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Sponsor: Sanofi Pasteur **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** U1111-1122-1892, 11219, NCT01488890 **Study code:** CYD51
Title of the study: Evaluation of the Immune Response to Different Schedules of a Tetravalent Dengue Vaccine Administered With or Without Yellow Fever Vaccine in US Adults	
Study center(s): This was a multi-center trial involving 6 investigators in the USA	
Study period: Date first subject enrolled: 06/Dec/2011 Date last subject completed: 27/Sep/2013	
Phase of development: Phase II	

Objectives:

Primary Objectives:

Immunogenicity

1) To describe the humoral immune response to each of the 4 parental dengue virus serotypes at baseline and 28 days after CYD dengue vaccine Dose 3 in Group 1 (M13) and Group 2 (M07), irrespective of whether or not YF vaccine has been previously administered
2) To describe the persistence of the humoral immune response to each of the 4 parental dengue virus serotypes 6 months after CYD dengue vaccine Dose 3 in Group 1 (M18) and Group 2 (M12), irrespective of whether or not YF vaccine has been previously administered

Secondary Objectives:

Immunogenicity

1) To describe the humoral immune response to each of the 4 parental dengue virus serotypes at baseline and 28 days after CYD dengue vaccine Dose 1 and Dose 2 in Groups 1 and 2, irrespective of whether or not YF vaccine has been previously administered
2) To describe the humoral immune response to each of the 4 parental dengue virus serotypes at baseline and 28 days after CYD dengue Dose 1 in the combined YF- subjects from Group 1 (N=60) and Group 2 (N=60), and in Group 3 (N=120)
3) To describe by flavivirus (FV) status at baseline the humoral immune response to each of the 4 parental dengue virus serotypes at baseline and 28 days after each injection of CYD dengue vaccine in Groups 1, 2, and 3
4) To describe by FV status at baseline the persistence of the humoral immune response of the 4 parental dengue virus serotypes at 4 months after Dose 2 in Groups 2 and 3 and at 3, 6, and 12 months after the CYD dengue vaccine Dose 3
5) To describe by FV status at baseline the persistence of the humoral immune response of the 4 parental dengue virus serotypes at 6 months after each injection of CYD dengue vaccine in Group 1
6) To describe the kinetics of the neutralizing Ab responses to each parental dengue virus serotype, dengue specific IgM and dengue specific IgG following each injection of CYD dengue vaccine and by FV status at baseline in Subgroups 1K and 2K
7) To describe the YF neutralizing Ab at baseline and 28 days after each injection of CYD dengue vaccine in YF+ subjects in Groups 1 and 2
8) To describe the YF humoral immune response at baseline and 1, 3, and 7 months after injection of the YF vaccine at M00 in Groups 3 and 4

Safety

1) To describe the safety profile after each injection of CYD dengue vaccine and/or YF vaccine

Methodology:

This was a Phase II, randomized, open-label, multicenter study planned to be conducted in 390 healthy adults aged ≥ 18 years to ≤ 45 years, in the US.

Subjects were randomized to 4 different groups to receive either CYD dengue vaccine and/or yellow fever (YF) vaccine as follows:

Vaccination Group	Month				Number of Subjects per Group
	00	02	06	12	
1	CYD dengue vaccine		CYD dengue vaccine	CYD dengue vaccine	120*
2	CYD dengue vaccine	CYD dengue vaccine	CYD dengue vaccine		120*
3	YF vaccine and CYD dengue vaccine	CYD dengue vaccine	CYD dengue vaccine		120
4	YF vaccine				30

* Includes equal numbers of subjects who were YF+ or YF-

Groups 1 and 2 were stratified into those subjects who had not received the YF vaccine (YF-) (N = 60) and those who had previously received the YF vaccine (YF+) 3 months to 10 years before administration of CYD dengue vaccine at Month (M) 00 (N = 60).

In both Groups 1 and 2, 40 of the 120 subjects enrolled (Subgroups 1K and 2K, respectively; 20 who were YF- and 20 who were YF+) were planned to provide additional blood samples for determination of the kinetics of neutralizing antibody (Ab), dengue specific immunoglobulin M (IgM), and dengue specific immunoglobulin G (IgG) responses.

Subjects were randomly assigned to one of the groups or subgroups through an interactive voice response system (IVRS)/interactive web response system (IWRS).

Blood samples (10 mL) for immunogenicity and kinetics of Ab responses were to be collected at each month and/or day (D) in each group as follows:

- Group 1: M00, M01, M06, M07, M12, M13, and M18
- Subgroup 1K: M00, M00+7D, M00+14D, M01, M02, M04, M06, M06+7D, M06+14D, M07, M08, M12, M12+7D, M12+14D, M13, M14, and M18
- Group 2: M00, M01, M02, M03, M06, M07, M09, M12, and M18
- Subgroup 2K: M00, M00+7D, M00+14D, M01, M02, M02+7D, M02+14D, M03, M04, M06, M06+7D, M06+14D, M07, M08, M09, M12, and M18
- Group 3: M00, M01, M02, M03, M06, M07, M09, M12, and M18
- Group 4: M00, M01, M03, and M07

Reactogenicity data were to be collected after each vaccine dose. Unsolicited adverse events (AEs) were to be collected up to 28 days after each vaccine dose. Serious adverse events (SAEs) including serious adverse events of special interest (AESIs) were to be collected throughout the study in all groups.

An Independent Data Monitoring Committee (IDMC) was promptly informed of the occurrence of any fatal or related SAEs. At the end of the study, the IDMC reviewed the overall safety profile of all subjects.

Number of subjects:

Planned: 390

Randomized: 390

Treated: 390

Evaluated:

Immunogenicity: 349

Safety: 389

Diagnosis and criteria for inclusion:

An individual was to fulfill all of the following criteria in order to be eligible for trial enrollment:

1) Aged ≥ 18 to ≤ 45 years on the day of inclusion
2) Informed consent form has been signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures
4) For subjects classified as YF+ to be included in Groups 1 and 2, previous vaccination (3 months to 10 years) with YF vaccine confirmed by acceptable documentation.

Study treatments

Investigational product 1: CYD Dengue Vaccine

Formulation: Powder and solvent for suspension for injection.

Composition: Each 0.5 mL of reconstituted dose contains:

- 5 ± 1 log10 cell-culture infectious dose 50% (CCID50) of each live, attenuated, recombinant dengue serotype 1, 2, 3, 4 virus
- Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminomethane, and urea
- Solvent: NaCl (0.4%) Solvent: NaCl 0.4%

Route of administration: Subcutaneous (SC)

Investigational product 2: YF-VAX® (Yellow Fever Vaccine)

Formulation: Lyophilized

Composition: 17D strain of YF virus cultured in living avian leucosis virus-free chicken embryos.

YF-VAX is formulated to contain not less than 4.74 log10 plaque forming units per 0.5 mL dose

Diluent: sodium chloride solution

Rout of administration: SC

Duration of participation:

The expected duration of a subject's participation in the trial was 18 months for subjects in Groups 1, 2, and 3 or 7 months for subjects in Group 4.

Criteria for evaluation:

Primary Endpoints :

Immunogenicity

1) Neutralizing Ab levels (measured by a dengue plaque reduction neutralization test [PRNT]) against each of the 4 parental dengue virus serotypes at baseline and 28 days after CYD dengue vaccine Dose 3 in Groups 1 and 2
2) Neutralizing Ab levels (measured by PRNT) against each of the 4 parental dengue virus serotypes 6 months after CYD dengue vaccine Dose 3 in Groups 1 and 2

Secondary Endpoints :

Immunogenicity

1) Neutralizing Ab levels (measured by dengue PRNT) against each of the 4 parental dengue virus serotypes at baseline and 28 days after CYD dengue vaccine Dose 1 and Dose 2 in Groups 1 and 2
2) Neutralizing Ab levels (measured by dengue PRNT) against each of the 4 parental dengue virus serotypes at baseline and 28 days after CYD dengue Dose 1 in the combined YF- subjects in Groups 1 and 2, and in Group 3, the YF concurrent group
3) Neutralizing Ab levels (measured by dengue PRNT) by FV status at baseline against each of the 4 parental dengue virus serotypes at baseline and 28 days after each injection of CYD dengue vaccine in Groups 1, 2, and 3
4) Neutralizing Ab levels (measured by dengue PRNT) by FV status at baseline against each of the 4 parental dengue virus serotypes at 4 months after Dose 2 in Groups 2 and 3 and 3, 6, and 12 months after the CYD dengue vaccine Dose 3
5) Neutralizing Ab levels (measured by dengue PRNT) against each of the 4 parental dengue virus serotypes by FV status at baseline at 6 months after each injection of CYD dengue vaccine in Group 1

6) Neutralizing Ab levels (measured by dengue PRNT) by FV status at baseline against each of the 4 parental dengue virus serotypes, and dengue specific IgM and IgG antibodies (measured by enzyme linked immunosorbent assay [ELISA]) following each injection of CYD dengue vaccine in Subgroups 1K and 2K
7) Neutralizing Ab levels (measured by YF PRNT) against YF at baseline and 28 days after each injection of CYD dengue vaccine in YF+ subjects in Groups 1 and 2
8) Neutralizing Ab levels (measured by YF PRNT) against YF at baseline and 1, 3, and 7 months after injection of the YF vaccine at M00 in Groups 3 and 4

Safety

1) Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after each dose of CYD dengue vaccine and/or YF vaccine
2) Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (i.e., prelisted in the subject's diary card [DC] and electronic case report form [eCRF]), injection site reactions (pain, erythema, and swelling) occurring up to 7 days after each dose of CYD dengue vaccine and/or YF vaccine
3) Occurrence, time to onset, number of days of occurrence, intensity, and action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions (fever, headache, malaise, myalgia, and asthenia) occurring up to 14 days after each dose of CYD dengue vaccine and/or YF vaccine
4) Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only) and whether the reaction led to early termination from the study, of unsolicited (spontaneously reported) AEs up to 28 days after each dose of CYD dengue vaccine and/or YF vaccine
5) 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 of CYD dengue vaccine and/or YF vaccine
6) Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial

Statistical methods:

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

Three statistical analyses of immunogenicity and safety by group were performed. These included a planned preliminary analysis (data up to M07) and an analysis at the end of the active phase of the trial (data up to M13), both performed before the final and complete analysis. This CSR presents the results of the final analysis.

The immunogenicity populations (Full and Per-Protocol Analysis Sets) were used for the main immunogenicity analyses, and the safety population was used for the safety analysis.

Hypothesis and Statistical Methods for Primary Objectives

No hypotheses were tested.

Immunogenicity:

The timepoints used for the descriptive comparisons for the humoral immune response to the CYD dengue vaccine were at baseline and 28 days post-Dose 3 for Groups 1 and 2.

Immunogenicity was assessed descriptively using the following parameters:

- Geometric mean titers (GMTs) against each serotype with the parental dengue virus strains
- Geometric mean of individual titers ratios (GMTRs) against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dilution (dil) against each serotype with the parental dengue virus strains
- Number and percentage of subjects with a titer ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Distribution of titers against each of the 4 serotypes with parental dengue virus strains

Ab persistence:

The timepoints used for the descriptive comparisons for the persistence of the humoral immune response to the CYD dengue vaccine were 6 months post-Dose 3 for Groups 1 and 2.

Ab persistence was assessed descriptively using the following parameters:

- GMTs against each dengue serotype with the parental dengue virus strains
- GMTRs against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against each serotype with the parental dengue virus strains
- Number and percentage of subjects with a titer ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Distribution of titers against each of the 4 serotypes with parental dengue virus strains

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

It was assumed that neutralizing Ab titers were log-normally distributed.

Reverse cumulative distribution curves (RCDCs) of the neutralizing Ab titers were plotted for each of 4 dengue serotypes at each timepoint.

Hypotheses and Statistical Methods for Secondary Objectives

No hypotheses were tested.

Immunogenicity:

The timepoints used for the descriptive comparisons for the humoral immune response to the CYD dengue vaccine were at baseline and 28 days post-Dose 1 and post-Dose 2 for Groups 1 and 2.

Immunogenicity was assessed descriptively using the following parameters:

- GMTs against each dengue serotype with the parental dengue virus strains
- GMTRs against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against each serotype with the parental dengue virus strains
- Number and percentage of subjects with a titer ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Distribution of titers against each of the 4 serotypes with parental dengue virus strains

Immunogenicity for YF- subjects receiving CYD dengue vaccine alone or in co-administration with YF:

The timepoints used for the descriptive comparisons for the humoral immune response to the CYD dengue vaccine were at baseline and 28 days post-Dose 1 in the combined YF- subjects from Groups 1 and 2, and in Group 3.

Immunogenicity was assessed descriptively using the following parameters:

- GMTs against each dengue serotype with the parental dengue virus strains
- GMTRs against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against each serotype with the parental dengue virus strains
- Number and percentage of subjects with a titer ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Distribution of titers against each of the 4 serotypes with parental dengue virus strains

Immunogenicity according to baseline FV status:

The timepoints used for the descriptive comparisons for the humoral immune response to the CYD dengue vaccine according to the baseline FV status were at baseline and 28 days after each injection of CYD dengue vaccine in Groups 1, 2, and 3

Immunogenicity according to the baseline FV was assessed descriptively using the following parameters:

- GMTs against each dengue serotype with the parental dengue virus strains
- GMTRs against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against each serotype with the parental dengue virus strains
- Number and percentage of subjects with a titer ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Distribution of titers against each of the four serotypes with parental dengue virus strains

Ab persistence according to baseline FV status:

The timepoints used for the descriptive comparisons by FV status at baseline for the persistence of the humoral immune response to the CYD dengue vaccine were 3, 6, and 12 months after the CYD dengue vaccine Dose 3 and at 4 months after Dose 2 in Groups 2 and 3. Similarly, the timepoints used for the descriptive comparisons for the persistence of the humoral immune response to the CYD dengue vaccine by FV status at baseline were 6 months after each injection of CYD dengue vaccine in Group 1.

Ab persistence according to the baseline FV status was assessed descriptively using the following parameters:

- GMTs against each dengue serotype with the parental dengue virus strains
- GMTRs against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against each serotype with the parental dengue virus strains
- Number and percentage of subjects with a titer ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains
- Distribution of titers against each of the four serotypes with parental dengue virus strains

Ab kinetics:

For the kinetics of Ab responses, descriptive summary statistics including median, geometric mean, standard deviations, range, quartile Q1, and Q3 were presented.

In addition, plots for all the parameters listed below were generated over time by group for Subgroups 1K and 2K and by FV baseline status to assess persistence and/or kinetics using the following parameters:

- GMTs against each dengue serotype with the parental dengue virus strains (measured by dengue PRNT)
- GMTRs against each serotype with the parental dengue virus strains (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose) (measured by dengue PRNT)
- Number and percentage of subjects with a titer ≥ 10 1/dil against each serotype with the parental dengue virus strains (measured by dengue PRNT)
- Number and percentage of subjects ≥ 10 1/dil for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains(measured by dengue PRNT)
- Dengue specific IgM (measured by ELISA) displayed by GMTs; number and percentage of subjects positive for IgM
- Dengue specific IgG (measured by ELISA) displayed by GMTs; number and percentage of subjects positive for IgG and a 4-fold rise in IgG
- Dengue specific IgM and IgG displayed by number and percentage of subjects with positive IgM titers and/or 4-fold rise in IgG

YF Immunogenicity for YF+ subjects at baseline:

The timepoints used for the descriptive comparisons for YF Ab were at baseline and 28 days after each injection of CYD dengue vaccine in subjects YF+ in Groups 1 and 2.

Immunogenicity was assessed descriptively using the following parameters:

- GMTs against YF
- GMTRs against YF (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against YF

YF immunogenicity in subjects receiving YF vaccine:

The timepoints used for the descriptive comparisons for YF humoral immunity were at baseline, 1, 3, and 7 months after injection of the YF vaccine at M00 in Groups 3 and 4

Immunogenicity was assessed descriptively using the following parameters:

- GMTs against YF
- GMTRs against YF (post-dose i/pre-dose i or post-dose i/baseline, where "i" refers to any dose)
- Number and percentage of subjects with a titer ≥ 10 1/dil against YF

For the secondary endpoints, the same statistical methods were used as mentioned for the primary immunogenicity endpoints.

Additional analyses were performed to characterize the Ab responses and kinetics (for example analysis according to baseline YF status based on vaccination history) and are presented in the report.

Safety:

The safety profile was described after each dose of CYD dengue vaccine and/or YF vaccine by group.

The safety analysis addressed the number and percentage of subjects with injection site reactions (pain, erythema, and swelling) from D00 and D07, solicited systemic reactions (fever, headache, malaise, myalgia, and asthenia) from D00 to D14, unsolicited AEs until D28, SAEs throughout the trial including serious dengue cases (serious AESI), serious and non-serious hypersensitivity/allergic reactions (AESIs) from D00 to D07, other serious AESIs from D00 to D30 and unsolicited immediate systemic event occurring within 30 minutes after each dose of CYD dengue vaccine and/or YF vaccine.

Solicited injection site reactions or solicited systemic reactions were described according to time of onset, number of days of occurrence, action taken, and intensity.

Unsolicited AEs or non-serious AESIs were described according to nature (MedDRA preferred term), time to onset, duration, intensity, and relationship to vaccination.

Unsolicited immediate systemic events were described according to nature (MedDRA preferred term) and relationship to vaccination.

The number and percentage of subjects with SAEs, including serious AESIs were described according to nature (MedDRA preferred term), seriousness criteria, outcome, and relationship to vaccination as per Investigator throughout the trial.

All AEs leading to study termination were described according to nature (MedDRA preferred term) and relationship to vaccination.

The exact binomial distribution (Clopper-Pearson method) for proportions was used in calculations of the 95% CIs.

Summary:

Population characteristics:

A total of 390 subjects were included and randomized in the study.

	Group 1	Group 2	Group 3	Group 4	All
Vaccination Schedule	**CYD dengue vaccine at M00, M06, M12**	**CYD dengue vaccine at M00, M02, M06**	**CYD dengue vaccine at M00, M02, M06 + YF vaccine at M00**	**YF vaccine at M00**	
Number of Randomized Subjects	120	120	120	30	390

Among the randomized subjects, 99.7% were included in the Safety Analysis Set (SafAS) for all doses, and 96.9% were included in the Full Analysis Set (FAS). Among subjects of the FAS, 92.3% were included in the Per-Protocol Analysis Set (PPAS) post-injection 1. Among the subjects of Groups 1, 2, and 3 that were included in the FAS, 78.9% were included in the PPAS post-injection 2, and 64.0% were included in the PPAS post-injection 3.

A total of 298 (76.4%) subjects completed the study. Whatever the group, the most frequent reasons for withdrawal were "lost to follow-up" and "voluntary withdrawal not due to an AE". Two subjects in Group 1 were discontinued from the study because of an SAE (vaginal cancer that was not related to vaccination, and blighted ovum that was related to vaccination).

Demographic characteristics (SafAS)

Overall, all the treatment groups were comparable in terms of mean age (mean age ranged from 31.6 years to 34.8 years) and male/female distribution. In all groups, subjects were mostly of White origin and the ethnicity of most subjects was different from Hispanic or Latino.

Baseline FV status

At baseline, the proportion of dengue immune subjects was low (7.4%) and similar in Groups 1 to 3.
Regarding the YF baseline status, based on vaccination history, half of the subjects included in Groups 1 and 2 were considered as YF immune, and all the subjects in Groups 3 and 4 were considered as YF non-immune.
However, among the subjects considered as YF non-immune based on vaccination history, around 30% in each group presented with YF Ab titers ≥ 10 (1/dil), using the YF PRNT50 assay. The reasons for these unexpected results were not known (based on data up to M13). For this reason, Sanofi Pasteur's clinical team decided to further analyze the YF and FV status at baseline according to YF PRNT80 derived results. Both YF PRNT50 and YF PRNT80 analyses are presented in the report.

IMMUNOGENICITY RESULTS

- **PRIMARY OBJECTIVES**

Dengue Immune Response in Groups 1 and 2, at Baseline and 28 Days post-dose 3

Baseline GMTs were low (≤5.8) and similar in both treatment groups and for each serotype.

Summary of GMTs of Ab against each serotype with the parental dengue virus strains - Dengue PRNT – FAS

			Group 1 (N=117)			Group 2 (N=119)	
Component	Timepoint	M	GM	(95% CI)	M	GM	(95% CI)
Serotype 1	Post-Inj 3	93	14.8	(11.3; 19.4)	108	15.9	(12.6; 20.0)
Serotype 2	Post-Inj 3	94	51.2	(38.2; 68.6)	108	59.9	(45.8; 78.4)
Serotype 3	Post-Inj 3	94	45.7	(35.0; 59.8)	107	59.3	(47.0; 74.7)
Serotype 4	Post-Inj 3	94	66.8	(50.9; 87.8)	107	83.1	(61.4; 112)

Whatever the schedule (0-6-12 months [Group 1] or 0-2-6 months [Group 2]), the GMTs and the percentage of seropositive subjects, for each serotype, increased 28 days after the third dengue injection compared to baseline. Post-injection 3, the results were comparable, in terms of GMTs and in terms of percentage of seropositive subjects, between the 2 schedules for each serotype.

Whatever the group, the levels of GMTs post-injection 3 were the lowest for serotype 1 and the highest for serotype 4; the percentage of seropositive subjects was above 80% for serotypes 2, 3, and 4 and was around 50% for serotype 1.

- **SECONDARY OBJECTIVES**

Dengue Immune Response

Dengue Immune Response in Groups 1 and 2, 28 Days post-dose 1 and post-dose 2

For the 2 schedules, the GMTs and the percentage of seropositive subjects increased 28 days after each injection compared to each pre-injection timepoint, for each serotype but to a lower extent for serotype 1. Post-dose 2 (PD2), GMTs were higher than PD1 for all serotypes. PD3 GMTs were similar to PD2 GMTs (serotypes 1, 2, and 3) or lower (serotype 4). The percentage of seropositive subjects PD2 was higher than PD1 and similar to PD3, for each serotype. The results were comparable in terms of GMTs and in terms of percentages of seropositive subjects between the 2 schedules, for each serotype, post-injection 2 and post-injection 3.

Dengue Immune Response 28 Days post-dose 1 in the combined YF- subjects in Group 1 and Group 2, and in Group 3: Impact of Concomitant YF and CYD Vaccination on Dengue Immune Response post-dose 1

As previously explained, due to the discrepancy between the YF PRNT50 assay and the YF vaccination history for the determination of the subjects' baseline YF status, the YF status of subjects at baseline was re-calculated using YF PRNT80, a more stringent assay compared to YF PRNT50.

Summary of GMTs of Ab titers against each serotype with the parental dengue virus strains in YF non-immune subjects (YF PRNT50) at baseline - Dengue PRNT - FAS

			Group 1 and 2 pooled YF Non-Immune (N=79)			**Group 3 YF Non-Immune (N=80)**	
Component	**Timepoint/Ratio**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Serotype 1	**Post-Inj 1**	79	**8.27**	(6.35; 10.8)	80	**7.87**	(6.43; 9.63)
Serotype 2	**Post-Inj 1**	79	**18.4**	(12.9; 26.1)	80	**11.1**	(8.63; 14.2)
Serotype 3	**Post-Inj 1**	77	**23.1**	(15.8; 33.8)	80	**9.17**	(7.24; 11.6)
Serotype 4	**Post-Inj 1**	77	**202**	(109; 375)	79	**23.1**	(15.0; 35.6)

For serotypes 1 and 2, GMTs PD1 were similar in YF non-immune subjects of Group 1 and 2 and in subjects who received concomitantly the YF vaccine (Group 3). For serotype 3 and particularly serotype 4, GMTs PD1 were higher in YF non-immune subjects of Group 1 and 2 than in subjects who received concomitantly the YF vaccine (Group 3).

The reduction of the dengue immune response post-dose 1 shown in YF non-immune subjects of Group 3 compared to Group 1and 2, in terms of GMTs for serotypes 3 and 4, was also observed when taking into account the YF baseline status based on YF PRNT80.

A reduction of the dengue immune response post-dose 1 in terms of percentage of seropositive subjects for serotypes 3, and 4, was also observed whatever the analysis.

Dengue Immune Response by Baseline FV Status

The impact of the FV baseline status on the dengue immune response was assessed using the FV baseline status based on YF PRNT50 and YF PRNT80 assays. Different trends were observed depending on the considered serotype and discrepancies were observed between both methods used. However, after a complete vaccination schedule (3 doses), no real priming effect of the previous YF vaccination on the dengue immune response has been observed. The unexpected results obtained with the YF PRNT50 assay did not seem to impact the final conclusions.

The analysis of dengue immune response by FV status provided also data on the impact of the co-administration of YF and CYD dengue vaccines on dengue immune response post-dose 2 and post-dose 3.

Summary of GMTs of Ab titers against each serotype with the parental dengue virus strains, by baseline FV status (YF + dengue PRNT50) - Dengue PRNT - FAS

		Group 2 FV Non-Immune (N=39)			Group 3 FV Non-Immune (N=76)		
Component	**Timepoint**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Serotype 1	**Post-Inj 2**	38	**12.6**	(8.25; 19.4)	65	**12.1**	(8.96; 16.2)
	Post-Inj 3	34	**13.7**	(8.69; 21.5)	60	**18.8**	(13.3; 26.6)
Serotype 2	**Post-Inj 2**	38	**67.8**	(37.0; 124)	65	**36.0**	(24.3; 53.4)
	Post-Inj 3	34	**60.1**	(34.2; 105)	60	**50.7**	(34.4; 74.8)
Serotype 3	**Post-Inj 2**	38	**52.1**	(29.6; 91.8)	65	**18.7**	(13.2; 26.5)
	Post-Inj 3	33	**44.7**	(29.6; 67.3)	60	**27.3**	(19.7; 37.8)
Serotype 4	**Post-Inj 2**	37	**131**	(67.2; 257)	65	**38.9**	(23.9; 63.3)
	Post-Inj 3	33	**85.0**	(47.8; 151)	60	**65.9**	(44.4; 97.7)

Summary of GMTs of Ab titers against each serotype with the parental dengue virus strains, by baseline FV status (YF + dengue PRNT80) - Dengue PRNT - FAS

		Group 2 FV Non-Immune (N=54)			Group 3 FV Non-Immune (N=103)		
Component	**Timepoint**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Serotype 1	**Post-Inj 2**	53	13.0	(9.12; 18.5)	90	10.9	(8.55; 14.0)
	Post-Inj 3	49	14.4	(10.1; 20.7)	84	18.5	(13.9; 24.8)
Serotype 2	**Post-Inj 2**	53	58.8	(36.5; 94.8)	90	30.8	(22.3; 42.6)
	Post-Inj 3	49	51.4	(32.8; 80.6)	84	46.4	(33.8; 63.6)
Serotype 3	**Post-Inj 2**	53	54.1	(33.3; 87.8)	90	18.5	(13.6; 25.2)
	Post-Inj 3	48	47.3	(32.5; 69.0)	83	30.2	(22.8; 40.1)
Serotype 4	**Post-Inj 2**	52	145	(83.0; 253)	90	42.8	(29.2; 62.7)
	Post-Inj 3	48	89.2	(53.3; 149)	83	71.2	(52.0; 97.7)

The differences in the dengue immune response observed post-dose 1 between subjects who received CYD dengue vaccine only and subjects who received CYD dengue and YF vaccines concomitantly (Group 3) were still observed post-dose 2, but disappeared post-dose 3, meaning that following a 3-dose schedule, no difference was observed. These conclusions were drawn whatever the analysis: the FV baseline status based on YF PRNT50 and the YF PRNT80 assays (tables above). Regarding percentages of seropositive subjects, discrepancies were observed between the 2 analyses. Post-dose 2, a reduction of the percentage of seropositive subjects in the co-administered group was observed for serotypes 3 and 4 with the YF PRNT50 assay. A reduction of the percentage of seropositive subjects in the co-administered group was only observed for serotype 3 with the YF PRNT80 assay. Post-dose 3, a reduction of the percentage of seropositive subjects in the co-administered group was observed for serotype 3 with the YF PRNT50 assay while the results were similar in both groups for all serotypes with the PRNT80 assay.

YF Immune Response

Impact of CYD Vaccination on YF Antibody Levels in YF Immune Subjects

Whatever the schedule (standard [Group 1] or compressed [Group 2]), in subjects who were YF immune at baseline, there was more than 2 fold-increase in YF Ab titer on average compared to baseline after the first dose of CYD dengue vaccine: the first dose of CYD dengue vaccine induced a boost of the YF Ab titers. However, this effect was numerically reduced with the YF PRNT80 assay.

Impact of Concomitant CYD and YF Vaccination on YF Immune Response

No impact of CYD dengue and YF concomitant vaccination was observed on YF immune response, whatever the YF PRNT assay used. One month after injection of the YF vaccine, YF GMTs were similar in subjects who received concomitantly YF and CYD dengue vaccines at M00 (Group 3) and in subjects who received YF vaccine only at M00 (Group 4). Three and 7 months after injection of the YF vaccine, YF GMTs were also similar in Groups 3 and 4.

SAFETY RESULTS

Immediate AEs

Only 1 subject (Group 3) reported an immediate AE within the 30-minute observation period after the first injections (Grade 1 dizziness), which was assessed as related to vaccination.

Solicited Reactions

Solicited injection site reactions

After the first injection, the percentage of subjects experiencing at least 1 solicited injection site reaction at the CYD injection site was similar in Groups 1, 2, and 3: 28.8%, 35.3%, and 34.8%, respectively. This proportion remained similar after each dose. Injection site pain was the most frequently reported injection site reaction after each dose. Most of these reactions were of Grade 1 intensity, started within the first 3 days after vaccine injection, and resolved spontaneously within 3 days.

As regards to YF co-administration at the first injection, The percentage of subjects experiencing at least 1 solicited injection site reaction (all injection sites combined) was higher (51.3%) in subjects who received concomitantly CYD and YF vaccines (Group 3) than in subjects who received only CYD dengue vaccine (Groups 1and 2) or only YF vaccine (Group 4, 37.0%).

Solicited systemic reactions

After the first injection, the percentage of subjects experiencing at least 1 solicited systemic reaction was similar in Groups 1 and 2 (55.1% and 57.1%, respectively). In subjects who received concomitantly CYD dengue and YF vaccines (Group 3), this percentage was higher (67.0%) than in Groups 1 and 2, and tended to be slightly higher than in subjects of Group 4 who received only YF vaccine (59.3%).

The proportion of subjects experiencing solicited systemic reactions decreased post-injection 2 and then remained steady post-injection 3.

Headache, malaise, and myalgia were the most frequently reported solicited systemic reactions after each CYD dengue vaccine dose. Most of these reactions were of Grade 1 intensity, started within the first 3 days after vaccine injection, and resolved spontaneously within 3 days.

Unsolicited Non-Serious AEs

After the first injection(s), the percentage of subjects experiencing at least 1 unsolicited non-serious AE was similar in Groups 1, 2, and 3 (28.3%, 26.7%, and 22.7%, respectively) and tended to be slightly higher in Group 4 (33.3%). The proportion of subjects experiencing unsolicited non-serious AEs decreased post-injection 2 and then steady post-injection 3.

In all groups, the large majority of the unsolicited non-serious AEs were systemic AEs. They were mainly assessed as not related to vaccination and most of them were of Grade 1 or 2 intensity.

After the first injection(s), unsolicited non-serious ARs were reported by ≤10% of the subjects. Most of these adverse reactions

were of Grade 1 intensity, started within the first 3 days after vaccine injection(s), and resolved within 7 days. In each group, the most frequently observed unsolicited ARs were reported in the SOC "General disorders and administration site conditions". The proportion of subjects experiencing unsolicited non-serious ARs tended to decrease post-injection 2 (< 3%) and post-injection 3.

AEs leading to Discontinuation

No AE leading to study discontinuation was reported in any group in the 28 days following any injection.

SAEs

Overall, during the entire trial, a total of 13 subjects experienced 18 SAEs: 4 (3.3%) subjects in Groups 1, 2, and 5 (4.2%) subjects in Group 3 experienced at least one SAE. No SAE occurred in Group 4. Among them, one (blighted ovum) was assessed by the Investigator as related to vaccination. No serious AESIs occurred during the whole trial.

AESIs

Three subjects experienced 3 AESIs after the first injection(s); all were non-serious and belonged to the category of hypersensitivity/allergic reactions occurring in the 7 days following injection(s):

- Flushing of the face (Group 2), assessed as related to vaccination
- Asthma (Group 3), assessed as related to vaccination
- Rash on the right side of the neck (Group 3), assessed as not related to vaccination

All were rated as Grade 1.

Pregnancies

A total of 7 subjects reported 10 pregnancies during the study. Outcome of these pregnancies were 1 blighted ovum, 2 elective abortions, and 5 live births; 2 pregnancy outcomes remained unknown. The SAE regarding blighted ovum was assessed as related to vaccination by the Investigator, and the same subject had another pregnancy during the trial that resulted in live birth of twins. No safety concern was raised regarding inadvertent exposure to CYD dengue vaccine before or during pregnancy.

Issue date: 22- Jul-2020