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Sponsor: Sanofi Pasteur	Study Identifiers: U1111-1114-7909, NCT01550289
Drug substance(s): CYD Dengue Vaccine	Study code: CYD47
Title of the study: Immunogenicity and Safety of a Tetravalent Dengue Vaccine in Healthy Adult Subjects Aged 18 to 45 Years in India	
Study center(s): This was a multi-center trial conducted in India with multiple investigators.	
Study period: Date first subject enrolled: 27/Mar/2012 Date last subject completed: 07/Dec/2013	
Phase of development: Phase II	
Objectives: Primary Objectives: <u>Immunogenicity:</u> To describe the neutralizing antibody (Ab) response to each dengue virus serotype before the first vaccination and after each vaccination with CYD dengue vaccine in all subjects. <u>Safety:</u> To describe the safety of the CYD dengue vaccine after each dose in all subjects. Secondary Objectives: <u>Detection of dengue cases:</u> To detect symptomatic dengue cases occurring at any time in the trial. <u>Immunogenicity:</u> To describe the Ab response to each dengue virus serotype before the first vaccination and after each vaccination according to FV immune status at baseline in all subjects. <u>Safety:</u> To describe the safety of CYD dengue vaccine after each dose according to the FV immune status at baseline in all subjects.	
Methodology: This was a multi-center, observer-blind, randomized, placebo-controlled, Phase II trial in 189 healthy adults aged 18 to 45 years in India. Each subject was to receive 3 injections (Day 0 [D0], D0+6 months, and D0+12 months), followed by a 6-month safety follow-up. There were 2 groups of subjects: <ul style="list-style-type: none">• CYD Dengue Vaccine group: 126 subjects were planned to receive CYD dengue vaccine at 0, 6, and 12 months.• Placebo group: 63 subjects were planned to receive a placebo at 0, 6, and 12 months	

<p>Number of subjects:</p> <p>Planned: 189 Randomized: 189</p> <p>Evaluated:</p> <p>Immunogenicity: 187 Safety: 188</p>
<p>Diagnosis and criteria for inclusion:</p> <p>A potential subject had to meet all of the following criteria to be considered for trial enrollment:</p> <ol style="list-style-type: none"> 1) Aged 18 to 45 years on the day of inclusion 2) Informed consent form has been signed and dated by the subject (and by an independent witness, if applicable) 3) Subject is able to attend all scheduled visits and to comply with all trial procedures 4) Subject in good health, based on medical history and physical examination
<p>Study treatments</p> <p>Investigational product: CYD Dengue Vaccine</p> <p>Formulation: 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;">4.5 – 6.0 log₁₀ cell -culture infectious dose 50% (CCID₅₀) of each live, attenuated, dengue serotype 1, 2, 3, 4 virus</p> <p>Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminomethane, and urea</p> <p>Solvent: NaCl 0.4%</p> <p>Route of administration: Subcutaneous (SC)</p>
<p>Control product: Placebo (sodium chloride, NaCl)</p> <p>Formulation: Solution</p> <p>Composition: NaCl 0.9%</p> <p>Route of administration: SC</p>
<p>Duration of participation: The treatment of each subject's participation in the trial was approximately 18 months</p>
<p>Criteria for evaluation:</p> <p>Primary Endpoints</p> <p><u>Immunogenicity:</u></p> <p>Neutralizing Ab levels against each of the four parental dengue virus strains of CYD dengue vaccine constructs were measured before the first vaccination and 28 days after each vaccination (dengue plaque reduction neutralization test [PRNT]).</p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> • 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 dose • Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (i.e., pre-listed in the subject's diary card and electronic case report form), injection site reactions occurring up to 7 days after each dose • Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited systemic reactions occurring up to 14 days after each dose • Occurrence, nature (MedDRA 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 dose • Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination of non-serious AESIs occurring up to 7 days after each dose

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

Secondary Endpoints:

Detection of dengue cases:

Using a definition aligned with the World Health Organization (WHO) case definition, in the event of temperature $\geq 38^{\circ}\text{C}$ on at least 2 consecutive days, the following tests were performed to identify any potential dengue case: dengue reverse transcriptase-polymerase chain reactions (RT-PCRs), dengue non-structural protein (NS) 1 antigen (Ag) enzyme-linked immunosorbent assay (ELISA) and immunoglobulin (Ig) M/IgG ELISA (at the Global Clinical Immunology [GCI] or GCI designated laboratory). Testing for biological parameters and routine diagnostic tests were set up locally for case management purposes.

Two consecutive febrile episodes were considered as separate episodes if the interval between these two episodes was > 14 days. An acute febrile episode was considered to have ended once the temperature was $< 38^{\circ}\text{C}$.

Flavivirus (dengue and Japanese encephalitis [JE]) serology:

Neutralizing Ab level against FV (dengue and JE) on a blood sample taken at V01 (dengue PRNT and JE PRNT).

In addition, the primary endpoints of safety and immunogenicity were used to evaluate the secondary objectives.

Statistical methods:

All analyses were descriptive; no hypotheses were tested.

The full analysis set and the per-protocol population were used for the main immunogenicity analyses, and the safety population was used for the safety analyses.

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

Exploratory analyses of immunogenicity data included the investigation of the baseline FV (dengue and JE) immune status effect.

A first statistical analysis was performed to address the safety and immunogenicity objectives post-Dose 3. This analysis was performed once the database obtained 28 days post-Dose 3 had been locked.

A final statistical analysis was produced after the 6-month safety follow-up.

Summary:

Population characteristics:

A total of 189 subjects were enrolled in the study: 128 subjects in the CYD dengue vaccine group and 61 subjects in the Placebo group.

From the 128 subjects randomized in the CYD dengue vaccine group, 127 (99.2%) subjects received the first injection and one subject in the CYD dengue vaccine group met the exclusion criterion #9 (chronic illness, type 2 diabetes mellitus) and did not receive vaccination. Hundred seventeen (91.4%) subjects received the second injection, and 115 (89.8%) subjects the received the third injection.

A total of 17 subjects (9.0%) discontinued the study: 10.2% (13/128) of the subjects in the CYD dengue vaccine group and 6.6% (4/61) of the subjects in the Placebo group. The reasons for not completing the study were voluntary withdrawal not due to an AE with 8.6% (11/128) of the subjects in the CYD dengue vaccine group and 4.9% (3/61) of the subjects in the Placebo group, non-compliance with the protocol with 0.8% (1/128) of the subjects in the CYD dengue vaccine group, and lost to follow-up with 0.8% (1/128) of the subjects in the CYD dengue vaccine group and 1.6% (1/61) of the subjects in the Placebo group. No subjects were withdrawn from the study due to SAE or AE.

All randomized subjects (except one in the CYD dengue vaccine group who did not comply with the protocol) were included in the safety analysis set for all doses. A total of 187 subjects out of the 189 subjects randomized (98.9%) were included in the FAS. There were 186/189 (98.4%) subjects included in the PP analysis set post-Inj 1, 166/189 subjects (87.8%) subjects were included in the PP analysis set post-Inj 2, and 172/189 subjects (91.0%) were included in the PP analysis set post-Inj 3.

Overall, 80.7% (151/187) of the subjects were male and 19.3% (36/187) of the subjects were female in the FAS. In both groups, the percentages of male subjects were higher than female subjects. The mean age was similar between the treatment groups, with an overall mean age of 29.5 years (range 18.0 to 45.5 years) at enrollment.

Immunogenicity:

The immunogenicity section provides results from the FAS. Similar results to the FAS were observed for the PP analysis set.

Primary objective: Ab response against each serotype after each injection

Seropositivity (Ab titer \geq 10 [1/dil]) against each dengue virus serotype

At baseline, the percentage of subjects who were seropositive for each dengue serotype was high and similar in both groups. In the CYD dengue vaccine group, the percentage of subjects ranged from 77.0% (97/126) for serotype 4 to 84.9% (107/126) for serotype 3; in the Placebo group, the percentage of subjects ranged from 80.3% (49/61) for serotypes 1 and 4 to 86.9% (53/61) for serotypes 2 and 3.

In the CYD vaccine group, seropositivity rates increased after each injection with a more pronounced increase post Inj 1. The seropositivity rates post-Inj 1 ranged from 91.2% (114/125) for serotype 1 to 98.4% (124/126) for serotype 3. At post-Inj 3, the net increase from baseline in the percentage of seropositive subjects was higher for serotype 4 (33.0%) as compared to the other serotypes which were similar: 14.1% for serotypes 1 and 2, and 14.2% for serotype 3. At post-Inj 3 in the CYD dengue vaccine group, seropositivity rates were 97.4%, 97.4%, 99.1%, and 100%, respectively for serotypes 1, 2, 3, and 4.

In the Placebo group, seropositivity rates against each serotype remained comparable to baseline and after each of the 3 injections. The seropositivity rates at post-Inj 1 ranged from 83.6% (51/61) for serotype 1 to 90.2% (55/61) for serotype 3. The seropositivity rates post-Inj 3 ranged from 84.2% (48/57) for serotype 4 to 91.2% (52/57) for serotype 2.

Seropositivity against at least 1, 2, 3 and all 4 serotypes

In the CYD dengue vaccine group, the percentage of subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes were 86.5% (109/126), 84.1% (106/126), 82.5% (104/126), and 75.4% (95/126), respectively. The increases in the percentages of subjects who were seropositive for at least 1 or at least 2 serotypes were more pronounced at post-Inj 1 (99.2% and 98.4% of subjects) than for the subsequent injections. The percentage of subjects who were seropositive for at least 3 or all 4 serotypes increased more gradually after first and second injections. No increase in seropositivity rates for at least 1 or 3 serotypes was observed at post-Inj 3 and a marginal increase was observed for at least 2 or all 4 serotypes. At post-Inj 3, all subjects (100% [115/115]) were seropositive for at least 1 serotype, 99.1% (114/115) were seropositive for at least 2 serotypes, and 97.4% (112/115) were seropositive for at least 3 serotypes or all serotypes.

In the Placebo group, the same range of seropositivity rate against 1, 2, 3 or all 4 serotypes was observed at baseline and after each of the 3 injections.

GMTs

In the CYD dengue vaccine group, the baseline GMTs were 184, 204, 219, and 55.4 (1/dil) for serotypes 1, 2, 3, and 4 respectively. After the first injection, GMTs increased from baseline and ranged from 358 (1/dil) for serotype 4 to 951 (1/dil) for serotype 3. For each serotype, the GMT tended to decrease at post-Inj 2 (except for serotype 2) and post-Inj 3 (except for serotype 4) but remained elevated versus baseline. At post-Inj 3, GMTs were 461, 484, 709, and 336 (1/dil) for serotypes 1, 2, 3, and 4, respectively. The GMTRs ranged from 3.23 for serotype 1 to 6.46 for serotype 4 (post-Inj 1 versus baseline), from 3.15 for serotype 1 to 5.16 for serotype 4 (post-Inj 2 versus baseline), and from 2.64 for serotype 1 to 6.11 for serotype 4 (post-Inj 3 versus baseline).

In the Placebo group, GMTs remained similar to baseline after each injection. The GMTRs ranged from 1.23 for serotypes 1 and 2 to 1.36 for serotype 3 (post-Inj 1 versus baseline), from 1.13 for serotype 3 to 1.26 for serotype 1 (post-Inj 2 versus baseline), and from 1.05 for serotype 2 to 1.44 for serotype 4 (post-Inj 3 versus baseline).

Secondary objective: Ab response according to FV immune status at baseline

The majority of subjects in both treatment groups were FV immune at baseline: 89.7% (113/126) of subjects in the CYD dengue vaccine group and 91.8% (56/61) of subjects in the Placebo group.

Seropositivity (Ab titer ≥ 10 [1/dil]) against each dengue virus serotype

Regarding FV immune subjects, in the CYD dengue vaccine group, the seropositivity rates at baseline for each serotype were similar to those observed in the Placebo group: 92.9% (105/113) for serotypes 1 and 2, 94.7% (107/113) for serotype 3, and 85.8% (97/113) for serotype 4. For each of the serotypes, a more pronounced increase in seropositivity was observed post-Inj 1, with additional increases at post-Inj 2. At post-Inj 3, the percentage of subjects who were seropositive was 100% (102/102) for each of the four serotypes. The seropositivity rates reached higher values for the subjects who were FV immune at baseline as compared to those who were FV non-immune at baseline.

Seropositivity against at least 1, 2, 3 and all 4 serotypes

Regarding FV immune subjects, in the CYD dengue vaccine group, the percentage of subjects who were seropositive at baseline for at least 1, 2, 3, or all 4 serotypes was 96.5% (109/113), 93.8% (106/113), 92.0% (104/113), and 84.1% (95/113), respectively. All subjects were seropositive for at least 2 serotypes at post-Inj 1, for at least 3 serotypes at post-Inj 2, and for all 4 serotypes at post-Inj 3. The seropositivity rates reached slightly higher values for the subjects who were FV immune at baseline as compared to those who were FV non-immune at baseline.

GMTs

Regarding FV immune subjects, in the CYD dengue vaccine group, the baseline GMTs were 279, 312, 338, and 73.1 (1/dil) for serotypes 1, 2, 3, and 4 respectively. After the first injection, GMTs increased from baseline and ranged from 424 (1/dil) for serotype 4 to 1324 (1/dil) for serotype 3. For each serotype, GMTs tended to decrease at post-Inj 2 and post-Inj 3 (except for serotype 4) but remained elevated versus baseline. At post-Inj 3, GMTs were 636, 624, 912, and 387 (1/dil) for serotypes 1, 2, 3, and 4, respectively. The GMTRs ranged from 3.24 for serotype 1 to 5.80 for serotype 4 (post-Inj 1 versus baseline), from 2.93 for serotype 1 to 4.56 for serotype 4 (post-Inj 2 versus baseline), and from 1.91 for serotype 2 to 5.18 for serotype 4 (post-Inj 3 versus baseline). Overall, the GMTs were higher in FV immune subjects at baseline as compared to FV non-immune subjects at baseline.

Safety results:**Primary objective: Safety data after each injection**

Overall, the percentage of subjects experiencing at least one solicited reaction (including both solicited injection site and solicited systemic reactions) after any injection tended to be higher in the CYD dengue vaccine group than in the placebo group (21.4% [27/126] and 8.2% [5/61], respectively).

Pain was the most commonly reported solicited injection site reaction after each injection in both groups. In the CYD dengue vaccine group, the percentage of subjects who reported pain was 6.3% (8/126), 1.7% (2/117), and 2.6% (3/115) respectively after the first, second, and third injection. In the Placebo group, the percentage of subjects who reported pain was 4.9% (3/61) and 3.4% (2/58), respectively after the first and second injection (no solicited injection site reactions were reported after the third injection). Most of the solicited injection site reactions were of Grade 1 intensity.

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The percentage of subjects experiencing unsolicited AEs was slightly higher in CYD dengue vaccine group as compared to the Placebo group. None were of Grade 3 intensity or were considered as related to the injection by the Investigator. After the first injection, a total of 7 subjects (5.5%) experienced at least one unsolicited AE (abdominal pain, viral infection, rash and pruritus) in the CYD dengue vaccine group and one subject (1.6%) experienced pyrexia in the Placebo group. After the second injection, only one subject in the CYD dengue vaccine group experienced nasopharyngitis. After the third injection, a total of 4 subjects (3.5%) experienced at least one unsolicited AE (conjunctivitis, dyspepsia, pain, and back pain) in the CYD dengue vaccine group and 3 subjects (5.3%) experienced at least one unsolicited AE (vomiting, back pain, and headache) in the Placebo group.

During the trial, a total of 3 SAEs were reported by one subject in the CYD dengue vaccine group and one subject in the Placebo group. In the CYD dengue vaccine group, a subject experienced pyrexia and megaloblastic anemia 65 days after the first injection. In the Placebo group, a subject experienced viral upper respiratory tract infection 149 days after the third injection. Both subjects were considered as recovered. All 3 SAEs reported were assessed as not related to the study vaccine by both the Investigator and the Sponsor.

No deaths were reported during this study.

No virologically-confirmed dengue cases were reported during this study.

No serious AESI was reported. A total of 3 (2.4%) subjects reported non-serious AESIs in the CYD dengue vaccine group after the first injection (2 subjects reported pruritus and one subject reported rash papular). No AESI was reported after the second or third injection. All AESIs were considered as not related to study vaccine.

Secondary objective: Safety by baseline FV immune status

Solicited injection site reactions in the CYD dengue vaccine group were reported by 8.0% (9/113) of FV immune subjects and 23.1% (3/13) of FV non-immune subjects. In the Placebo group, the rates were 1.8% (1/56) of FV immune subjects and 40.0% (2/5) of FV non-immune subjects.

Solicited systemic reactions in the CYD dengue vaccine group were reported by 16.8% (19/113) of FV immune subjects and 38.5% (5/13) of FV non-immune subjects. In the Placebo group, the rates were 5.4% (3/56) of FV immune subjects and 20.0% (1/5) of FV non-immune subjects.

Unsolicited AEs in the CYD dengue vaccine group were reported by 7.0% (8/114) of FV immune subjects and 30.8% (4/13) of FV non-immune subjects. In the Placebo group, the rates were 7.1 % (4/56) of FV immune subjects and no unsolicited AEs were reported by FV non-immune subjects.

The 2 subjects who reported at least one SAE were FV immune at baseline.

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