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<b>Sponsor:</b> Sanofi Pasteur	<b>Study Identifiers:</b> NCT00875524, 2014-001709-41
<b>Drug substance:</b> CYD Dengue Vaccine	<b>Study code:</b> CYD22
<b>Title of the study:</b> Immunogenicity and Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Viet Nam	
<b>Study center(s):</b> One study center in Vietnam	
<b>Study period:</b> Date first subject enrolled: 14/Mar/2009 Date last subject completed: 12/Jul/2014	
<b>Phase of development:</b> Phase II	
<b>Main Objectives:</b> <ol style="list-style-type: none"><li>1) To describe the humoral immune response to dengue before and after each vaccination with CYD dengue vaccine in 4 age cohorts: adults (18 to 45 years), adolescents (12 to 17 years), and children (6 to 11 years and 2 to 5 years).</li><li>2) To evaluate the safety of each vaccination with CYD dengue vaccine in the 4 age cohorts.</li><li>3) To evaluate the persistence of antibodies (Abs) against dengue during 5 years after the first vaccination with CYD dengue vaccine in the 4 age cohorts</li></ol>	
<b>Secondary Objectives:</b> <ol style="list-style-type: none"><li>1) To describe the serological status for Japanese encephalitis (JE) in the study population at baseline.</li><li>2) To detect symptomatic dengue cases occurring at any time in the study.</li><li>3) To detect dengue vaccine viremia and evaluate biological parameters in the event of temperature <math>\geq 38^{\circ}\text{C}</math> for <math>\geq 48</math> hours in the 28 days following each vaccination.</li></ol>	
<b>Methodology:</b> <p>This was a randomized, blind-observer, controlled, monocenter, Phase II trial in 180 subjects in Viet Nam. Enrolment was sequential (per age cohort). There were 3 vaccinations (Day [D] 0, D0 + 6 months, and D0 + 12 months) and 2 groups of subjects:</p> <ul style="list-style-type: none"><li>• <b>Dengue Group</b> received CYD dengue vaccine as first, second, and third vaccinations.</li><li>• <b>Control Group</b> received Meningococcal Polysaccharide Vaccine A + C as first vaccination, a placebo (sodium chloride [NaCl] containing human serum albumin [HSA]) as second vaccination, and Typhoid Vi polysaccharide vaccine (Typhim Vi®) as third vaccination.</li></ul> <p>A stepwise approach for the first vaccination was performed as follows:</p> <ul style="list-style-type: none"><li>• Vaccination of adult subjects (18 to 45 years old).</li><li>• Vaccination of adolescent subjects (12 to 17 years old) <math>14 \pm 7</math> days later.</li><li>• Safety review of D28 data of the adult and adolescent cohorts.</li><li>• Vaccination of children (6 to 11 years old).</li><li>• Vaccination of children (2 to 5 years old) <math>14 \pm 7</math> days later.</li><li>• Safety review of D28 data of the children cohorts (6 to 11 years old and 2 to 5 years old).</li></ul>	

<p><b>Number of subjects:</b></p> <p><b>Evaluated:</b></p>	<p>Planned: 180 Randomized: 180</p> <p>Immunogenicity: 180 Safety: 180</p>
<p><b>Diagnosis and criteria for inclusion:</b></p> <ol style="list-style-type: none"> <li>1) Aged 2 to 45 years on the day of inclusion.</li> <li>2) Provision of Informed Consent/Assent Form signed by the subject (and/or by the parent or another legally acceptable representative for subjects &lt;18 years).</li> <li>3) Subject (and parent/guardian for subjects &lt;18 years) able to attend all scheduled visits and to comply with all trial procedures.</li> <li>4) 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 the first vaccination, until at least 4 weeks after the last vaccination.</li> <li>5) Subject in good health, based on medical history, physical examination and laboratory parameters</li> </ol>	
<p><b>Study treatments</b></p> <p><b>Investigational Product:</b> CYD dengue vaccine</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 ± 1 log<sub>10</sub> cell-culture infectious dose 50% (CCID<sub>50</sub>) 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) aminomethane, and urea</p> <p style="padding-left: 40px;">Solvent: NaCl 0.4% containing HSA 2.5%</p> <p>Route of administration : Subcutaneous (SC)</p>	
<p><b>Control Product for First Vaccination:</b> Meningococcal Polysaccharide Vaccine A+C</p> <p>Form: Powder and solvent for suspension for injection (pre-filled syringe)</p> <p>Composition: Each 0.5 mL dose of reconstituted vaccine contains:</p> <p style="padding-left: 40px;"><u>Active substance</u></p> <p style="padding-left: 80px;"><i>Neisseria meningitidis</i> group A polysaccharide.....50 µg</p> <p style="padding-left: 80px;"><i>Neisseria meningitidis</i> group C polysaccharide.....50 µg</p> <p style="padding-left: 40px;"><u>Excipients</u></p> <p style="padding-left: 40px;">Powder: lactose</p> <p style="padding-left: 40px;">Isotonic buffer solution: sodium chloride, disodium phosphate, monosodium phosphate, water for injections.....qs. 0.50 mL</p> <p>Route of administration : SC</p>	
<p><b>Control Product for Second Vaccination:</b> Placebo (NaCl containing HSA)</p> <p>Form: Liquid</p> <p>Composition: NaCl 0.4% containing HSA 2.5%</p> <p>Route of administration : SC</p>	

**Control Product for Third Vaccination:** Typhoid Vi polysaccharide vaccine (Typhim Vi Vaccine)

Form: Liquid

Composition: Each 0.5 mL dose contains:

Component	Quantity (per container)	Function
Purified Vi capsular polysaccharide of <i>Salmonella typhi</i> (Ty2 strain)	25 µg	Active substance
Phenol	≤1.250 mg	Preservative
Sodium chloride	4.150 mg	Stabiliser
Disodium phosphate dihydrate	0.065 mg	Stabiliser
Sodium dihydrogen phosphate dihydrate	0.023 mg	Stabiliser
Water for injections	q.s 0.5 ml	Diluent

Route of administration: SC

**Duration of treatment/participation:** The expected duration of each subject's participation in the trial was 5 years (including the first year for the vaccinations and the 4-year follow-up after the third vaccination).

**Criteria for evaluation:**

**Main Endpoints:**

**Immunogenicity**

- Neutralizing Ab levels against each of the 4 parental dengue virus strains of CYD dengue vaccine constructs measured in sera collected from all the subjects before and 28 days after each vaccination, and each year during 5 years after the first vaccination (dengue plaque reduction neutralization test [PRNT]).
- **Safety**
- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (pre-listed in the subject's diary and electronic case report form) injection site reactions occurring up to 7 days after each vaccination.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited systemic reactions occurring up to 14 days after each vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each vaccination.
- Occurrence of serious adverse events (SAEs) throughout the trial, as follows:
  - Up to 6 months after the last vaccination: all SAEs
  - From 6 months after the last vaccination until the end of trial: only related and fatal (even if unrelated) SAEs

**Secondary Endpoints:**

**Japanese encephalitis serology**

- Neutralizing Ab level against JE on a blood sample taken at screening (PRNT).

**Detection of symptomatic dengue cases**

- In the event of temperature  $\geq 38^{\circ}\text{C}$  for  $\geq 48$  hours with a suspicion of dengue, the following tests were performed to identify any potential dengue case:
  - Routine dengue immunoglobulin (Ig) M test and hematology, and routine dengue IgM test, hematology, and biochemistry (only in case of symptomatic dengue suspicion occurring within 28 days after vaccination) for dengue cases management (diagnosis)

- Dengue IgM/IgG enzyme-linked immunosorbent assay (ELISA) and virus isolation
- Quantitative dengue reverse transcriptase polymerase chain reaction (RT-PCR), non-structural protein (NS) 1 antigen (Ag) ELISA, and IgM/IgG ELISA (by Sanofi Pasteur Global Clinical Immunology [GCI] or GCI designated laboratory)

**Detection of dengue vaccine viremia**

In the event of temperature  $\geq 38^{\circ}\text{C}$  for  $\geq 48$  hours within 28 days after each vaccination, the occurrence and the level of dengue vaccine viruses in serum were measured by quantitative and serotype specific RT-PCRs and biological parameters of the subject were evaluated (biochemistry and hematology).

**Statistical methods:**

For this final CSR, all statistical analyses were descriptive and are presented with 95% confidence intervals (CIs) by using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.

All analyses were performed on each cohort separately as well as combined.

Listings of safety data were produced after the adult (18 to 45 years) and adolescent (12 to 17 years) cohorts completed V04 (D28). These data were provided by the Sponsor's Data Management department to the Sponsor and the Investigator.

An interim analysis of safety and immunogenicity was performed on unblinded data up to 28 days after the third vaccination and 1, 2, and 3 years after the third vaccination. A final analysis of safety and immunogenicity was performed on unblinded data after the end of the 4-year follow-up.

**Summary:**

This final CSR includes immunogenicity results from the vaccination period until 4-year after the third vaccination and safety results from the vaccination period until 28 days after the third vaccination (except for all SAEs, which were collected until 6 months after the third vaccination, and related and fatal SAEs and symptomatic dengue cases, which were collected until the date that the database was available for the 4-year follow-up statistical analysis).

**Population characteristics:**

A total of 180 subjects were randomized into 2 groups (120 subjects in the dengue group and 60 subjects in the control group). Among subjects included in the full analysis set (FAS), 166 (92.2%) subjects completed the study (112 subjects in the dengue group and 54 in the control group) and 14 (7.8%) subjects discontinued the study. Up to the 4-year follow-up after the third vaccination, the reasons for not completing the study were: SAE (i.e., 1 subject [1.7%] in the control group), non-compliance with the protocol (i.e., 4 subjects [3.3%] in the dengue group), lost to follow-up (i.e., 1 subject [0.8%] in the dengue group), or voluntary withdrawal not due to an AE (i.e., 3 subjects [2.5%] in the dengue group and 5 subjects [8.3%] in the control group).

Up to 28 days after the third vaccination, no subjects in either study group discontinued the study due to an AE or SAE.

A total of 171 of the 172 subjects who completed the study up to 28 days after the third vaccination were present at Visit 10, 1 year after the third vaccination

A total of 170 of the 171 subjects present at Visit 10 had a blood sample drawn.

Of the 172 subjects who completed the study up to 28 days after the third vaccination, a total of 170 subjects (113 in the dengue group and 57 in the control group) continued the study.

All 170 subjects who completed the study up to 1-year after the third vaccination were present at Visit 11, 2 years after the third vaccination..

The 169 subjects who had a blood sample drawn at Visit 11 continued the study.

A total of 167 of the 169 subjects who completed the study up to 2-year after the third vaccination were present at Visit 12, 3 years after the third vaccination. Two subjects were not present at Visit 12 and did not have a blood sample drawn

The 167 subjects who had a blood sample drawn at Visit 12 continued the study.

A total of 166 of the 167 subjects who completed the study up to 3-year after the third vaccination were present at Visit 13, 4 years after the third vaccination. One subject was not present at Visit 13 and did not have a blood sample drawn

The 166 subjects who had a blood sample drawn at Visit 13 completed the study. Thus over 90% of the study subjects were contacted at the year 4 follow-up visit.

## IMMUNOGENICITY

### **HUMORAL IMMUNE RESPONSE TO DENGUE**

#### **Baseline for both study groups**

For all subjects, before the first vaccination, baseline seropositivity against each of the 4 parental dengue virus strains was high in both study groups. In the dengue group, baseline seropositivity ranged from 45.0% (54/120) for serotype 4 to 63.3% (76/120) for serotype 3. In the control group, baseline seropositivity ranged from 37.3% (22/59) for serotype 4 to 52.5% (31/59) for serotype 3.

In the dengue group, baseline GMTs for each dengue virus serotype (1, 2, 3, and 4) were 32.8 (1/dil), 33.7 (1/dil), 32.5 (1/dil), and 17.1 (1/dil), respectively.

In the control group, baseline GMTs for each dengue virus serotype (1, 2, 3, and 4) were 19.6 (1/dil), 27.2 (1/dil), 20.5 (1/dil), and 13.9 (1/dil) respectively.

#### *Age cohort comparison*

A significant number of subjects from both treatment groups had baseline seropositivity against each of the 4 parental dengue virus strains and baseline seropositivity rates appeared to increase with each successive age cohort.

In the dengue group, baseline seropositivity was lowest in children (2-5 years) (ranged from 17.5% [7/40] for serotype 2 to 52.5% [21/40] for serotype 3) but increased in each age cohort: for children (6-11 years) baseline seropositivity ranged from 42.5% [17/40] for serotype 4 to 55.0% [22/40] for serotype 3; for adolescents (12-17 years) baseline seropositivity ranged from 55.0% [11/20] for serotype 4 to 70.0% [14/20] for serotype 3; and for adults (18-45 years) baseline seropositivity ranged from 85.0% [17/20] for serotype 4 to 95.0% [19/20] for serotypes 1, 2 and 3.

Similarly in the control group, baseline seropositivity was lowest in children (2-5 years) (ranged from 15.0% [3/20] for serotype 4 to 42.1% [8/19] for serotype 3) but increased in each age cohort: for children (6-11 years) baseline seropositivity ranged from 25.0% [5/20] for serotype 2 to 40.0% [8/20] for serotype 3; for adolescents (12-17 years) baseline seropositivity ranged from 50.0% [5/10] for serotype 4 to 70.0% [7/10] for serotype 1; and for adults (18-45 years) baseline seropositivity ranged from 80.0% [8/10] for serotypes 1 and 4 to 90.0% [9/10] for serotypes 2 and 3.

Baseline GMTs appeared to increase with each successive age cohort.

In the dengue group, baseline GMTs were lowest in children (2-5 years) (ranged from 8.01 [1/dil] for serotype 2 to 18.7 [1/dil] for serotype 3) but increased in each age cohort: for children (6-11 years) baseline GMTs ranged from 12.9 (1/dil) for serotype 4 to 28.1 (1/dil) for serotype 2; for adolescents (12-17 years) baseline GMTs ranged from 26.9 (1/dil) for serotype 4 to 83.2 (1/dil) for serotype 2; and for adults (18-45 years) baseline GMTs ranged from 75.0 (1/dil) for serotype 4 to 350 (1/dil) for serotype 2.

Similarly in the control group, baseline GMTs were lowest in children (2-5 years) (ranged from 6.34 [1/dil] for serotype 4 to 10.9 [1/dil] for serotype 3) but increased in each age cohort: for children (6-11 years) baseline GMTs ranged from 12.0 (1/dil) for serotype 4 to 15.7 (1/dil) for serotype 2; for adolescents (12-17 years) baseline GMTs ranged from 18.7 (1/dil) for serotype 4 to 91.3 (1/dil) for serotype 2; and for adults (18-45 years) baseline GMTs ranged from 66.6 (1/dil) for serotype 4 to 200 (1/dil) for serotype 2.

#### **Dengue Group**

##### **Seropositivity**

##### Vaccination Period

CYD dengue vaccine induced a neutralizing Ab response against each of the 4 parental dengue virus strains after each successive vaccination.

For all subjects in the dengue group, seropositivity against each serotype increased with the successive vaccinations. One month after the first vaccination, serotype-specific seropositivity rates ranged from 62.2% (74/119) for serotype 1 to 84.9% (101/119) for serotype 3. One month after the second vaccination, seropositivity rates ranged from 79.1% (91/115) for serotype 1 to 94.8% (109/115) for serotype 3. One month after completion of the 3 vaccinations, seropositivity rates ranged from 93.0% (106/114) for serotype 1 to 99.1% (113/114) for serotypes 2 and 3.

##### 1-Year Follow-Up

One year after the third vaccination, seropositivity against each serotype remained high compared to baseline: the seropositivity rates ranged from 78.8% (89/113) for serotype 1 to 92.9% (105/113) for serotype 3.

### 2-Year Follow-Up

Two years after the third vaccination, seropositivity rates against each parental dengue virus serotype are comparable to those observed one year after the third vaccination. Seropositivity rates remained high compared to baseline: the seropositivity rates ranged from 74.1% (83/112) for serotype 1 to 90.2% (101/112) for serotype 4.

### 3-Year Follow-Up

Three years after the third vaccination, seropositivity rates against each parental dengue virus serotype were numerically slightly lower than those observed one year and two years after the third vaccination. Seropositivity rates remained high compared to baseline: the seropositivity rates ranged from 59.8% (67/112) for serotype 1 to 87.5% (98/112) for serotype 4.

### 4-Year Follow-Up

Four years after the third vaccination, seropositivity rates against each parental dengue virus serotype were numerically lower than those observed one year, two years, and three years after the third vaccination. Seropositivity rates remained high compared to baseline: the seropositivity rates ranged from 61.6% (69/112) for serotype 1 to 76.8% (86/112) for serotype 4.

## **GMTs**

### Vaccination Period

Similarly to seropositivity rates, geometric mean titers (GMTs) increased for all serotypes in the dengue group. GMTs increased from baseline after each CYD dengue vaccination. One month after completion of the 3 dengue vaccinations, GMTs for each dengue serotype (1, 2, 3 and 4) were approximately 3 to 8-fold higher than at baseline GMTs (129 [1/dil], 216 [1/dil], 169 [1/dil] and 146 [1/dil] respectively).

### 1-Year Follow-Up

One year after the third vaccination, GMTs for each dengue serotype (1, 2, 3 and 4) remained 3 to 5-fold above baseline (103 [1/dil], 133 [1/dil], 145 [1/dil], 87.5 [1/dil] respectively).

### 2-Year Follow-Up

Two years after the third vaccination, GMTs are lower than those observed one year after the third vaccination but remained 2 to 3.5-fold above baseline for each dengue virus serotype (1, 2, 3 and 4): 72.9 (1/dil), 118 (1/dil), 88.2 (1/dil) and 56.9 (1/dil) respectively.

### 3-Year Follow-Up

Three years after the third vaccination, GMTs were lower than those observed two years after the third vaccination but remained 1.7 to 2.8-fold above baseline for each dengue virus serotype (1, 2, 3 and 4): 56.0 (1/dil), 78.1 (1/dil), 66.6 (1/dil) and 47.3 (1/dil) respectively.

### 4-Year Follow-Up

Four years after the third vaccination, GMTs for serotypes 1 and 2 tended to be similar to those observed three years after the third vaccination; GMTs for serotypes 3 and 4 were lower than those observed three years after the third vaccination. GMTs remained 1.3 to 2.2-fold above baseline for each dengue virus serotype (1, 2, 3 and 4): 52.6 (1/dil), 73.7 (1/dil), 42.7 (1/dil) and 30.2 (1/dil) respectively.

### *Age cohort comparison*

## **Seropositivity**

### Vaccination Period

Overall, after completion of the 3 doses of CYD dengue vaccine administered on a 0-, 6-, and 12-month schedule seropositivity increased for all serotypes in all age groups, as follows:

- In children aged 2 to 5 years, the post-Dose 3 seropositivity rates against each of the 4 serotypes (1, 2, 3, and 4) were 87.2% (34/39), 100.0% (39/39), 100.0% (34/39), and 92.3% (36/39), respectively. Post-Dose 3, a total of 87.2% (34/39) of children (2 to 5 years) were seropositive against all 4 serotypes

- In children aged 6 to 11 years, the post-Dose 3 seropositivity rates against each of the 4 serotypes (1, 2, 3, and 4) were 94.6% (35/37), 97.3% (36/37), 100.0% (37/37), and 97.3% (36/37), respectively. Post-Dose 3, a total of 94.6% (35/37) of children (6 to 11 years) were seropositive against all 4 serotypes
- In adolescents aged 12 to 17 years, the post-Dose 3 seropositivity rates against the each of the 4 serotypes (1, 2, 3, and 4) were 95.0% (19/20), 100.0% (20/20), 95.0% (19/20), and 95.0% (19/20), respectively. Post-Dose 3, a total of 90% (18/20) of adolescent subjects were seropositive against all 4 serotypes
- In adults aged 18 to 45 years, the post-Dose 3 seropositivity rates against the each of the 4 serotypes (1, 2, 3, and 4) were 100.0% (18/18), 100.0% (18/18), 100.0% (18/18), and 100.0% (18/18), respectively. All adult subjects post-Dose 3 (18/18) (and post-Dose 2 [19/19]) were seropositive against all 4 serotypes

#### 1-Year Follow-Up

Overall, one year after the third vaccination, the seropositivity rates against each parental dengue virus serotype remained high compared to baseline for all serotypes and for all age groups. The results were as follows:

- In children aged 2 to 5 years, the 1-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 74.4% (29/39), 76.9% (30/39), 82.1% (32/39), and 79.5% (31/39), respectively. One year post-Dose 3, a total of 61.5% (24/39) of children (2 to 5 years) were seropositive against all 4 serotypes
- In children aged 6 to 11 years, the 1-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 75.0% (27/36), 94.4% (34/36), 100.0% (36/36), and 94.4% (34/36), respectively. One year post-Dose 3, a total of 72.2% (26/36) of children (6 to 11 years) were seropositive against all 4 serotypes
- In adolescents aged 12 to 17 years, the 1-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 80.0% (16/20), 85.0% (17/20), 95.0% (19/20), and 85.0% (17/20), respectively. One year post-Dose 3, a total of 75.0% (15/20) of adolescent subjects were seropositive against all 4 serotypes
- In adults aged 18 to 45 years, the 1-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 94.4% (17/18), 94.4% (17/18), 100.0% (18/18), and 100.0% (18/18), respectively. One year post-Dose 3, a total of 94.4% (17/18) of adult subjects were seropositive against all 4 serotypes

#### 2-Year Follow-Up

Overall, two years after the third vaccination, the seropositivity rates against each parental dengue virus serotype remained high compared to baseline for all serotypes and for all age groups. Compared to one year results after the third vaccination, the seropositivity rates against all 4 serotypes remained comparable for adults, adolescents and children aged 6 to 11 years, whereas they were lower for children aged 2 to 5 years. The results were as follows:

- In children aged 2 to 5 years, the 2-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 60.5% (23/38), 65.8% (25/38), 78.9% (30/38), and 86.8% (33/38), respectively. Two years post-Dose 3, a total of 50.0% (19/38) of children (2 to 5 years) were seropositive against all 4 serotypes
- In children aged 6 to 11 years, the 2-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 75.0% (27/36), 83.3% (30/36), 86.1% (31/36), and 88.9% (32/36), respectively. Two years post-Dose 3, a total of 69.4% (25/36) of children (6 to 11 years) were seropositive against all 4 serotypes
- In adolescents aged 12 to 17 years, the 2-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 80.0% (16/20), 95.0% (19/20), 95.0% (19/20), and 95.0% (19/20), respectively. Two years post-Dose 3, a total of 80.0% (16/20) of adolescent subjects were seropositive against all 4 serotypes
- In adults aged 18 to 45 years, the 2-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 94.4% (17/18), 100.0% (18/18), 94.4% (17/18), and 94.4% (17/18), respectively. Two years post-Dose 3, a total of 94.4% (17/18) of adult subjects were seropositive against all 4 serotypes

#### 3-Year Follow-Up

Overall, three years after the third vaccination, the seropositivity rates against each parental dengue virus serotype remained high compared to baseline for all serotypes and for all age groups. Compared to two-year results after the third vaccination, the

seropositivity rates against all 4 serotypes remained comparable for adults and children aged 6 to 11 years, whereas they were lower for children aged 2 to 5 years and adolescents. The results were as follows:

- In children aged 2 to 5 years, the 3-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 31.6% (12/38), 50.0% (19/38), 57.9% (22/38), and 78.9% (30/38), respectively. Three years post-Dose 3, a total of 28.9% (11/38) of children (2 to 5 years) were seropositive against all 4 serotypes
- In children aged 6 to 11 years, the 3-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 66.7% (24/36), 77.8% (28/36), 83.3% (30/36), and 91.7% (33/36), respectively. Three years post-Dose 3, a total of 63.9% (23/36) of children (6 to 11 years) were seropositive against all 4 serotypes
- In adolescents aged 12 to 17 years, the 3-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 70.0% (14/20), 75.0% (15/20), 75.0% (15/20), and 85.0% (17/20), respectively. Three years post-Dose 3, a total of 70.0% (14/20) of adolescent subjects were seropositive against all 4 serotypes
- In adults aged 18 to 45 years, the 3-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 94.4% (17/18), 94.4% (17/18), 94.4% (17/18), and 100% (18/18), respectively. Three years post-Dose 3, a total of 94.4% (17/18) of adult subjects were seropositive against all 4 serotypes

#### 4-Year Follow-Up

Overall, four years after the third vaccination, the seropositivity rates against each parental dengue virus serotype remained high compared to baseline for all serotypes and for all age groups. Compared to three-year results after the third vaccination, the seropositivity rates against all 4 serotypes remained comparable for adults and children aged 2 to 5 years, whereas they were slightly lower for children aged 6 to 11 years and adolescents. The results were as follows:

- In children aged 2 to 5 years, the 4-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 36.8% (14/38), 50.0% (19/38), 55.3% (21/38), and 71.1% (27/38), respectively. Four years post-Dose 3, a total of 34.2% (13/38) of children (2 to 5 years) were seropositive against all 4 serotypes
- In children aged 6 to 11 years, the 4-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 63.9% (23/36), 69.4% (25/36), 72.2% (26/36), and 75.0% (27/36), respectively. Four years post-Dose 3, a total of 58.3% (21/36) of children (6 to 11 years) were seropositive against all 4 serotypes
- In adolescents aged 12 to 17 years, the 4-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 75.0% (15/20), 80.0% (16/20), 75.0% (15/20), and 75.0% (15/20), respectively. Four years post-Dose 3, a total of 65.0% (13/20) of adolescent subjects were seropositive against all 4 serotypes
- In adults aged 18 to 45 years, the 4-year post-Dose 3 seropositivity rates against each serotype (1, 2, 3, and 4) were 94.4% (17/18) for each of the four serotypes, respectively. Four years post-Dose 3, a total of 94.4% (17/18) of adult subjects were seropositive against all 4 serotypes

#### **GMTs**

##### Vaccination Period

Overall, after completion of the 3 doses of CYD dengue vaccine, GMTs increased several fold from baseline GMT levels for all serotypes in all age groups as follows:

- In children aged 2 to 5 years, the post-Dose 3 GMTs for each of the 4 serotypes (1, 2, 3, and 4) were 64.7 (1/dil), 107 (1/dil), 143 (1/dil) and 92.7 (1/dil); representing approximately a 6 to 13-fold increase from baseline GMTs
- In children aged 6 to 11 years, the post-Dose 3 GMTs for each of the 4 serotypes (1, 2, 3, and 4) were 93.9 (1/dil), 185 (1/dil), 147 (1/dil) and 131 (1/dil); representing approximately a 3 to 10-fold increase from baseline GMTs
- In adolescents aged 12 to 17 years, the post-Dose 3 GMTs for each of the 4 serotypes (1, 2, 3, and 4) were 192 (1/dil), 334 (1/dil), 135 (1/dil) and 183 (1/dil); representing approximately a 3 to 6-fold increase from baseline GMTs
- In adults aged 18 to 45 years, the post-Dose 3 GMTs for each of the 4 serotypes (1, 2, 3, and 4) were 695 (1/dil), 825 (1/dil), 424 (1/dil) and 375 (1/dil); representing approximately a 2 to 5-fold increase from baseline GMTs

#### 1-Year Follow-Up

Overall, one year after the third vaccination, GMTs remained several fold above baseline for each age group. The results were as follows:

- In children aged 2 to 5 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 2 to 7-fold above baseline and were respectively 62.5 (1/dil), 37.6 (1/dil), 40.6 (1/dil), and 42.9 (1/dil)
- In children aged 6 to 11 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 3 to 7-fold above baseline and were respectively 87.2 (1/dil), 143 (1/dil), 167 (1/dil), and 75.6 (1/dil)
- In adolescents aged 12 to 17 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 2 to 9-fold above baseline and were respectively 128 (1/dil), 324 (1/dil), 323 (1/dil), and 160 (1/dil)
- In adults aged 18 to 45 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained unchanged from baseline to 4-fold above baseline and were respectively 325 (1/dil), 652 (1/dil), 701 (1/dil), and 269 (1/dil)

#### 2-Year Follow-Up

Overall, two years after the third vaccination, GMTs were slightly lower than those observed one year after the third vaccination but remained unchanged from baseline or several fold above baseline for each age group. The results were as follows:

- In children aged 2 to 5 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 2 to 3.5-fold above baseline and were respectively 31.6 (1/dil), 29.0 (1/dil), 36.0 (1/dil), and 32.9 (1/dil)
- In children aged 6 to 11 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 2.5 to 4-fold above baseline and were respectively 68.6 (1/dil), 105 (1/dil), 94.3 (1/dil), and 40.7 (1/dil)
- In adolescents aged 12 to 17 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 1.5 to 5.5-fold above baseline and were respectively 113 (1/dil), 493 (1/dil), 155 (1/dil), and 127 (1/dil)
- In adults aged 18 to 45 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained unchanged from baseline to 2-fold above baseline and were respectively 294 (1/dil), 595 (1/dil), 274 (1/dil), and 145 (1/dil)

#### 3-Year Follow-Up

Overall, three years after the third vaccination, most GMTs were slightly lower than those observed two years after the third vaccination (some GMTs were slightly higher or remained the same as those observed two years after the third vaccination) but remained unchanged from baseline or above baseline for each age group. The results were as follows:

- In children aged 2 to 5 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 1.6 to 2.8-fold above baseline and were respectively 17.5 (1/dil), 19.6 (1/dil), 29.2 (1/dil), and 24.2 (1/dil)
- In children aged 6 to 11 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 2 to 4.6-fold above baseline and were respectively 53.5 (1/dil), 118 (1/dil), 104 (1/dil), and 52.7 (1/dil)
- In adolescents aged 12 to 17 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 1.4 to 2.1-fold above baseline and were respectively 124 (1/dil), 120 (1/dil), 56.9 (1/dil), and 57.3 (1/dil)
- In adults aged 18 to 45 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained unchanged from baseline to 1.7-fold above baseline and were respectively 297 (1/dil), 393 (1/dil), 185 (1/dil), and 126 (1/dil)

#### 4-Year Follow-Up

Overall, four years after the third vaccination, most GMTs were slightly lower than those observed three years after the third vaccination but remained unchanged or above baseline for each age group:

- In children aged 2 to 5 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 1.3- to 2.6-fold above baseline and were respectively 20.0 (1/dil), 20.8 (1/dil), 24.9 (1/dil), and 19.4 (1/dil)
- In children aged 6 to 11 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 1.4- to 2.5-fold above baseline and were respectively 44.4 (1/dil), 71.2 (1/dil), 34.8 (1/dil), and 24.4 (1/dil)
- In adolescents aged 12 to 17 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained 1.4- to 2.0-fold above baseline and were respectively 110 (1/dil), 165 (1/dil), 56.5 (1/dil), and 36.5 (1/dil)

- In adults aged 18 to 45 years, GMTs for each of the 4 serotypes (1, 2, 3, and 4) remained above baseline only for serotype 2 (1.3-fold) and were respectively 249 (1/dil), 464 (1/dil), 148 (1/dil), and 96.3 (1/dil)

The fold-increase GMTs presented in this report are purely descriptive and are used to provide additional characterization of vaccine responses. These were not a part of the planned analyses described in the protocol or statistical analysis plan (SAP).

### **Control Group**

There was no significant increase in the rates of seropositivity against any serotype after each vaccination. The same trend was observed one, two, three, and four years after the third vaccination.

GMTs remained similar to baseline after each vaccination. One month after completion of the 3 vaccinations, GMTs ranged from 17.4 (1/dil) for serotype 4 to 30.4 (1/dil) for serotype 2. The same trend was observed one year after the third vaccination, GMTs ranged from 19.0 (1/dil) for serotype 4 to 36.9 (1/dil) for serotype 2. Two years after the third vaccination, the same trend was observed, GMTs ranged from 17.5 (1/dil) for serotype 4 to 42.6 (1/dil) for serotype 2. Three years after the third vaccination, the same trend was observed, GMTs ranged from 21.7 (1/dil) for serotype 4 to 45.2 (1/dil) for serotype 2. Four years after the third vaccination, the same trend was observed, GMTs ranged from 18.2 (1/dil) for serotype 4 to 50.7 (1/dil) for serotype 2.

#### *Age cohort comparison*

Overall, there was no significant increase in the rates of seropositivity against any serotype after any control vaccination.

In addition, GMTs remained similar to baseline levels after each vaccination within each age group.

Overall, the same trends were observed 1 year, 2 years, 3 years and 4 years after the third control vaccination.

### **JAPANESE ENCEPHALITIS (JE) SEROLOGY**

Baseline seropositivity against the JE virus (i.e.,  $\geq 10$  [1/dil]) was similar in both study groups (37.0% [44/119] in the dengue group and 41.7% [25/60] in the control group). Across the 2 study groups, the percentage of seropositive subjects (38.5% [69/179]) was lower than the percentage of seronegative ( $< 10$  [1/dil]) subjects (61.5% [110/179]).

#### *Age cohort comparison*

The same trend of the percentage of seropositive subjects being lower than the percentage of seronegative subjects was seen in children (both 2 to 5 years and 6 to 11 years). In adolescents and adults, however, the proportion of seropositive subjects was higher (65.5% [19/29] in adolescents and 86.7% [26/30] in adults) than the proportion of seronegative subjects (34.5% [10/29] in adolescents and 13.3% [4/30] in adults).

In both study groups, baseline GMTs were lower in children (2 to 11 years) (7.28 [1/dil] in children [2 to 5 years] and 9.04 [1/dil] in children [6 to 11 years]) than in adolescents and adults (41.0 [1/dil] in adolescents and 160 [1/dil] in adults).

### **SYMPTOMATIC DENGUE CASES**

Symptomatic dengue was defined as temperature  $\geq 38^{\circ}\text{C}$  for  $\geq 48$  hours with suspicion of dengue. Symptomatic dengue cases were detected after each vaccination up to four years after the third vaccination. During the entire study, symptomatic dengue was reported in 9 subjects (3.3% [4/120] in the dengue group and 8.3% [5/60] in the control group).

Following the first vaccination, there were 2 cases of symptomatic dengue that occurred  $> 28$  days after the first vaccination (one case in the dengue group and one case in the control group and both were considered as probable (i.e., IgM positive [ $> 1$ ] in the acute or convalescent samples and/or a 4-fold increase of IgG between the acute and the convalescent samples with IgG positive [ $> 1$ ] in convalescent sample) dengue cases that were not virologically-confirmed.

Following the second vaccination, there were 3 cases of symptomatic dengue. In the dengue group, there was one case reported that occurred within 28 days of the second vaccination and was neither determined as probable nor virologically-confirmed. In the control group, there were two virologically-confirmed cases with serotype 1 (positive with dengue WT RT-PCR [ $\geq$  LLOQ] and / or dengue NS1 Ag ELISA [ $\geq 1$ ]) that occurred  $> 28$  days after the second vaccination.

Following the third vaccination, there were 4 cases of symptomatic dengue that occurred > 28 days after the third vaccination. Two cases occurred approximately 3 months after the third vaccination both in the dengue group and were neither determined as probable nor virologically-confirmed. Two cases occurred approximately 15 months after the third vaccination both in the control group. One was determined to be probable dengue case and one was determined to be virologically-confirmed dengue case with serotype 4, with baseline GMT against serotype 4 of 23 (1/dil) and 33 (1/dil) 1 year after the third injection.

Up to 6 months after the third vaccination, four symptomatic dengue cases (1 in the dengue group [Subject] and 3 in the control group [Subjects]) required hospitalization and were thus considered as a SAE by the Investigator as per the protocol definition. None were considered as related to vaccination by the Investigator or the Sponsor.

Of the total of 9 subjects with febrile episodes, 8 subjects reported biological abnormalities. The proportion of Grade 3 abnormalities was lower in the dengue group (25.0% [1/4]) than in the control group (60.0% [3/5]).

Dengue cases were reviewed by an Independent Data Monitoring Committee and were considered as not related to the study vaccine.

All subjects fully recovered and continued the study.

No new symptomatic dengue case was detected up to the 4-year follow-up after the third vaccination for all subjects in the safety analysis set.

## **SAFETY**

There were no immediate unsolicited AEs (i.e., within the 30-minute observation period) in either study group following any vaccination.

### **SOLICITED REACTIONS**

#### **Solicited Injection Site Reactions**

##### After the first vaccination

Overall, in both study groups, pain was the most frequently reported injection site reaction followed, by a lesser extent, by erythema and swelling.

Pain was reported in a higher proportion of subjects in control group which received Meningococcal Polysaccharide Vaccine A + C (73.3% [44/60]) than in the dengue group (15.8% [19/120]).

A higher proportion of subjects also had erythema or swelling in the control group (16.7% [10/60], and 6.7% [4/60], respectively) than in the dengue group (4.2% [5/120], and 1.7% [2/119], respectively).

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

##### *Age cohort comparison*

The rates of pain were higher in the control group (50.0% [10/20]) in children [2 to 5 years], 95.0% [19/20] in children [6-11 years], 80.0% [8/10] in adolescents [12 to 17 years] and 70.0% [7/10] in adults [18 to 45 years]) than in the dengue group (7.5% [3/40] in children [2 to 5 years], 15.0% [6/40] in children [6 to 11 years], 25.0% [5/20] in adolescents [12 to 17 years] and 25.0% [5/20] in adults [18 to 45 years]).

The same trend of a higher proportion of subjects having erythema or swelling in the control group was also observed within each age group except in adults (18 to 45 years) where only 1 subject in the dengue group had swelling (5.0% [1/20]). No swelling occurred in adolescents (12 to 17 years) in either group.

##### After the second vaccination

Similarly to after the first vaccination, overall, in both study groups, pain was the most frequently reported solicited injection site, followed, to a lesser extent, by erythema and swelling in both study groups.

Pain was reported in a similar proportion of subjects in both study groups (15.5% [18/116] for the dengue group and 15.5% [9/58] for the control group which received placebo). Erythema and swelling were also reported in a similar proportion of subjects in both study groups (4.3% [5/116] and 2.6% [3/116], respectively for the dengue group and 5.2% [3/58] and 3.4% [2/58], respectively for the control group).

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

In the dengue group, the rates of solicited injection site reactions were similar after the first and second vaccinations.

No subject experienced a Grade 3 injection site reaction in either study group.

#### *Age cohort comparison*

The rates of pain in children (2 to 5 years) were higher in the control group (15.8% [3/19]) than in the dengue group (5.1% [2/39]); the rates of pain in children (6 to 11 years) were similar in both the dengue group (21.1% [8/38]) and in the control group (20.0% [4/20]); the rates of pain in adolescents (12 to 17 years) were higher in the dengue group (40.0% [8/20]) than in the control group (11.1% [1/9]); and in adults (18 to 45 years) pain was only reported in the control group (10.0% [1/10]).

The rates of erythema and swelling were also reported in a similar proportion of subjects within each age group.

#### After the third vaccination

Similarly to the first and second vaccination, overall, in both study groups, pain was the most frequently reported solicited injection site.

Pain was reported in a higher proportion of subjects in the control group which received Typhim Vi vaccine (41.4% [24/58]) than in the dengue group (11.4% [13/114]).

The rates of erythema were higher in the control group (5.2% [3/58]) than in the dengue group (2.6% [3/114]).

No swelling was reported in the dengue group. In the control group, the rate of swelling was 6.9% (4/58).

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

In the dengue group, the rates of solicited injection site reactions were less frequent after the third vaccination than after the first and second vaccinations.

No subject experienced a Grade 3 injection site reaction in either study group.

#### *Age cohort comparison*

Pain was reported in a higher proportion of subjects in control group in all age groups.

The rates of erythema were higher in the control group than in the dengue group in all age groups except that no erythema occurred in the control group in children (6 to 11 years) and no erythema occurred in the dengue group in children (2 to 5 years) or in adults (18 to 45 years).

In the dengue group, in general, the rates of solicited injection site reactions were less frequent after the third vaccination than after the first and second vaccinations.

### **Solicited Systemic Reactions**

#### After the first vaccination

In the dengue group, headache, malaise, fever, and myalgia were the most frequently reported solicited systemic reactions, followed, to a lesser extent, by asthenia.

In the control group which received Meningococcal Polysaccharide Vaccine A + C, headache, myalgia, malaise and fever were the most frequently reported solicited systemic reactions; no asthenia was reported in the control group.

The rates of headache, malaise, fever, and myalgia were similar in both study groups (29.4% [35/119], 21.8% [26/119], 19.2% [23/120], and 15.1% [18/119], respectively in the dengue group and 28.3% [17/60], 16.7% [10/60], 15.0% [9/60], and 20.0% [12/60], respectively in the control group).

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

Four subjects (2 subjects in the dengue group and 2 subjects in the control group) had Grade 3 reactions.

#### *Age cohort comparison*

In the dengue group, the most frequently reported reactions were: headache, fever and malaise (7.7% [3/39]) for each of these reactions in children (2 to 5 years); malaise (13.5% [5/37]) in children (6 to 11 years); headache (50.0% [10/20]) in adolescents (12 to 17 years); and headache (5.3% [1/19]) and myalgia (5.3% [1/19]) in adults (18 to 45 years).

In the control group, the most frequently reported reactions were: fever (10.0% [2/20]) in children (6 to 11 years); headache (44.4% [4/9]) in adolescents (12 to 17 years); and malaise (20.0% [2/10]) in adults (18 to 45 years); for children (2 to 5 years) the rates of each solicited systemic reactions were the same at 5.3% (1/19).

In all age groups, solicited systemic reactions were less frequent after the second vaccination than after the first vaccination except in adolescents (12 to 17 years) where solicited systemic reactions were higher for some reactions following the second vaccination.

#### After the second vaccination

In the dengue group, headache, malaise and fever were the most frequently reported solicited systemic reactions.

In the control group which received placebo, headache, malaise, fever and myalgia were the most frequently reported solicited systemic reactions, followed by a lesser extent, by asthenia.

The rates of headache, malaise, fever, myalgia and asthenia were higher in the dengue group (15.7% [18/115], 13.0% [15/115], 12.1% [14/116], 9.6% [11/115], and 6.1% [7/115], respectively) than in the control group (8.6% [5/58], 8.6% [5/58], 6.9% [4/58], 5.2% [3/58], and 1.7% [1/58], respectively).

In both groups, solicited systemic reactions were less frequent after the second vaccination than after the first vaccination.

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

#### *Age cohort comparison*

In the dengue group, the most frequently reported reactions were: fever (22.5% [9/40]) in children (2 to 5 years); headache (28.2% [11/39]) in children (6 to 11 years); headache (45.0% [9/20]) in adolescents (12 to 17 years); and headache (35.0% [7/20]) and malaise (35.0% [7/20]) in adults (18 to 45 years).

In the control group, the most frequently reported reactions were: fever (20.0% [4/20]) and headache (20.0% [4/20]) in children (2 to 5 years); headache (35.0% [7/20]) in children (6 to 11 years); headache (50.0% [5/10]) in adolescents (12 to 17 years); and malaise (40.0% [4/10]) in adults (18 to 45 years).

In all age groups, solicited systemic reactions were less frequent after the second vaccination than after the first vaccination except in adolescents (12 to 17 years) where solicited systemic reactions were higher for some reactions following the second vaccination.

#### After the third vaccination

In the dengue group, headache, malaise and myalgia were the most frequently reported solicited systemic reactions.

In the control group which received Typhim Vi vaccine, headache, myalgia, fever and malaise were the most frequently reported solicited systemic reactions, followed by a lesser extent, by asthenia.

The rates of headache, myalgia, fever, malaise and asthenia were higher in the control group (10.3% [6/58], 10.3% [6/58], 8.6% [5/58], 8.6% [5/58], and 3.4% [2/58], respectively) than in the dengue group (8.8% [10/114], 4.4% [5/114], 3.5% [4/114], 5.3% [6/114] and 0.9% [1/114], respectively).

In the dengue group, solicited systemic reactions were less frequent after the third vaccination than after the first and the second vaccinations.

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

No subject experienced a Grade 3 systemic reaction in either study group.

#### *Age cohort comparison*

In the dengue group, the most frequently reported reactions were: fever and malaise (2.6% [1/39]) for each of these reactions in children (2-5 years); headache and malaise (5.4% [2/37]) for each of these reactions in children (6 to 11 years); headache (25.0% [5/20]) in adolescents (12 to 17 years); and headache (16.7% [3/18]) in adults (18 to 45 years).

In the dengue group, solicited systemic reactions were less frequent after the third vaccination than after the first and the second vaccinations in all age groups except in adults where headache and malaise were reported in a slightly higher proportion of subjects.

In the control group, the most frequently reported reactions were: fever (10.5% [2/19]) in children (2 to 5 years); headache (10.0% [2/20]) in children (6 to 11 years); headache (33.3% [3/9]) in adolescents (12 to 17 years); and malaise (30.0% [3/10]) in adults (18 to 45 years).

In summary, after any CYD dengue vaccination, the rates of solicited AEs tended to be lower in children (2 to 5 years) and children (6 to 11 years) than in adolescents (12 to 17 years) and adults (18 to 45 years).

### **Unsolicited AEs**

#### After the first vaccination

The rates of unsolicited AEs were similar in both groups (20.8% [25/120] in the dengue group and 26.7% [16/60] in the control group which received Meningococcal Polysaccharide Vaccine A + C). For both study groups, the most frequently reported unsolicited AEs were in the SOC of infections and infestations (14.2% [17/120] in the dengue group and 18.3% [11/60] in the control group).

A total of 2 subjects (one in the dengue group and one in the control group) had a Grade 3 unsolicited non-serious systemic AEs; and none were considered as related to vaccination:

In the dengue group, 2 subjects reported at least 1 unsolicited reaction (AR) (1.7% [2/120]). For both subjects, the ARs were considered related to vaccination as defined in the protocol but reported as non-serious of Grade 1 intensity:

One SAE occurred within 28 days of the first vaccination in the dengue group. This SAE was assessed by the Investigator as not related to the study vaccine.

#### *Age cohort comparison*

Similarly by age group, the rates of unsolicited AEs were similar in both groups and the most frequently reported unsolicited AEs were in the SOC of infections and infestations.

#### After the second vaccination

The rates of unsolicited AEs were similar in both groups (8.6% [10/116] in the dengue group and 5.2% [3/58] in the control group which received placebo) and these rates were lower than after the first vaccination. For both study groups, the most frequently reported unsolicited AEs were in the SOC of infections and infestations (6.0% [7/116] in the dengue group and 3.4% [2/58] in the control group).

No Grade 3 unsolicited AEs were reported after the second vaccination in either study group.

There was 1 unsolicited AR in the dengue group

No SAEs occurred within 28 days of the second vaccination in either group.

#### After the third vaccination

No unsolicited AEs were reported after the third vaccination in the control group which received Typhim Vi vaccine).

In the dengue group, unsolicited AEs were less frequent after the third vaccination (2.6% [3/114]) than after the first vaccination (20.8% [25/120]) and the second vaccination (8.6% [10/114]) vaccination.

The 3 unsolicited AEs in the dengue group occurred in the SOCs of infections and infestations; injury, poisoning and procedural complications; and reproductive system and breast disorders, respectively.

No Grade 3 unsolicited AEs were reported after the third vaccination in the dengue group.

There were no ARs or SAEs that occurred within 28 days of the third vaccination in the dengue group.

Overall, the reactogenicity decreased after the second and third doses of CYD dengue vaccine in all age groups, and even tended to be similar or lower than the reactogenicity profile of the control vaccines (Meningococcal Polysaccharide Vaccine A + C, placebo, and Typhim Vi vaccine).

In summary, after any CYD dengue vaccination, the rates of unsolicited AEs tended to be lower in children (2 to 5 years) and children (6 to 11 years) than in adolescents (12 to 17 years) and adults (18 to 45 years). Solicited and unsolicited events in vaccinated subjects were mostly mild, of short duration, and reversible. Furthermore, AEs and SAEs were mostly unrelated to vaccination and were medical conditions commonly associated with these age groups.

**Serious Adverse Events (SAEs)**

A total of 6 non-fatal SAEs occurred during the trial (3 in the dengue group and 3 in the control group) and none were considered related to the study vaccines by both the Investigator and the Sponsor.

In the dengue group, all SAEs occurred after the first vaccination

All subjects fully recovered and continued the study.

In addition, during the long-term follow-up, 1 fatal SAE was reported after the third vaccination in the control group. This SAE was assessed by the Investigator as not related to vaccination.

***Dengue and dengue vaccine viremia***

There were 3 virologically-confirmed dengue cases that occurred within the first year of the study (all in the control group).

No dengue vaccine viremia was detectable by RT-PCR.

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