These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** 2014-001534-29 **Study code:** CYD05
Title of the study: Safety of ChimeriVax™ Dengue Tetravalent Vaccine in Subjects Aged 2 to 45 Years in the Philippines.	
Study center(s): One center in the Philippines	
Study period: Date first subject enrolled: 02/Mar/2006 Date last subject completed: 09/Oct/2007	
Phase of development: Phase I	

Objectives:

1) To describe the **safety** of each injection of ChimeriVax™ dengue tetravalent vaccine in four age groups of subjects: adults (18 to 45 years), adolescents (12 to 17 years), children (6 to 11 years), and children (2 to 5 years).
2) To describe **viremia** after each injection of ChimeriVax™ dengue tetravalent vaccine in the four age groups of subjects.
3) To describe the **humoral immune response** against dengue before injection, and after each injection of ChimeriVax™ dengue tetravalent vaccine in the four age groups of subjects.
4) To evaluate **the persistence of antibodies** against dengue during five years after the last injection of ChimeriVax™ dengue tetravalent vaccine in the four age groups of subjects.

Methodology:

Blind observer (first injection) and open (second and third injections), monocenter, randomized, controlled, Phase I study in 126 subjects in the Philippines: 18 adults, 36 adolescents aged 12 to 17 years, 36 children aged 6 to 11 years, and 36 children aged 2 to 5 years.

Three injections were given on D0 (V01), D105 (V06) and D365 (V11) to two groups of subjects for each age cohort: Group 1 (dengue vaccine) and Group 2 (Control Group).

Group 1 received the dengue vaccine as first, second, and third injections.

Group 2 (control group) received typhoid vaccine (Typhim Vi®) as first injection and dengue vaccine as second and third injections.

As a safety precaution, this trial used a stepwise approach: adults (18 to 45 years) were vaccinated first, then adolescents (12 to 17 years), then children aged 6 to 11 years, and finally children aged 2 to 5 years.

For adults, the safety data recorded up to 28 days after the first injection was evaluated by an Independent Data Monitoring Committee (IDMC). For adolescents and children the safety data recorded up to 14 days after the first injection was evaluated by the IDMC. The decision on whether or not to proceed with the enrolment of each following age cohort and to proceed with further injections for the ongoing cohort was taken by the Sponsor and the Principal Investigator, based upon the recommendations of the IDMC.

For the second and third injections, the subjects from the different age cohorts were vaccinated with at least 14-day intervals, starting with adults. If one of the stopping rules applied, vaccinations were to be suspended during IDMC safety review. The Sponsor and the Principal Investigator were to decide whether to continue, based on IDMC recommendations.

Number of subjects:	Planned: 126 subjects corresponding to 84 subjects in the Group 1 (i.e. 12 subjects for adults and 24 subjects for each non-adult group) and 42 subjects in the Group 2 (i.e. 6 subjects for adults and 12 subjects for each non-adult group) Randomized: 126 (84 in Group 1, 42 in Group 2) Treated: 126
Evaluated:	
	Immunogenicity: 126 Safety: 126

Diagnosis and criteria for inclusion:

Inclusion criteria were checked at Screening only (Scr.), at Screening and at the first vaccination visit (Scr.+V01), or at the first vaccination visit only (V01).

1) Aged 2 to 45 years on the day of inclusion (Scr.).
2) Informed consent form signed by the subject and by the parent(s) or another legal representative for subjects under 18 years old (Scr.).
3) For a woman, inability to bear a child or negative serum pregnancy test at screening (Scr.).
4) Able to attend all scheduled visits and to comply with all trial procedures (Scr.+V01).
5) For a woman of childbearing potential, use of an effective method of contraception or abstinence for at least 4 weeks prior to the first vaccination and at least 4 weeks after each vaccination (Scr.+V01).
6) For a woman, inability to bear a child or negative urine pregnancy test on the day of the first injection (V01).

Study treatments

Investigational Product: ChimeriVax™ Dengue Tetravalent Vaccine

Form: Liquid/Frozen

Composition: Each 0.5 mL dose contains: ~5 log_{10} cell culture infectious dose 50% ($CCID_{50}$) of each chimeric dengue serotype (1, 2, 3, 4)

Route of administration: Subcutaneous (SC)

Control Product: Typhim Vi®

Form: Liquid

Composition: Each 0.5 mL dose contains:

- *Salmonella typhi* (Ty2 strain) purified Vi capsular polysaccharide	25 µg
- phenol (as preservative)	0.25% w/v
- isotonic buffer solution	up to 0.5 mL

Route of administration: SC

Duration of participation: The expected total duration of follow-up is five years for each subject (including the four-year follow-up after the third vaccination).

Criteria for evaluation:

Safety

- Occurrence, time to onset, number of days of occurrence, severity, and action taken of solicited (i.e., prelisted in the subject's diary card and Case Report Form, CRF) injection site reactions occurring up to 7 days after each injection and solicited systemic reactions occurring up to 14 days after each injection.
- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time to onset, duration, severity, action taken, and relationship to vaccination of unsolicited (spontaneously reported) injection site and systemic adverse events (AEs) up to 28 days after each injection.
- Serious adverse events (SAEs) throughout the trial as follows: all SAEs up to V13 (i.e., 28 days after the third injection), and only SAEs that were neither accidents, hospitalizations related to the treatment of pre-existing conditions, or planned surgeries during the 4-year follow-up period (from V13 to V17). Deaths were collected whatever the cause.
- Occurrence and timing of out-of-normal-range biological test results up to 28 days after each injection.

Viremia

- Occurrence and maximum level of the four dengue serotypes in sera collected on the day of each injection, 7 and 14 days following the first and the second injections, and 7 days following the third injection in all the subjects: quantitative and serotype-specific reverse transcriptase-polymerase chain reaction (RT-PCR) and dengue plaque assay (PA).

Humoral Immune Response

- Neutralizing antibody levels against each of the four parental dengue virus serotype strains of ChimeriVax™ dengue tetravalent vaccine constructs and against the Thai Mahidol four dengue virus serotype strains, were measured on sera collected in all the subjects before injection, and 28 days after the first, second, and third injections (Plaque Reduction Neutralization Test, PRNT) and each year during four years after the last study injection (by microneutralization, only with the parental dengue virus serotype strains of ChimeriVax™. dengue tetravalent vaccine constructs). Additional PRNT could be set up with other dengue strains if relevant (World Health Organization strains).
- Non-serotype specific Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibody levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) before injection and 28 days after the first, second, and third injections.

Statistical methods:

The analysis was descriptive and presented by group with 95% Confidence Intervals (CIs) for main parameters. Listings of uncleaned safety data were performed by Data Management after each age cohort had completed Day 14 visit (including viremia data). These data were provided by the Sponsor to the IDMC. The main listings included in this analysis were defined in agreement with the members of the IDMC. Two interim statistical analyses of safety, viremia, and immunogenicity were performed on unblinded Day 28 data of the first and second injections in the whole study population.

Summary:

Population characteristics

For the first vaccination, 84 subjects received Sanofi Pasteur's dengue vaccine (Group 1) and 42 subjects received Typhim Vi® (Group 2). For the second vaccination, 3 to 4 months after the first vaccination, 82 subjects in Group 1 and 39 in Group 2 received the dengue vaccine. For the third vaccination, one year after the first one, 80 subjects in Group 1 and 39 subjects in Group 2 received the dengue vaccine.

Five subjects discontinued the study between the first two vaccinations: three subjects (two subjects in Group 1, and one subject in Group 2) were withdrawn after experiencing biological abnormalities (increase of either aspartate aminotransferase [AST]/alanine aminotransferase [ALT] or creatine phosphokinase [CPK]), one subject voluntarily withdrew and the other one did not comply with the protocol in Group 2. In addition, two subjects in Group 1 discontinued the study between the second and third vaccinations: one subject experienced elevated AST/ALT at the pre-vaccination 3 visit, and the second subject did not comply with the protocol.

Demographic characteristics were similar in the two groups with slightly more female than male subjects in Group 2.

Safety

During the study, two subjects in Group 2 experienced one SAE each after the second vaccination: one subject experienced an episode of dyspepsia (not related) associated with pyrexia (related by default as solicited reaction) 2 days after the dengue vaccination. The same subject had a second episode of dyspepsia approximately 2 months later (second episode was associated with upper respiratory tract infection). Another subject developed urinary tract infection (not related). No SAEs were reported after the first or third vaccination.

All injection site reactions were mild or moderate and most were present for a maximum of 3 days. No severe injection site reaction occurred during the study. More injection site reactions were observed in Group 2 (83.3% of subjects) than in Group 1 (29.8%) after the first vaccination (Typhim Vi® vaccination vs dengue vaccine vaccination).

Pain was the most frequent injection site reaction after one, two, or three vaccinations, followed by erythema and edema. The proportion of subjects who reported at least one episode of pain within the 7 days after the first vaccination was: 21 subjects (25.0%) in Group 1 (who received the dengue vaccine) and 28 subjects (66.7%) in Group 2 (after Typhim Vi® vaccination). After the second vaccination (with dengue vaccine in both groups), the proportion of subjects reporting pain was 15 subjects (18.3%) in Group 1 and 10 subjects (25.6%) in Group 2, and after the third vaccination 11 subjects (13.8%) in Group 1 and 10 subjects (25.6%) in Group 2.

Headache was the most frequently reported solicited systemic reaction after each vaccination (from 35.7% to 28.0% and to 17.5% in Group 1 after the first, second and third doses of dengue vaccine respectively, and from 23.8% [after Typhim Vi® vaccination) to 25.6% and to 20.5% in Group 2 after the first and second doses of dengue vaccine, respectively) followed by malaise, myalgia, fever and asthenia. In the two groups after each vaccination, most episodes of solicited systemic reactions occurred between D0 and D3 post-vaccination (until D7 for fever), and were present for a maximum of 3 days. Most episodes were mild to moderate and resolved spontaneously.

A trend towards a decrease of both injection site and systemic reactions after the first dose of dengue vaccine was noticed when moving from adult to younger populations (except for asthenia in adolescents and pyrexia in children). A trend of decreased reactogenicity was also noticed after the second and third doses of dengue vaccine.

Three severe reactions (fever) were reported, but no vaccinal viremia was detected in these subjects by quantitative RT-PCR. One case occurred on Day 1 after the first dose of dengue vaccine and was concomitant with an acute bronchitis. The second case was related to a wild type dengue serotype 3 infection concomitant with the second vaccination with dengue vaccine. The last case occurred on Day 7 after the second dose of dengue vaccine (2 days of fever at 38 to 39°C), and no other etiology than vaccination itself could be identified.

Unsolicited AEs were reported in 48.8% of subjects in Group 1 and 54.8% in Group 2 after the first vaccination. These proportions were stable after the second and third vaccinations (51.2% in Group 1 and 61.5% in Group 2, and 48.8% in Group 1 and 53.8% in Group 2, respectively). The most frequently reported unsolicited AEs were upper respiratory tract infection and neutropenia in the two groups.

There were few biological abnormalities reported after each vaccination. Most changes in biological parameters were mild and transient, and not deemed clinically significant (without medical consequences) by the Investigator. Cases of CPK increases were quite constantly reported during the trial and reported as linked to physical activity in most cases.

A limited number of biological abnormalities were reported as severe: one subject in Group 2 presented an increase in CPK after the first vaccination with Typhim Vi®, two subjects in Group 1 reported increases in CPK rates after the second and third doses of dengue vaccine, respectively. There was no link between these severe abnormalities and occurrence of clinical adverse reactions or vaccinal viremia.

Viremia

After each vaccination vaccinal viremia was observed at low levels: the viremia was quantified by PCRs from only 6, 2 and no subjects 7 days after the first, second and third doses of dengue vaccine respectively (none by PA). At the peak of viremia, 7 days after the first dose of dengue vaccine, 12 subjects (14.3%) in Group 1 and 7 subjects (17.9%) in Group 2 had a non serotype-specific viremia detected with the yellow fever reverse transcriptase polymerase chain reaction (YF RT-PCR). Viremia was most frequently detected in adults and adolescents.

Seven days after the second dose of dengue vaccine (i.e. second vaccination in Group 1, and third vaccination in Group 2), viremia by YF RT-PCR was detected in five subjects (12.8%) in Group 2 and four subjects (4.9%) in Group 1, mainly in children.

Seven days after the third dose of dengue vaccine (i.e. third vaccination in Group 1), viremia by YF RT-PCR was detected in five subjects (6.3%) in Group 1.

The serotype 4 was the serotype the most frequently detected with CYD RT-PCR, followed by the serotype 3.

Immunogenicity

Humoral Immune Response

Sanofi Pasteur's dengue vaccine induced a neutralizing antibody response to the four serotypes: Overall, geometric mean titers (GMTs) and percentage of seropositivity (antibody level ≥10 1/dil) increased after each vaccination for all serotypes.

A predominance of the immune response to serotype 4 was observed after the first dose of dengue vaccine. The second and third doses of dengue vaccines afforded a complementation of the immune response to the other serotypes, with an increasing proportion of seropositive subjects to the four serotypes, and an increase of the GMTs for all serotypes.

After the first dose of dengue vaccine (first vaccination in Group 1 and second vaccination in Group 2), GMTs and seropositivity rates were similar for Group 1 and Group 2. However, higher GMTs and seropositivity rates for all serotypes were recorded in Group 2 than in Group 1 after the second dose of dengue vaccine (given 8 to 9 months versus 3 to 4 months after the first dose). Moreover, GMTs and seropositivity rates in Group 2 after a two-dose vaccination schedule reached equivalent levels compared to Group 1 after the third vaccination.

Seropositivity rates and GMTs were similar when assessed with parental and Mahidol strains for each of the four serotypes, except against Mahidol strain serotype 2 where the rates of seropositivity (and GMTs) where lower compared to the parental strain.

The proportion of subjects with at least three successes against parental and Mahidol dengue strains (i.e. percentage of seropositivity for three or four dengue serotypes regardless of the serotype) increased with the successive vaccinations as follows: in Group 1 that received three doses of dengue vaccine, the proportion of subjects with at least three successes increased with the successive vaccinations (from 50.0% at inclusion to 65.5%, 80.5%, and 93.8% with parental strains; from 46.4% at inclusion to 58.3%, 72.0% and 86.3% with Mahidol strains). In Group 2 that received two doses of dengue vaccine, the proportion of subjects with at least three successes increased from 54.8% to 64.1% and 89.7% with parental strains, and from 50.0% to 59.0% and 79.5% with the Mahidol strains.

Similarly to GMTs and seropositivity rates, the proportion of subjects with at least three and four successes was similar in the two groups at the end of the vaccination schedule, i.e. after two doses given 8 to 9 months apart for Group 2 versus three doses given at 0, 3 to 4, and 12 months for Group 1.

As expected, IgM response was observed mainly after the first dose of dengue vaccine. Seropositivity was only 19.0% in Group 1 and 9.5% in Group 2, 28 days after the first dose of dengue vaccine, with no significant difference between age groups.

IgG response rates were high in Group 1 28 days after the first vaccination with dengue vaccine (97.6%), and reached 100.0% after the second vaccination. In Group 2, 100.0% of subjects were positive (antibody level ≥1 1/dil.) for IgG after the first administration of dengue vaccine.

Seropositivity against Typhoid Fever (TF) was observed in almost all subjects in Group 2 (95.2%) and none in Group 1 (except one adolescent who had Vi antibodies both before and after dengue vaccination).

Issue date: 22-Jun-2020

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** 2014-001534-29 **Study code:** CYD05
Title of the study: Safety of ChimeriVax™ Dengue Tetravalent Vaccine in Subjects Aged 2 to 45 Years in the Philippines.	
Study center(s): One center in the Philippines	
Study period: Date first subject enrolled: 02/Mar/2006 Date last subject completed: 11/Sep/2012	
Phase of development: Phase I	

Objectives:

1) To describe the **safety** of each injection of ChimeriVax™ dengue tetravalent vaccine (CYD dengue vaccine) in four age groups of subjects: adults (18 to 45 years), adolescents (12 to 17 years), children (6 to 11 years), and children (2 to 5 years).
2) To describe **viremia** after each injection of CYD dengue vaccine in the four age groups of subjects.
3) To describe the **humoral immune response** against dengue before injection, and after each injection of CYD dengue vaccine in the four age groups of subjects.
4) To evaluate **the persistence of antibodies** against dengue during five years after the last injection of CYD dengue vaccine in the four age groups of subjects.

Only objectives 3 and 4, as well as serious adverse events (SAEs) occurring during the follow-up are assessed and detailed in the present report. Details (endpoints, assessment methods, and results) linked to remaining objectives are provided in the interim CSR, version 1.0 dated 15 September 2008.

Methodology:

Blind observer (first injection) and open (second and third injections), monocenter, randomized, controlled, Phase I study in 126 subjects in the Philippines: 18 adults aged 18 to 45 years, 36 adolescents aged 12 to 17 years, 36 children aged 6 to 11 years, and 36 children aged 2 to 5 years.

Three injections were given on D0 (V01), D105 (V06) and D365 (V11) to two groups of subjects for each age cohort:

Group 1 received the CYD dengue vaccine as first, second, and third injections with a 0, 3/4, 12 months regimen.

Group 2 received typhoid vaccine (Typhim Vi) as first injection and CYD dengue vaccine as second and third injections 8/9 months apart.

As a safety precaution, this trial used a stepwise approach: adults (18 to 45 years) were vaccinated first, then adolescents (12 to 17 years), then children aged 6 to 11 years, and finally children aged 2 to 5 years.

For adults, the safety data recorded up to 28 days after the first injection was evaluated by an Independent Data Monitoring Committee (IDMC). For adolescents and children the safety data recorded up to 14 days after the first injection was evaluated by the IDMC. The decision on whether or not to proceed with the enrollment of each following age cohort and to proceed with further injections for the ongoing cohort was taken by the Sponsor and the Principal Investigator, based upon the recommendations of the IDMC.

For the second and third injections, the subjects from the different age cohorts were vaccinated with at least 14-day intervals, starting with adults. If one of the stopping rules applied, vaccinations were to be suspended during IDMC safety review. The Sponsor and the Principal Investigator were to decide whether to continue, based on IDMC recommendations.

After completion of the 3 vaccinations, subjects were asked to participate in a 4-year follow-up in order to evaluate the persistence of the humoral immune response and the long-term vaccine safety. After the 4-year follow-up visit, subjects were asked to come for an additional fifth-year follow-up visit.

The dengue neutralizing antibody assay applied to assess immunogenicity in CYD vaccine trials has evolved during the conduct of CYD05 study, from the Plaque Reduction Neutralization Test ($PRNT_{Phase\ I}$, to microneutralization, then to an optimized PRNT (a modified $PRNT_{Phase\ I}$). Table 1 below summarizes at which timepoint each test was used. The optimized PRNT, called here "PRNT" and used in the further phase II and phase III studies, has been used to re-test some samples of the vaccination period in order to be able to describe the kinetics of dengue neutralizing antibodies during the whole trial using the same neutralizing antibody assay.

Table 1: Neutralizing Antibody Titration Methods

Assays	Vaccination period						Follow-up				
	Baseline	Post-Vac1	Pre-Vac2	Post-Vac2	Pre-Vac3	Post-Vac3	Y1	Y2	Y3	Y4	Y5
	V01	V04	V06	V09	V11	V13	V14	V15	V16	V17	V18
$PRNT_{Phase\ I}$	X	X	X	X	X	X	X*				
PRNT	X			X		X	X	X	X	X	X
Microneutralization							X	X			

Post-Vac1: 28 days after the first vaccination; Post -Vac2: 28 days after the second vaccination; Post -Vac3: 28 days after the third vaccination; Pre-Vac2: day of second vaccination; Pre-Vac3: day of third vaccination
Y1: 1 year after the third vaccination; Y2: 2 years after the third vaccination; Y3: 3 years after the third vaccination; Y4: 4 years after the third vaccination; Y5: 5 years after the third vaccination.
*$PRNT_{Phase\ I}$ Y1: in a subset of the first 19 children enrolled in each children age-group (37 subjects in total; one subject was missing).

SAE that were neither accident, hospitalizations related to the treatment of pre-existing conditions, or planned surgeries were collected during the first 4 years of the follow-up (from V13 to V17). Hospitalized dengue cases occurring between V17 and V18 (and any reportable SAEs upon Investigator's judgment) were retrospectively collected at V18. Deaths were collected whatever the cause.

Number of subjects:

Planned: 126 subjects corresponding to 84 subjects in the Group 1 (i.e. 12 subjects for adults and 24 subjects for each non-adult group) and 42 subjects in the Group 2 (i.e. 6 subjects for adults and 12 subjects for each non-adult group)

Randomized: 126 (84 in Group 1, 42 in Group 2)

Treated: 126

Evaluated:

Immunogenicity: 126

Safety: 126

Follow-up Analysis Set: 120

Diagnosis and criteria for inclusion:

Inclusion criteria were checked at Screening only (Scr.), at Screening and at the first vaccination visit (Scr.+V01), or at the first vaccination visit only (V01).

1) Aged 2 to 45 years on the day of inclusion (Scr.).
2) Informed consent form signed by the subject and by the parent(s) or another legal representative for subjects under 18 years old (Scr.).
3) For a woman, inability to bear a child or negative serum pregnancy test at screening (Scr.).
4) Able to attend all scheduled visits and to comply with all trial procedures (Scr.+V01).
5) For a woman of childbearing potential, use of an effective method of contraception or abstinence for at least 4 weeks prior to

the first vaccination and at least 4 weeks after each vaccination (Scr.+V01).

6) For a woman, inability to bear a child or negative urine pregnancy test on the day of the first injection (V01).

Study treatments

Investigational Product: CYD Dengue Vaccine

Form: Liquid/Frozen

Composition: Each 0.5-mL reconstituted dose of CYD dengue vaccine that contained 5 +/-1 log_{10} cell culture infectious dose 50% ($CCID_{50}$) of each chimeric dengue serotype (1, 2, 3, 4).

Route of administration: Subcutaneous (SC)

Control Product: Typhim Vi vaccine

Form: Liquid

Composition: Each 0.5 mL dose contains:

- *Salmonella typhi* (Ty2 strain) purified Vi capsular polysaccharide	25 µg
- phenol (as preservative)	0.25% w/v
- isotonic buffer solution	up to 0.5 mL

Route of administration: SC

Duration of participation: The total duration for each subject was 6 years (including the five-year follow-up after the last vaccination).

Criteria for evaluation:

Safety

- Occurrence of SAEs over the safety observation period by treatment group, in each age group and overall.

  Note: SAEs that were neither accidents, hospitalizations related to the treatment of pre-existing conditions, or planned surgeries were collected during the first 4 years of the follow-up (from V13 to V17). Hospitalized dengue cases occurring between V17 and V18 (and any reportable SAEs upon Investigator's judgment) were retrospectively collected at V18. Deaths were collected whatever the cause.

Humoral Immune Response

- Geometric mean of titers (GMTs) against each of the four serotypes with the parental dengue virus strains of tetravalent dengue vaccine
- Geometric mean of individual titer ratios (GMTRs)

  Post-inj 2 / Pre-inj 1

  Post-inj 3 / Pre-inj 1

  Post-inj 3 / Post-inj 2
- Number and percentage of subjects ≥ 10 (1/dil) against each of four serotypes with the parental dengue virus strains.
- Number and percentage of subjects ≥ 10 (1/dil) against at least 1, 2, 3, or 4 serotypes with the parental dengue virus strains.
- Number and percentage of subjects with neutralizing Ab titer ≥ various titer thresholds against at least 1, 2, 3, or 4 parental dengue virus serotypes.
- Distribution of titers against each of four serotypes with the parental dengue virus strains.

Additionally, detailed descriptive immunogenicity results were given including mean, median and range of titers, and log_{10} titer mean and standard deviation (SD).

Statistical methods:

The analysis was descriptive and presented by vaccine group and age group with 95% Confidence Intervals (CIs) for main parameters.

Three analyses were done on data collected 28 days after the first, second and third injections. These results are described in the interim CSR. In addition, yearly analyses were performed for the assessment of antibodies persistence and long term safety. The analysis performed 5 years after the last injection included immunogenicity re-test assessed with the PRNT assay.

Summary:

Population characteristics

A total of 126 subjects were randomized (18 adults, 36 adolescents, 36 children aged 6 to 11 years and 36 children aged 2 to 5 years) with respectively 84 and 42 subjects in Group 1 and in Group 2, in accordance with the protocol.

All subjects received the first injection at V01. A total of 7 subjects discontinued the trial during the vaccination period (4 subjects in Group 1 and 3 subjects in Group 2): 5 subjects discontinued after the first injection and did not receive the second and third injections, and 2 subjects discontinued after the second injection and did not receive the third injection. The discontinuations were due to AEs, non-compliance with the protocol, and voluntary withdrawal.

A total of 120 subjects were enrolled in the long term follow-up and only 7 subjects did not complete the 5-year follow-up period; 4 subjects in Group 1 and 2 subjects in Group 2 because of non-compliance with the protocol (they missed at least 1 of the follow-up visits), and 1 subject in Group 2 was lost to follow-up.

Overall, the participation rate was high.

Demographic characteristics, i.e., age, male/female ratio were similar between the two vaccine groups allowing for descriptive comparison between the two treatment groups. However, flavivirus (FV) status at baseline was slightly different between the two treatment groups, in the overall population and in the pediatric populations.

Safety

Safety during the follow-up

No SAE were reported up to 4 years after the last vaccination. No safety concerns emerged during the conduct of the long-term follow-up.

During the fifth year of the follow-up, 2 SAEs were reported:

- A subject who was an adolescent at the time of enrollment in Group 1 experienced an SAE (myofascial pain syndrome), which was not considered by the Investigator to be related to treatment.
- A child who was aged 2 to 5 years at the time of enrollment in Group 1 was hospitalized due to a dengue episode which was therefore reported as an SAE. This hospitalized dengue case occurred in a subject who had low neutralizing antibody titers against each serotype at the pre-infection assessment timepoint (at V17, maximal neutralizing titer was at 51 [against serotype 3], with neutralizing titer to serotype 1 <10). Dengue infection by serotype 1 was confirmed by RT-PCR. There were no signs of severity (no sign of shock, no hemorrhage, no signs of plasma leakage, and no thrombocytopenia) and the subject recovered 4 days after fever onset and was discharged 2 days later (6 days after fever onset).

A total of 4 pregnancies were reported up to the end of the pregnancy follow-up period, i.e., up to 2 years after the last vaccination (3 pregnancies in Group 1 and 1 in Group 2). None of the mothers were exposed to vaccination during their pregnancy, i.e., all pregnancies were reported at least 315 days after the last vaccination.

Immunogenicity

- Vaccination phase with the PRNT assay

Seropositivity against each dengue virus serotype

Across the 2 treatment groups, the percentage of seropositive subjects against each serotype at baseline tended to be lower for serotype 1 compared to the other serotypes. In children aged 6 to 11 years and in adolescents groups, baseline seropositivity rates were higher in Group 2 than in Group 1. In children aged 2 to 5 years and in adults groups, baseline seropositivity rates in Group 1 and in Group 2 were within similar ranges. In young populations, after the second dose of CYD dengue vaccine, which was given 3/4 months and 8/9 months after the first dose respectively in Group 1 and in Group 2, seropositivity rates against each serotype in Group 2 were higher than in Group 1. After the third dose of CYD dengue vaccine in Group 1, the increase of proportions of seropositive subjects was mainly observed for serotype 1 in children aged 2 to 5 years followed by children aged 6 to 11 years.

Seropositivity against at least 1, 2, 3, or 4 dengue virus serotypes

Baseline seropositivity rates against at least 1, 2, 3, and all 4 serotypes in adolescents and children (6 to 11 years and 2 to 5 years) were lower in Group 1 than in Group 2, and they were within similar ranges in adults. Overall in all age groups, after the second dose of CYD dengue vaccine, which was given 3/4 months and 8/9 months after the first dose respectively in Group 1 and in Group 2, seropositivity rates against at least 3 and all 4 serotypes were slightly higher in Group 1 than in Group 2. After the third dose of CYD dengue vaccine in Group 1, seropositivity rates against at least 3 and all 4 serotypes further increased, more markedly in children (aged 2 to 5 years and 6 to 11 years) than in adolescents and in adults.

GMTs

In adults, adolescents and children aged 6 to 11 years, baseline GMTs (expressed in 1/dil) were lower in Group 1 than in Group 2, and in children aged 2 to 5 years, baseline GMTs were within similar ranges. In Group 2, after the first dose of CYD dengue vaccine, GMTs increased in each age group. After the second dose of CYD dengue vaccine, which was given 3/4 months and 8/9 months after the first dose respectively in Group 1 and in Group 2, GMTs in Group 1 were lower than in Group 2 in pediatric populations, while GMTs in adults were higher in Group 1 than in Group 2. After the third dose of CYD dengue vaccine in Group 1, GMTs in children groups were within similar ranges than after the second dose, except for serotype 1; and GMTs in adolescents and adults were similar or lower than after the second dose but remained higher than at baseline.

- 5-year Follow-up

Seropositivity against each dengue virus serotype assessed by the PRNT assay

One year after the last injection, seropositivity rates were similar between treatment groups for adults and children aged 2 to 5 years, were lower in Group 1 than in Group 2 for adolescents, and were slightly higher in Group 1 than in Group 2 for children aged 6 to 11 years. Overall, seropositivity rates during the remaining 4 years of the follow-up remained stable or fluctuated from year to year (increase followed by decrease and vice versa) in both treatment groups but remained high up to five years after the last injection as compared to baseline. At the end of the 5-year follow-up, seropositivity rates were similar between

Group 1 and Group 2 for adults and adolescents, and slightly lower in Group 1 than in Group 2 in children of both age groups. Five years after the last injection, seropositivity rates were similar to those observed after the end of the vaccination period in adults and adolescents, and were slightly lower in children (both age groups).

Seropositivity against at least 1, 2, 3, or 4 dengue virus serotypes assessed by the PRNT assay

One year after the last injection, seropositivity rates against at least 1, 2, 3, and all 4 serotypes were high in both groups and for each age group. At 1-year follow-up, seropositivity rates against all 4 serotypes in Group 1 tended to be higher than in Group 2 in adults and children of both age groups, and were lower in Group 1 than in Group 2 in adolescents. Overall, seropositivity rates during the remaining 4 years of the follow-up remained stable or fluctuated from year to year in both treatment groups but remained high up to five years after the last injection as compared to baseline. At the end of the 5-year

follow-up, seropositivity rates against at least 1, 2, 3, or all 4 serotypes were similar in both treatment groups in adults and adolescents, and were slightly lower in Group 1 than in Group 2 in children. At the end of the 5 year follow-up, seropositivity rates against all 4 serotypes were similar between treatment groups and, as compared to those observed at the end of the vaccination period, they were similar in adults and adolescents and slightly lower in children aged 2 to 5 years and 6 to 11 years.

GMTs assessed by PRNT assay

GMTs decreased during the follow-up period. The decrease was more pronounced during the first year of the follow-up, but 1 year after the last injection, GMTs remained 2- to 4-fold higher compared to baseline for all serotypes, all age groups, and in both treatment groups. Overall, 1 year after the last injection, GMTs were lower in Group 1 than in Group 2 in adults and adolescents, higher in Group 1 than in Group 2 in children aged 6 to 11 years, and similar between treatment groups in children aged 2 to 5 years. During the remaining 4 years of the follow-up period, GMTs fluctuated from year to year but remained overall similar to those observed 1 year after the last injection in both treatment groups. At the end of the 5-year follow-up period, GMTs were similar between treatment groups and were lower than after the vaccination period in both treatment groups and all age groups; however, 5 years after the last injection all GMTs remained high compared to baseline in both treatment groups.

GMTs 1 and 2 years *after the last injection assessed by microneutralization*

One year after the last injection, which corresponds to the third dose of CYD dengue vaccine in Group 1 and to the second dose of CYD dengue vaccine in Group 2, GMTs (expressed in 1/dil) were slightly higher in Group 2 than in Group 1: from 168 (serotype 4) to 342 (serotype 3) in Group 1 and from 217 (serotype 4) to 396 (serotype 2) in Group 2. Two years after the last vaccination, GMTs for serotypes 1, 2, and 3 in both groups increased compared to 1 year after the last injection, and GMTs for serotype 4 in both groups decreased. Overall, 2 years after the last injection, GMTs in Group 2 were confirmed to be slightly higher than in Group 1, ranged from 149 (serotype 4) to 581 (serotype 3) versus 116 (serotype 4) to 502 (serotype 3) in Group 1.

Neutralizing *antibody response 1 year after the last injection by* $PRNT_{Phase\ I}$ *versus Microneutralization against each dengue serotype*

One year after the last vaccination, sera collected from the first 19 children enrolled in both age-group (i.e., 37 sera in total; serum from 1 subject was missing) were assayed using the $PRNT_{Phase\ I}$ to describe the correlation between the $PRNT_{Phase\ I}$ and the microneutralization.

Overall, GMTs measured by both methods were higher in Group 1 than in Group 2. GMTs with the $PRNT_{Phase\ I}$ were higher than GMTs with the microneutralization assay, especially for the serotype 2.

Issue date: 22-Jun-2020