESIs

No cases of serious AESI were reported after any injection during the overall study: no serious hypersensitivity/allergic reactions occurring within 7 days after injection, no serious neurotropic or viscerotropic events, and no serious dengue disease cases.

The percentage of subjects experiencing at least one non-serious AESI (all of allergic origin) was similar across CYD dengue vaccine groups: 1.8% of subjects (3/163) in the Phase III Lot 1 group, 1.9% of subjects (3/161) in the Phase III Lot 2 group, 1.2% of subjects (2/164) in the Phase III Lot 3 group and 0.6% of subjects (1/167) in the Phase II lot group. There were no AESIs reported in the placebo group.

The incidence of non-serious AESIs decreased after each injection: 6 subjects experienced at least one AESI (1 subject with pruritus [Subject 002-00109], 4 subjects with rash and 1 subject with rash generalized) after the first injection, 2 subjects experienced at least one AESI (rash erythematous and swelling of the face) after the second injection and 1 subject experienced at least one AESI (rash) after the third injection of CYD dengue vaccine.

Pregnancies

Four pregnancies occurred during the study: One in the Phase III Lot 1 group and one in the Phase II lot group became pregnant after the first injection, and one in the Phase III Lot 3 group and one in the Phase III lot 2 group became pregnant during the 6 month follow-up period, after having received 3 injections.

Among these cases, only one was considered as exposed to the vaccine (i.e., the subject was vaccinated within 30 days before the last menstrual period [LMP] or later). This subject was vaccinated 18 days before the LMP date and had an elective abortion 2 months after the first injection for personal reasons. The other three pregnant subjects were considered as non-exposed to the vaccine and outcome of these three pregnancies was a normal alive baby.

Deaths

No deaths were reported during the study.

Immune Response According to Baseline FV Status

Baseline FV status was assessed by measuring dengue immunoglobulin G (IgG) Abs by ELISA. In total, 2.7% of subjects (19/712) were immune to FV at baseline (i.e., had an index value > 1.0 using the ELISA kit). The subjects FV immune at baseline were well-distributed across the treatment groups.

As the dengue IgG ELISA was shown to have less sensitivity for assessment of prior dengue exposure than the PRNT, the baseline status for the primary endpoint was defined using only the dengue PRNT assay.

For all lots, GMTs, seropositivity rates against each parental dengue serotype and seropositivity against at least 1, 2, 3 or 4 serotypes 28 days after the third injection were higher for subjects FV immune at baseline, compared to subjects FV non-immune at baseline.

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