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Sponsor: Sanofi Pasteur	**Study Identifiers:** U1111-1127-7380, NCT01983553, 2014-001737-88
Drug substance(s): CYD dengue vaccine	**Study code:** CYD57

Title of the study: Long-Term Follow-Up of Hospitalized Dengue and Safety in Thai Children Who Were Included in an Efficacy Study of a Tetravalent Dengue Vaccine

Study center(s): One center in Thailand

Study period:

Date first subject/patient enrolled: 10/Sep/2013

Date last subject/patient completed: 19/Feb/2016

Phase of development: Not applicable

Objectives:

The main objective of this study was to evaluate the continuous long-term follow-up of hospitalized dengue and safety of subjects who received CYD dengue vaccine in the PoC efficacy study (CYD23) including retrospective data collection (i.e., including the blood samples collected from 05 March 2012 to 09 September 2013) and prospective data collection from CYD57 study start (10 September 2013 until the end of the study), and the following activities were performed:

1) To describe the incidence of virologically-confirmed hospitalized dengue cases
2) To characterize hospitalized dengue cases
3) To evaluate the occurrence of related and fatal SAEs

Methodology:

Single-center, 4-year safety follow-up of up to 3997 subjects aged 4 to 11 years at enrollment in the first Proof of Concept (PoC) efficacy study of CYD dengue vaccine.

This study involved passive surveillance of hospitalized dengue cases in subjects participating in the initial PoC efficacy study where subjects were initially randomized to receive 3 injections of either CYD dengue vaccine or control at 6 months intervals. Any serious adverse event (SAE) related to a study procedure or related to a previous injection from the initial PoC efficacy study, or any fatal SAE (even if unrelated) was reported to the Sponsor.

An Independent Data Monitoring Committee (IDMC) was also involved in the regular review of virologically-confirmed hospitalized dengue cases. Any fatal outcome or related SAE was promptly reviewed by the IDMC.

No study vaccinations were administered.

A blood sample was taken at enrollment visit (Visit 00) in all subjects to test for dengue neutralizing antibodies (Abs) at baseline in case of further hospitalized virologically-confirmed dengue infection.

Number of subjects/patients: Planned: 3997

Enrolled: 3997

Evaluated: 3203

Surveillance, Case evaluation and Safety: 3203

Diagnosis and criteria for inclusion:

An individual had to fulfill *all* of the following criteria in order to be eligible for study enrollment:

1) Ongoing participation in study CYD23 at the time of enrollment
2) Assent form has been signed and dated by the subject (for subjects ≥ 7 years old), and informed consent form has been signed and dated by the parent(s) or another legally acceptable representative and by 2 independent witnesses
3) Subject and parent / legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

Study treatments: Not Applicable

Duration of observation: The duration of each subject's participation in the study was approximately 4 years.

Criteria for evaluation:

1) Hospitalized, virologically-confirmed dengue case was defined as:
   - An acute febrile illness with fever lasting for at least 1 day (temperature ≥ 37.5°C measured at least twice with an interval of at least 4 hours), and
   - Virologically-confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay (ELISA) antigen (Ag) test with the addition of serotype / strain specific analyses where appropriate and
   - In-patient hospitalization
2) Classification of dengue cases was based on:
   - Detection of dengue viremia, clinical signs and symptoms, duration of clinical syndrome, duration of hospitalization, neutralizing Ab titers and other pertinent criteria
   - A severity assessment using the World Health Organization (WHO) 1997 severity definition and the IDMC severity definition (see Assessment Methods)
   - A dengue serological profile based on immunoglobulin (Ig)G and IgM ELISA results in all acute febrile episodes. Neutralizing Ab titers were assessed in all virologically-confirmed dengue cases.
3) Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), seriousness criteria, relationship, outcome, and whether the SAE led to early termination from the study or SAEs related to study procedures or to previous injection from the PoC efficacy study and fatal (even if unrelated) SAEs in all subjects.

Statistical methods:

The statistical analysis was performed on retrospective data collected from the end of the Active Phase in the PoC efficacy study (CYD23) until 4 years of long-term follow-up (VY4).

Incidence and relative risk (RR) were presented for hospitalized virologically-confirmed dengue on each year of follow-up by vaccination group, for any serotype and by serotype. The 95% confidence intervals (CIs) for annual incidence were calculated with the exact binomial distribution for percentages (Clopper-Pearson's method, quoted by Newcombe). The 95% CIs for RR were calculated using the Exact method (Breslow & Day,1987).

For the entire passive surveillance period and from D0 of study CYD23 to the end of the passive surveillance, a time-to-event analysis approach was used. Cumulative incidences and 95% CI in each vaccination group were calculated using non-parametric Kaplan- Meier estimate and Greenwood's variance estimation, and tabulated every year. Moreover, a graph was presented.

The same methodology was applied for severe (as assessed by IDMC) hospitalized virologically-confirmed dengue cases and hospitalized virologically-confirmed dengue cases meeting WHO 1997 criteria.

The analyses were described according to treatment group from the PoC efficacy study.

Summary:

Incidence of Hospitalized Virologically-Confirmed Dengue Cases

During the first year of passive surveillance, there were 22 cases (5 due to serotype 1, 17 due to serotype 2 and 1 due to serotype 3) out of 2131 subjects in the CYD dengue vaccine group and 11 cases (5 due to serotype 1, 4 due to serotype 2, 1 due to serotype 3, and 2 were unserotyped) out of 1072 subjects in the control group. Among these cases, 2 subjects (1 in the control group and 1 in CYD dengue vaccine group) have been detected to be co-infected with both serotypes 1 and 2 (each of these cases has been counted once). Overall, for any of the 4 serotypes, the RR was 1.006 (95% CI: 0.47 ; 2.30). All the 4 serotypes were observed in the CYD dengue vaccine group, with a predominance of serotype 2 for the first year of passive surveillance.

During the second year of passive surveillance, there were 16 cases (4 due to serotype 1, 4 due to serotype 2, 6 due to serotype 3, and 2 due to serotype 4) out of 2131 subjects in the CYD dengue vaccine group and 17 cases (3 due to serotype 1, 6 due to serotype 2, 3 due to serotype 3, 4 due to serotype 4, and 1 was unserotyped) out of 1072 subjects in the control group. Overall during the second year of passive surveillance, it appears there was a positive trend (RR=0.473; 95% CI: 0.22 ; 1.00) on reduction of hospitalized virologically-confirmed dengue cases.

During the third year of passive surveillance, there were 8 cases (1 due to serotype 1, 4 due to serotype 3, and 3 due to serotype 4) out of 2093 subjects in the CYD dengue vaccine group and 4 cases (1 due to serotype 1, 1 due to serotype 3, 2 due to serotype 4) out of 1060 subjects in the control group. Overall during the third year of passive surveillance, the RR was 1.013 with 95% CI: 0.27 ; 4.60 for any of the 4 serotypes.

During the fourth year of passive surveillance, there were 39 cases (11 due to serotype 1, 8 due to serotype 2, 10 due to serotype 3, and 10 due to serotype 4) out of 2035 subjects in the CYD dengue vaccine group and 14 cases (2 due to serotype 1, 1 due to serotype 2, 5 due to serotype 3, 6 due to serotype 4) out of 1027 subjects in the control group. Overall during the fourth year of passive surveillance, the RR was 1.406 with 95% CI: 0.75 ; 2.80 for any of the 4 serotypes.

The RR for the entire passive surveillance period was 0.930 with 95% CI: 0.64 ; 1.36 for any of the 4 serotypes. Overall, from D0 of the PoC efficacy study up to the end of Hospital Phase (5 years after the third injection), the incidence of hospitalized virologically-confirmed dengue cases was lower in the CYD dengue vaccine group as compared to the control group with a hazard ratio of 0.775 with 95% CI: 0.58 ; 1.04.

In the 6-11 years group, the RR during the entire passive surveillance period was 0.807 with 95% CI: 0.53 ; 1.25 for any of the 4 serotypes. In the 4-5 years group, the RR during the entire passive surveillance period was 1.411 with 95% CI: 0.64; 3.42 for any of the 4 serotypes.

Incidence of Severe Hospitalized Virologically-Confirmed Dengue Cases

During the entire passive surveillance period, there were 8 severe hospitalized virologically-confirmed dengue casesin the CYD dengue vaccine group and 3 in the control group:

- During the first year of passive surveillance, 4 hospitalized virologically-confirmed dengue cases in the CYD dengue vaccine group and none in the control group have been considered as severe by IDMC.
- During the second year of passive surveillance, 1 hospitalized virologically-confirmed dengue case in the CYD dengue vaccine group and 2 in the control group have been considered as severe by IDMC.
- During the third year of passive surveillance, 1 hospitalized virologically-confirmed dengue case in the CYD dengue vaccine group and 1 in the control group have been considered as severe by IDMC.
- During the fourth year of passive surveillance, 2 hospitalized virologically-confirmed dengue cases in the CYD dengue vaccine group have been considered as severe by IDMC. There was no hospitalized virologicallyconfirmed dengue case considered as severe by IDMC in the control group.

According to WHO 1997 criteria, 2 cases were considered of Grade III (in CYD dengue vaccine group with clinical shock, during the first year of passive surveillance) and all other cases were considered of Grade I or II.

Overall, from D0 of the PoC efficacy study up to the Hospital Phase (5 years after the third injection), there were 10 severe hospitalized virologically-confirmed dengue cases in the CYD dengue vaccine group and 5 in the control group (meaning a RR close to 1 due to the 2:1 randomization ratio).

The very limited number of severe cases does not allow the interpretation of results by serotype and by age group.

Dengue Viremia

During the first year of passive surveillance, the wild type dengue viremia mean (± SD) was 3.98 (± 1.04) log_{10} pfu/mL in the CYD dengue vaccine group and 3.93 (± 1.58) log_{10} pfu/mL in the control group.

During the second year of passive surveillance, the viremia mean (± SD) was 3.75 (± 1.26) log_{10} pfu/mL in the CYD dengue vaccine group and 3.36 (± 1.12) log_{10} pfu/mL in the control group.

During the third year of passive surveillance, the viremia mean (± SD) was 3.47 (± 0.942) log_{10} pfu/mL in the CYD dengue vaccine group and 3.87 (± 0.815) log_{10} pfu/mL in the control group.

During the fourth year of passive surveillance, the viremia mean (± SD) was 3.45 (± 1.23) log_{10} pfu/mL in the CYD dengue vaccine group and 2.93 (± 1.02) log_{10} pfu/mL in the control group.

Overall during the entire passive surveillance, the quantified viremia was similar between the CYD dengue vaccine group and the control group with viremia means (± SD) of 3.64 (± 1.17) log_{10} pfu/mL and of 3.38 (± 1.21) log_{10} pfu/mL, respectively.

Clinical Signs and Symptoms

Overall, there was no difference between the CYD dengue vaccine group and the control group regarding the clinical symptoms observed. Clinical shock was reported for 2 subjects in the CYD dengue vaccine group during the first year of passive surveillance and for 2 subjects in the CYD dengue vaccine group and 1 subject in the control group during the fourth year of passive surveillance. These data come from the severe virologically-confirmed dengue cases. All children fully recovered after supportive medical care.

Among the 19 cases of plasma leakage, 18 had a hematocrit increase ≥ 20% during the entire passive surveillance. In the CYD dengue vaccine group, plasma leakage was generally not detected clinically and mainly corresponded to a hematocrit increased (11 out of 14 presented only with a hematocrit increased ≥ 20%).

Serological Profile

Overall in both groups, IgM and IgG were higher in virologically-confirmed dengue cases than in non virologically-confirmed dengue cases (especially for IgM). There was no clear difference between CYD dengue vaccine and control groups for IgG and IgM; however, in study CYD57, samples were collected far beyond the initial vaccination.

Safety

Five deaths were reported during the entire passive surveillance period (3 deaths in the CYD dengue vaccine group and 2 deaths in the control group); none of them was considered as related to the investigational vaccine by the Investigator and by the Sponsor.

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