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Sponsor: Sanofi Pasteur	Study Identifiers: 2014-001706-17
Drug substance(s): CYD Dengue Vaccine	Study code: CYD06
Title of the study: Safety of Chimerivax™ Dengue Tetravalent Vaccine in Subjects Aged 2 to 45 Years in Mexico	
Study center(s): 2 centers in Mexico	
Study period: Date first subject enrolled: 24/Jan/2006 Date last subject completed: 20/Aug/2007	
Phase of development: Phase I	
Objectives: <ol style="list-style-type: none">1) To describe the safety of each injection of ChimeriVax™ Dengue Tetravalent Vaccine in four age groups of subjects: adults (18 to 45), adolescents (12 to 17), children (6 to 11), and children (2 to 5).2) To describe the 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.	
Methodology: Blind observer (first injection), open (second and third injections), multicenter, randomized, Phase I study in 126 subjects in Mexico: 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, D0 + 3.5 months, and D0 + 12 months. Group 1 received Sanofi Pasteur's dengue vaccine as first, second and third injections. Group 2 (Control Group) received yellow fever (YF) vaccine (Stamaril Pasteur®) as first injection and Sanofi Pasteur's dengue vaccine as second and third injections. Adults and adolescents were included in Center 1 and children were included in Center 2 . The different age groups were vaccinated sequentially (from adults to children). After each first cohort of adolescents and children, safety was evaluated by an Independent Data Monitoring Committee (IDMC) and reported to the Institutional Review Board (IRB). The decision on whether to proceed with the enrolment of each following 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 groups were vaccinated with at least 14-day intervals (adults, then adolescents, then children 6 to 11 years, and finally children 2 to 5 years). Stopping rules had been defined in the protocol and in case one of these stopping rules applied, vaccinations were to be suspended and the IDMC was to meet to make a recommendation on the continuation of the study. The final decision was to be taken by the Sponsor and the Principal Investigator, based upon the IDMC's recommendation.	

Number of subjects:	<p>Planned: 126 corresponding to 84 (i.e. 12 for adults and 24 for each non-adult group) in Group 1 and 42 (i.e. 6 for adults and 12 for each non-adult group) in Group 2</p> <p>Randomized: 126 (84 in Group 1, 42 in Group 2)</p> <p>Number of subjects who received the first vaccination: 126 (84 in Group 1, 42 in Group 2)</p> <p>Number of subjects who received the second vaccination: 119 (79 in Group 1, 40 in Group 2)</p> <p>Number of subjects who received the third vaccination: 108 subjects (73 in Group 1, 35 in Group 2)</p>
Evaluated:	<p>Immunogenicity: 126</p> <p>Safety: 126</p>
Diagnosis and criteria for inclusion:	
<p>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).</p> <ol style="list-style-type: none"> 1) Aged 2 to 45 years on the day of inclusion (Scr.). 2) Informed consent form signed by the subject, by two independent witnesses, and by the parent(s) or legal representative(s) 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 child-bearing potential, use of an effective method of contraception or abstinence for at least four weeks prior to the first vaccination and at least four 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	
<p>Investigational Product: ChimeriVax™ Dengue Tetravalent Vaccine</p> <p>Form: Liquid/Frozen</p> <p>Composition: Each 0.5 mL dose contains: ~5 log₁₀ CCID₅₀ of each chimeric dengue serotype (1, 2, 3, 4)</p> <p>Route of administration: Subcutaneous (SC)</p>	
<p>Control Product: Sanofi Pasteur live attenuated YF vaccine (Stamaril Pasteur®)</p> <p>Form: Freeze-dried</p> <p>Composition: 17D strain of YF virus cultured in living avian leucosis virus-free chicken embryos; concentration: ≥ 1,000 mouse lethal dose 50% (LD₅₀).</p> <p>Diluent: sterile 4‰ NaCl solution.</p> <p>Route of administration: SC, deltoid region</p>	
Duration of participation: The total duration of follow-up was 14 months for each subject.	

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.
- 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).
- 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 safety data were performed for the first vaccination period after each cohort had completed Day 14 visit (including viremia data in case of SAE). These data were provided by the Sponsor's Data Management department 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 Stamaril pasteur®, a YF vaccine (Group 2). For the second vaccination, 3 to 4 months after the first vaccination, 79 subjects in Group 1 and 40 in Group 2 received the dengue vaccine. For the third vaccination, one year after the first one, 73 subjects in Group 1 and 35 subjects in Group 2 received the dengue vaccine.

Eight subjects discontinued the study between the first two vaccinations: six subjects (four subjects in Group 1, and two subjects in Group 2) were withdrawn after experiencing eosinophilia, one subject in Group 1 was lost to follow-up, and one subject in Group 2 did not comply with the protocol. In addition, ten subjects did not complete the third vaccination period: three subjects (Group 1) withdrew voluntarily, three subjects (one subject in Group 1, and two subjects in Group 2) did not comply with the protocol, two subjects (one in each group) experienced SAEs leading to discontinuation, one subject (Group 2) experienced another AE (clinically significant [CS] laboratory abnormalities), and one subject (Group 1) was lost to follow-up.

Demographic characteristics, i.e. age, weight, height, and body mass index (BMI), were similar in the two groups, except for gender due to a slight higher proportion of females in Group 1 (58.3%) than in Group 2 (50.0%), and a mean age for adults higher in Group 1 than in Group 2. The mean age (\pm standard deviation [SD]) was 12.1 years (\pm 9.2) in Group 1 and 11.6 years

(± 7.3) in Group 2. The mean BMI (\pm SD) was 19.5 kg/m² (± 4.2) in Group 1 and 19.4 kg/m² (± 4.3) in Group 2.

The analysis was descriptive.

Safety:

During the study, a total of four SAEs were reported. One of them occurred prior to the first vaccination (hepatitis A was detected at screening), the second SAE (upper respiratory tract infection) occurred 26 days after the first vaccination in Group 2. The two remaining SAEs occurred after the second vaccination: one in Group 2 (fatal road traffic accident) more than 5 months post-vaccination and another in Group 1 (partial seizures) 2 days post-vaccination. No SAEs occurred after the third vaccination. All these SAEs were considered to be unrelated to the study vaccine by the Investigator, the Sponsor, and the IDMC.

Most injection site reactions were mild or moderate and were present for a maximum of 3 days. However, there were four (two in each group) severe injection site reactions (two episodes of pain after 1 or 2 injections of dengue vaccine, one episode of edema after one dengue injection, and one episode of erythema after two dengue injections). Pain was the most frequent injection site reaction after one, two, or three vaccinations. The proportion of subjects who reported at least one episode of pain after the first vaccination in the 7 days post-vaccination was: 22 subjects (26.2%) in Group 1 and 9 subjects (21.4%) in Group 2. After the second vaccination, there were 20 subjects (26.0%) in Group 1 and 7 subjects (17.9%) in Group 2, and after the third vaccination 26 subjects (35.6%) in Group 1 and 8 subjects (22.9%) in Group 2.

Headache was the most frequent solicited systemic reaction after each administration of dengue vaccine. After a first administration of dengue vaccine, the most frequent solicited systemic reactions were (by decreasing frequency in Group 1): headache (32 subjects [38.1%] in Group 1, and 13 subjects [33.3%] in Group 2), myalgia (24 subjects [28.6%] in Group 1, and 11 subjects [28.2%] in Group 2), malaise (21 subjects [25.0%] in Group 1, and 6 subjects [15.4%] in Group 2), asthenia (17 subjects [20.2%] in Group 1, and 8 subjects [20.5%] in Group 2), and fever (8 subjects [9.5%] in Group 1, and 4 subjects [10.3%] in Group 2). After the second administration of dengue vaccine, the most frequent solicited systemic reactions were as follows: headache (23 subjects [29.5%] in Group 1, and 7 subjects [20.0%] in Group 2), asthenia (14 subjects [18.2%] in Group 1, and 3 subjects [8.6%] in Group 2), myalgia (13 subjects [16.9%] in Group 1, and 7 subjects [20.0%] in Group 2), malaise (12 subjects [15.6%] in Group 1, and 7 subjects [20.0%] in Group 2), and fever (11 subjects [14.3%] in Group 1, and 2 subjects [5.7%] in Group 2). After the third administration of dengue vaccine, the most frequent solicited reactions in Group 1 were headache (15 subjects, 20.5%), myalgia (14 subjects, 19.2%), asthenia (11 subjects, 15.1%), malaise (10 subjects, 13.7%), and fever (4 subjects, 5.5%).

In the two groups after each vaccination, most systemic or injection site 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.

Unsolicited AEs were reported in 45.2% of subjects in Group 1 and 50.0% in Group 2 after the first vaccination. These proportions were stable after the second vaccination with 43.0% in Group 1 and 60.0% in Group 2, and decreased markedly in each group after the third vaccination with 24.7% in Group 1 and 11.4% in Group 2. The most frequently reported unsolicited AEs were lymphadenopathy and neutropenia in the two groups, and pharyngolaryngeal pain and cough mostly in Group 2.

Overall, there were few biological abnormalities after each vaccination and they were recorded in approximately the same number of subjects in each group. After the first and second administration, the most frequently reported biological abnormalities were increase in creatinine phosphokinase (CPK) and decrease in neutrophil counts. After the second administration, increases in hemoglobin, hematocrit, and red blood cell count (RBC) were also observed in Group 1 while they were not found in Group 2. After the third administration, only CPK increase was observed. Biological abnormalities were rated as severe for seven subjects (4 in Group 1 and 3 in Group 2) after the first vaccination (four increases in CPK, two decreases in neutrophils, and one increase in total bilirubin), for six subjects (3 in each group) after the second vaccination (four severe decreases in absolute neutrophils, one increase in ALT, and one decrease in platelet counts), and for no subjects after the third vaccination. In all cases, values or concentrations returned within normal ranges on the next visits, except for bilirubin increase after the first vaccination that was not considered to be clinically significant. When looking at biological abnormalities per age group, there were no strong differences between the two groups in terms of number of changes in biological parameters. After each vaccination, regardless of the vaccine received, the same biological abnormalities were found to be the most frequent in each age group, i.e. CPK changes in adults, neutrophil decrease and hemoglobin increase in adolescents and in children [2;5].

Viremia

Non-serotype specific CYD viremia by flavivirus RT-PCR was slightly more frequently detected 7 days after the first administration of dengue vaccine (i.e. first vaccination in Group 1 [4.9% of the subjects], and second vaccination in Group 2 [10.5%]) than 14 days after the first administration of dengue vaccine (2.4% in Group 1 and 2.6% in Group 2). The same trend was observed for non-serotype specific CYD viremia detected by YF RT-PCR but with higher results than flavivirus RT-PCR: 35 subjects (43.2%) in Group 1 and 10 subjects (26.3%) in Group 2 had a detectable viremia by YF RT-PCR 7 days after the first dose of dengue vaccine and 21 subjects (25.0%) in Group 1 and 5 subjects (12.8%) in Group 2 had a detectable viremia by YF RT-PCR 14 days after the first dose of dengue vaccine. 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 26.5% of subjects in Group 2, but only 2.5% in Group 1.

Serotype-specific CYD viremia for dengue serotypes 1, 2, and 3 was not quantified (i.e. under the limit of quantitation) or at the limit of quantitation after each administration of dengue vaccine. Among the four serotypes, dengue serotype 4 was the most frequently detected. After the first administration of dengue vaccine, viremia was quantified by RT-PCR and PA in three subjects in Group 1 and in two subjects in Group 2. Few subjects presented a viremia after the second and third doses of dengue vaccine.

Immunogenicity: Humoral immune response

Sanofi Pasteur's dengue vaccine induced a neutralizing antibody response that was different according to the serotype. GMTs increased after each vaccination for all serotypes, except for serotype 4 for which the level of GMTs was lower after the second vaccination than it was after the first vaccination and for serotype 2 after the second dose with the non-parental (Mahidol) strain. However, the highest neutralizing antibody titers were observed for dengue serotype 4 (GMTs ranged from 47.2 to 62.4 after the second vaccination, and from 71.7 to 82.4 after the third vaccination). In Group 2, a similar trend towards predominant serotype 4, followed by serotype 3, was observed. In Group 1, after the first administration of dengue vaccine, seropositivity rates (antibody level ≥ 10 1/dil) were the highest against serotype 4 (67.9% to 82.5%) depending on the strain, followed by serotype 3 (34.1% to 49.4%), then, serotype 2 (33.3%), and serotype 1 (14.5% to 19.3%). The second and third vaccinations increased the proportion of seropositive subjects for serotypes 2, particularly for the parental strain, and serotypes 1, 3, and to a lesser extent for serotype 4. Moreover, GMTs and seropositivity rates tended to be higher in Group 2 than in Group 1 after the second dose of dengue vaccine with the parental strain for all serotypes, thus suggesting that a previous administration of YF vaccine might boost the humoral immune response to the dengue vaccine.

Assessment of the percentage of seropositivity against two, three, or four serotypes showed that the proportion of subjects with at least two successes, i.e. response ≥ 10 [I/dil] against two serotypes, increased with the successive vaccinations as follows: after the first dose of dengue vaccine, 49.4% to 54.2% of subjects in Group 1 and 53.8% to 74.4% of subjects in Group 2 were seropositive against at least two serotypes, with the Mahidol and parental strains respectively. This proportion increased to 73.4% - 87.3% in Group 1 and to 85.3% - 97.1% in Group 2 after the second dose of dengue vaccine, and reached 84.9% to 93.2% in Group 1 after the third dose for the Mahidol and parental strains respectively. The same trend was observed to a lesser extent in subjects with at least three or four successes.

As expected, an IgM response was observed mainly after the first administration of dengue vaccine in Group 1. Seropositivity was 81.9% in Group 1 and 7.7% in Group 2, 28 days after the first dose of dengue vaccine. In the two groups, the seropositivity rate to IgM was found to be the lowest in children [2;5] (52.2% in Group 1 and 0% in Group 2). Regarding seropositivity rates to IgG in Group 1, they were high 28 days after the first vaccination (96.4%) and all subjects had IgG antibodies after the second vaccination. In Group 2, 100% of subjects primed with YF vaccine had anti-dengue IgG after the first administration of dengue vaccine. The proportion of subjects with anti-dengue IgG antibodies after the first administration of dengue vaccine was the lowest in children [2;5] (91.3%) in Group 1 while there were no differences between each age group in Group 2.

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