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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:** U1111-1111-5855, NCT01064141, 2014-001694-14 **Study code:** CYD08

Title of the study: Immunogenicity and Safety of CYD Dengue Vaccine in Healthy Toddlers Aged 12 to 15 Months in the Philippines

Study center(s): Multi-center trial in the Philippines

Study period:

Date first subject enrolled: 18/Jan/2010

Date last subject completed: 08/May/2012

Phase of development: Phase II

Objectives:

Primary objectives:

1) To describe the safety of CYD dengue vaccine after each injection; first injection given alone or co-administered with measles, mumps, rubella (MMR) vaccine.

2) To describe dengue vaccinal viremia and the biological safety after the first dengue vaccination.

Secondary objectives:

1) To describe immunogenicity of CYD dengue vaccine after each injection; first injection given alone or co-administered with MMR vaccine.

2) To describe the immunogenicity of MMR vaccine, given alone or co-administered with CYD dengue vaccine.

Methodology:

CYD08 was a randomized, controlled, multi-center, Phase II trial with a stepwise enrollment of 210 toddlers in the Philippines in three steps, modified double-blind for the first dengue injection and open-label for the second and third dengue injections.

Overall, there were 4 different treatment groups. Toddlers in Group 1 (DV) and Group 2 (Control) received 5 injections and toddlers in Group 3 (Co-ad) and Group 4 (Seq) received 6 injections (MMR or placebo co-administered with the first injection of CYD dengue vaccine in two separate arms).

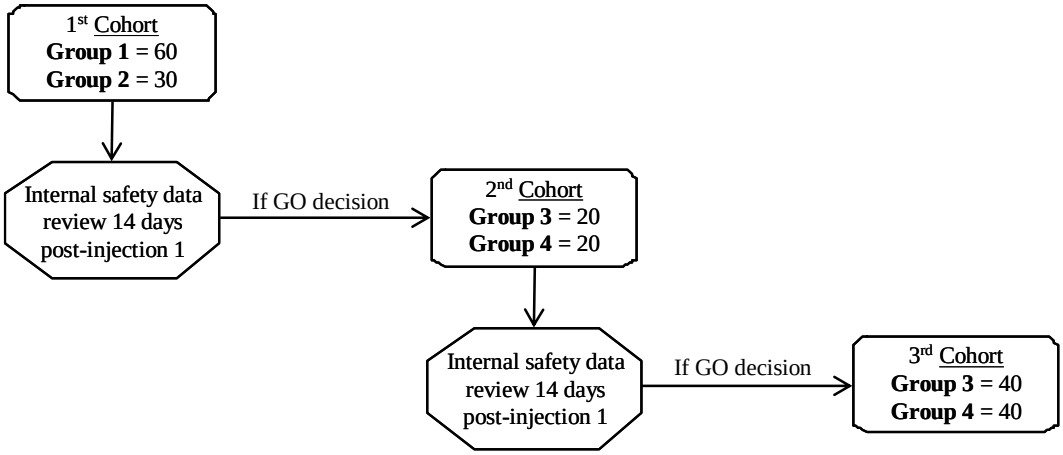
Table 1: **Treatment Groups**

Month	M-1	M0	M6	M9	M12
Visit	**V_MV**	**V01**	**V06**	**V08**	**V09**
Injection	**MMR**	**1**	**2**		**3**
Group 1 (DV) (n=60)	MMR	DV	DV	Combo	DV
Group 2 (Control) (n=30)	MMR	CT 1	CT 2	Combo	CT 2
Group 3 (Co-ad) (n=60)	CT 1	DV + MMR	DV	Combo	DV
Group 4 (Seq) (n=60)	MMR	DV + PL	DV	Combo	DV

DV: Dengue Vaccine; CT: Control Vaccine (CT 1: Varicella and CT 2: Hepatitis A); PL: placebo;
Co-ad: co-administration; Seq: Sequential administration; MMR: Measles, Mumps, Rubella vaccine; Combo: Diphtheria, Tetanus, Pertussis, Poliomyelitis and Hib vaccine

As a safety precaution, this trial used a stepwise approach. A first Cohort of 90 toddlers was enrolled to evaluate the safety of CYD dengue vaccine alone. After internal review of safety data 14 days post-injection 1 from the first Cohort, the decision was taken whether to proceed with the next enrollment step and whether further dengue injection should be administered. The second step of the trial evaluated the safety of CYD dengue vaccine when co-administered or not with MMR vaccine in a second Cohort of 40 toddlers. Then, after internal review of the 14-day post-injection 1 safety data from the second Cohort, the third enrollment step proceeded with a third Cohort of 80 toddlers.

Figure 1: **Stepwise Approach Enrollment**



Number of subjects:	Planned: 210
	Randomized: 210
	Vaccinated subjects at V01: 209
	Vaccinated subjects at V06: 208
	Vaccinated subjects at V09: 205
Evaluated:	
	Immunogenicity: 208
	Safety: 209

Diagnosis and criteria for inclusion:

Inclusion and exclusion criteria were checked either:

- at screening visit *(Scr.)*
- at screening and at first vaccination visits *(Scr.+V_MV)*
- at first vaccination visit *(V_MV)*

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

1) Toddler in good health based on medical history and medical examination *(Scr.+V_MV)*
2) Toddler aged 12 to 15 months on the day of inclusion *(Scr.)*
3) Born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 2.5 kg *(Scr.)*
4) Provision of informed consent form signed by the parent(s) or other legally acceptable representative (and by an independent witness if required by local regulations) *(Scr.)*

5) Subject and parent/delegate able to attend all scheduled visits and comply with all trial procedures *(Scr.)*

6) Completion of previous vaccination program according to the national immunization schedule, except for measles *(Scr.)*

Study treatments

Investigational Product: CYD Dengue Vaccine

Form: Powder and solvent for suspension for injection

Composition: Each injected (0.5 mL) dose of reconstituted vaccine contained:

5 ± 1 log10 cell-culture infectious dose 50% (CCID50) of each live, attenuated 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% containing human serum albumin 2.5%

Route of administration: Subcutaneous

Control Product 1: OKAVAX®

Form: Powder and solvent for suspension for injection

Composition: Each injected (0.5 mL) dose of reconstituted vaccine contained:

- Attenuated live varicella-zooster virus (Oka strain) not less than 1000 plaque-forming units (PFU)

Excipients: sodium chloride (1.14 mg), potassium chloride (0.03 mg), potassium dihydrogenphosphate (0.29 mg), disodium hydrogenphosphate 12-water (3.14 mg), purified sucrose (25.0 mg), sodium L-glutamate (0.36 mg), kanamycin sulfate (7 µg or less) and erythromycin lactobionate (2 µg or less)

Solvent: 0.7 mL of supplied water for injection

Route of administration: Subcutaneous

Control Product 2: AVAXIM® 80U

Form: Suspension for injection

Composition: One dose of 0.5 mL contained:

- Hepatitis A virus (GBM strain)*, inactivated** 80U***

*cultured on MRC-5 human diploid cells
**adsorbed on aluminum hydroxide (quantity equivalent to 0.15 mg of aluminum)
***Ag units expressed using an in-house reference

Excipients: phenoxyethanol, formaldehyde, hanks medium 199 which is a complex mixture of amino acids, mineral salts, vitamins, hydrochloric acid or sodium hydroxide for pH adjustment and water for injection

Route of administration: Intramuscular (IM)

Control Product 3: Placebo (NaCl)

Form: Liquid

Composition: NaCl 0.9%

Route of administration: Subcutaneous

Other Product 1: TRIMOVAX® (MMR)

Form: Powder and diluent for suspension for injection

Composition: Each injected (0.5 mL) dose of reconstituted vaccine contained:

- at least 1000 CCID50 measles virus (Schwarz strain) cultivated on primary culture of chicken embryo cells
- at least 5000 CCID50 mumps virus (Urabe AM-9 strain) cultivated in embryonated hen eggs
- at least 1000 CCID50 rubella virus (Wistar RA 27/3M) cultivated on human diploid cells

Excipient: human albumin (q.s. for lyophilization)

Solvent: 0.5 mL water for injection

Route of administration: Subcutaneous

Other Product 2: PENTAXIM® (Combo)

Form: Powder and suspension for injection

Composition: Each injected (0.5 mL) dose of reconstituted vaccine contained:

- Diphteria toxoid ..... ≥ 30 IU
- Tetanus toxoid ..... ≥ 40 IU
- Bordetella pertussis Ags:
  - Toxoid ..... 25 µg
  - Filamentous hemagglutinin ..... 25 µg
- Type 1 poliomyelitis virus (inactivated) ..... 40 DU*†
- Type 2 poliomyelitis virus (inactivated) ..... 8 DU*†
- Type 3 poliomyelitis virus (inactivated) ..... 32 DU*†
- Polysaccharide of Haemophilus influenzae type b conjugated to the tetanus protein ..... 10 µg

*DU: D Ag unit
† or equivalent antigenic quantity determined by a suitable immunochemical method

Excipients: saccharose, trometamol, aluminum hydroxide, Hank's medium without phenol red, acetic acid and/or sodium hydroxide for pH adjustment, formaldehyde, phenoxyethanol and water for injection

Route of administration: IM

Duration of participation: The expected duration per toddler was 19 months (including the 6-month safety follow-up).

Criteria for evaluation:

Primary endpoints:

Clinical Safety:

- Occurrence of unsolicited systemic AEs reported in the 30 minutes after each injection
- Occurrence of solicited (prelisted in the subject diary and eCRF) injection site reactions within 7 days following each injection
- Occurrence of solicited (prelisted in the subject diary and eCRF) systemic reactions within 14 days following each injection
- Occurrence of unsolicited (spontaneously reported) AEs within 28 days following each injection
- Occurrence of SAEs throughout the trial

Biological Safety:

Occurrence and timing of out-of-normal-range biological tests (biochemistry and hematology) results at baseline (screening visit, Scr./SC) and 8 days after the first dengue vaccination.

Dengue Vaccinal Viremia:

- 8 days after the first dengue vaccination, the occurrence and the level of dengue vaccine viruses were measured in serum of all toddlers by quantitative and serotype-specific reverse transcriptase polymerase chain reactions (RT-PCRs).

Secondary endpoints:

Immunogenicity:

- CYD dengue vaccine: neutralizing antibody (Ab) levels against each of the 4 parental dengue virus serotype strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured (dengue neutralization assay) in sera collected at baseline from all toddlers and 28 days post-injections 2 (V07) and 3 (V10) for toddlers from Groups 1 and 2 and 28 days post-injections 1 (V04), 2 (V07) and 3 (V10) for toddlers from Groups 3 and 4.
- MMR vaccine: Ab levels against measles, rubella and mumps were measured by enzyme-linked immunosorbent assay (ELISA) tests in sera collected from all toddlers from Groups 3 and 4 at baseline (Scr.) and 28 days post-vaccination with MMR (i.e. at V01 in Group 4 and at V04 in Group 3).

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.

For the stepwise approach, a blinded safety review was performed by an internal SMT on safety data (not yet cleaned by data management) obtained 14 days after the first injection with CYD dengue vaccine before to proceed to the next step.

Four statistical analyses were performed in order to support the design and provide preliminary data in toddlers for future studies in toddlers. The first analysis provided safety data 28 days post-injection 1 in all toddlers from Cohort 1; the data were partially unblinded for this analysis. The second analysis provided data 28 days post-injection 1 in all toddlers from all cohorts, as well as MMR immunogenicity data for all toddlers from Cohorts 2 and 3 after unblinding. The third statistical analysis provided safety and immunogenicity data at post-injection 2 of dengue injection in all toddlers from all cohorts.

The final statistical analysis provided safety and immunogenicity data at post-injection 3 of dengue injection in all toddlers from all cohorts, including the 6-month follow-up safety data after the last injection and collection of dengue cases.

Summary:

Trial Population:

Enrollment occurred as planned in the protocol. A total of 222 subjects were screened and 210 of them present at V_MV (day of the first vaccination) were randomized following the stepwise approach of 3 cohorts in 4 different groups. Of all randomized subjects, 97.6% (205) completed the study and 2.3% (5) discontinued: 2 subjects in Group 1 (DV) and 3 subjects in Group 3 (Co-ad).

Table 3: **Evaluable subjects and studied populations – Full and Per-protocol analysis sets**

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	All n (%)
Randomized subjects	60 (100.0)	30 (100.0)	60 (100.0)	60 (100.0)	210 (100.0)
MMR Full analysis set*	60 (100.0)	30 (100.0)	59 (98.3)	60 (100.0)	209 (99.5)
Full analysis set*	60 (100.0)	30 (100.0)	58 (96.7)	60 (100.0)	208 (99.0)
Per-protocol set post-dose MMR vaccine†	59 (98.3)	30 (100.0)	58 (96.7)	56 (93.3)	203 (96.7)
Per-protocol set post-injection 1†	-	-	58 (96.7)	60 (100.0)	118 (56.2)
Per-protocol set post-injection 2†	59 (98.3)	30 (100.0)	58 (96.7)	60 (100.0)	207 (98.6)
Per-protocol set post-injection 3†	57 (95.0)	30 (100.0)	54 (90.0)	53 (88.3)	194 (92.4)

n is the number of subjects in the specified population

* Subjects were classified according to the vaccine to which they were randomized

† Subjects were classified according to the vaccine they received.

Among the 210 randomized subjects, 99.5% (all but 1 in Group 3) were included in the MMR Full analysis set (MMR FAS) and 99.0% (all but 2 in Group 3) received at least one injection and were included in the Full Analysis set (FAS). Overall, a very good retention rate was observed, with the percentages of subjects in any of the 4 vaccine groups included in any of the Per Protocol analysis sets (PP) (i.e., at post-MMR injection and at post-injections 1, 2 and 3) ranging from 88.3% to 100.0%.

Table 4: **Evaluable subjects and studied populations – Safety analysis sets**

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	All n (%)
Randomized subjects	60 (100.0)	30 (100.0)	60 (100.0)	60 (100.0)	210 (100.0)
Safety analysis set for all injections†	60 (100.0)	30 (100.0)	59 (98.3)	60 (100.0)	209 (99.5)
Safety analysis set post-injection 1‡	60 (100.0)	30 (100.0)	59 (98.3)	60 (100.0)	209 (99.5)
Safety analysis set post-injection 2‡	60 (100.0)	30 (100.0)	58 (96.7)	60 (100.0)	208 (99.0)
Safety analysis set post-injection 3‡	58 (96.7)	30 (100.0)	57 (95.0)	60 (100.0)	205 (97.6)

n is the number of subjects in the specified population

† Subjects were classified according to the vaccine received at the first injection.

‡ Subjects were classified according to the vaccine they received.

The percentages of subjects in any of the 4 vaccine groups included in any of the safety analysis sets (i.e., at post-MMR injection and at post-injections 1, 2 and 3) ranged from 95.0% to 100.0%.

Demographic and Baseline Characteristics

Overall, the 4 vaccine groups were balanced in terms of age, gender, ethnic origin, height, weight, and body mass index. The mean age at inclusion was 13.0 months (range from 12.0 to 15.9 months) and was similar in the 4 vaccine groups. There were slightly less female (42.3%) than male subjects (57.7%) with the same trend in each vaccine group. All subjects were Asian.

Safety Findings

Table 5: Safety overview after any injection – Safety Analysis Set

	Group 1 (N=60)			**Group 2 (N=30)**			**Group 3 (N=59)**			**Group 4 (N=60)**		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Immediate unsolicited AE	0/60	0.0	(0.0; 6.0)	0/30	0.0	(0.0; 11.6)	0/59	0.0	(0.0; 6.1)	0/60	0.0	(0.0; 6.0)
Immediate unsolicited AR	0/60	0.0	(0.0; 6.0)	0/30	0.0	(0.0; 11.6)	0/59	0.0	(0.0; 6.1)	0/60	0.0	(0.0; 6.0)
Solicited reaction	35/60	58.3	(44.9; 70.9)	24/30	80.0	(61.4; 92.3)	32/59	54.2	(40.8; 67.3)	25/60	41.7	(29.1; 55.1)
Solicited injection site reaction	15/60	25.0	(14.7; 37.9)	8/30	26.7	(12.3; 45.9)	12/59	20.3	(11.0; 32.8)	7/60	11.7	(4.8; 22.6)
Solicited systemic reaction	29/60	48.3	(35.2; 61.6)	23/30	76.7	(57.7; 90.1)	30/59	50.8	(37.5; 64.1)	23/60	38.3	(26.1; 51.8)
Unsolicited AE	39/60	65.0	(51.6; 76.9)	22/30	73.3	(54.1; 87.7)	33/59	55.9	(42.4; 68.8)	29/60	48.3	(35.2; 61.6)
Unsolicited AR	0/60	0.0	(0.0; 6.0)	0/30	0.0	(0.0; 11.6)	0/59	0.0	(0.0; 6.1)	0/60	0.0	(0.0; 6.0)
AE leading to study discontinuation*	1/60	1.7	(0.0; 8.9)	0/30	0.0	(0.0; 11.6)	1/59	1.7	(0.0; 9.1)	0/60	0.0	(0.0; 6.0)
SAE**	1/60	1.7	(0.0; 8.9)	1/30	3.3	(0.1; 17.2)	7/59	11.9	(4.9; 22.9)	1/60	1.7	(0.0; 8.9)
Death	0/60	0.0	(0.0; 6.0)	0/30	0.0	(0.0; 11.6)	0/59	0.0	(0.0; 6.1)	0/60	0.0	(0.0; 6.0)

N: number of subjects in the safety analysis set
n: number of subjects experiencing the endpoint listed in the specified category
M: number of subjects with available data for the relevant endpoint
* Identified in the termination form as SAE or other AE

** Number of SAE occurring within 28 days post-injection

Overview of safety findings

The incidence of solicited reactions after any vaccination was the highest in Group 2 (Control) (80.0%), lower in Group 1 (DV) (58.3%), even lower in Group 3 (Co-ad) (54.2%), and the lowest in Group 4 (Seq) (41.7%). No Grade 3 solicited reactions were reported.

The incidence of unsolicited AEs after any vaccination ranged from 48.3% in Group 4 (Seq) to 73.3% in Group 2 (Control). None of these unsolicited AEs were of Grade 3 intensity or assessed as related to the vaccines. All unsolicited AEs were systemic, expected for a toddler population (in the SOC Infections and Infestations) and most were considered as non-serious events.

There were no immediate unsolicited AEs reported in any of the vaccine groups.

One subject in Group 1 (DV) (1.7%), 1 subject in Group 2 (Control) (3.3%), 7 subjects in Group 3 (Co-ad) (11.9%), and 1 subject in Group 4 (Seq) (1.7%) experienced at least 1 SAE during the study period. None of them was fatal. All SAEs were assessed as non related by the Investigator. One SAE of febrile convulsion in a context of systemic viral infection, occurring 10 days after CYD dengue vaccine + MMR vaccination, considered as non related by the Investigator, was assessed as possibly related to both vaccines by the Sponsor. One subject in Group 1 (DV) and 1 subject in Group 3 (Co-ad) experienced at least 1 AE that led to study discontinuation during the study period.

The safety profiles between Group 3 (Co-ad) and Group 4 (Seq) were globally similar except for the occurrences of SAEs: 7 subjects in Group 3 (Co-ad) (11.9%) versus 1 subject in Group 4 (Seq) (1.7%).

As there were neither major differences of safety profiles between Groups 1 and 4 (who received the CYD dengue vaccine sequentially) nor between Groups 1, 3 and 4 (who all received the CYD dengue vaccine), the data from the different vaccine groups were pooled to set up comparison, respectively, with Group 3 (Co-ad) (who underwent co-administration of the IP with the MMR vaccine) or with Group 2 (Control) (who received control licensed vaccines).

Injection site reactions

The injection site reactions reported were mainly pain and erythema of Grade 1 intensity, occurring within 3 days after vaccination, and lasting less than 3 days.

Following the first injection, injection site pain, erythema and swelling were more frequently reported in Group 2 (Control) (after Varicella vaccine injection) than in other groups. Following the second and the third injections, injection site pain remained, overall, the most frequently reported solicited injection site reaction, but the percentages of subjects reporting injection site pain did not exceed 5.0% and 3.4%, respectively. There were no substantial differences in frequency, time of onset, and duration of solicited injection site reactions after any injection between Group 3 (Co-ad) and pooled Group 1+4 (DV+Seq) and between Group 2 (Control) and pooled Group 1+3+4 (CYD dengue vaccine). No action was taken for any of the solicited injection site reactions.

Systemic reactions

The most frequently reported solicited systemic reactions varied across vaccine groups and were irritability, fever, crying abnormal, and vomiting. The majority of solicited systemic reactions were of Grade 1 or Grade 2 intensity; none were of Grade 3 intensity. In terms of time of onset, most solicited systemic reactions occurred within 3 days after injection. In terms of duration, most solicited systemic reactions lasted between 1 to 3 days. The most common action taken for fever was medication (paracetamol), while no action was taken for most other solicited systemic reactions.

Following the first injection, fever was the most frequent reaction, followed by irritability and crying abnormal. Overall, reported solicited systemic reactions were more frequently observed in Group 2 after the Varicella vaccination compared to other groups, with the exception of fever, which occurred more frequently in Group 3 (Co-ad) (28.8%) after the concomitant administration of MMR and CYD dengue vaccine (compared to other groups, from 11.7% to 20.0%). The most notable difference was observed for vomiting, with 30.0% of subjects in Group 2 (Control) reporting vomiting compared to less than 12.0% of subjects in Group 1 (DV) and less than 2.0% of subjects in Groups 3 and 4 after the first injection.

Overall, solicited systemic reactions in subjects from all 4 vaccine groups were much less frequent after the second and third injections than after the first injection (maximum percentages in a specified category ≤ 10.0% and ≤ 10.3%, respectively). After the second injection, reported solicited systemic reactions were more frequently observed in Group 2 (Control), compared to other groups, but they were equally frequent between Group 3 (Co-ad) and pooled Group 1+4 (DV+Seq).

There was no substantial difference in terms of time of onset of the reported solicited systemic reactions after the second and the third injections between Group 3 (Co-ad) and pooled Group 1+4 (DV+Seq) and between Group 2 (Control) and pooled Group 1+3+4 (CYD dengue vaccine). In terms of duration, there was no substantial difference between Group 3 (Co-ad) and pooled Group 1+4 (DV+Seq) after the second and third injections, but the solicited systemic reactions tended to last longer in Group 2 (Control) (up to 7 days) compared to pooled Group 1+3+4 (never more than 3 days) during the second (not the third) vaccination period.

Unsolicited adverse events

The incidence of unsolicited AEs within 28 days after any vaccination ranged from 48.3% in Group 4 (Seq) to 73.3% in Group 2 (Control). None of these unsolicited AEs were of Grade 3 intensity, and none were assessed as related to the vaccines. All unsolicited AEs were systemic, expected for a toddler population (in the SOC Infections and Infestations) and most were considered as non-serious events. The incidence of SAEs within 28 days after any injection was low: no SAE in Group 1 (DV), 1 SAE in 3.3% of subjects in Group 2 (Control), 4 SAEs in 5.1% of subjects in Group 3 (Co-ad), and 1 SAE in 1.7% of subjects in Group 4 (Seq). There were no unsolicited ARs in any vaccine group. There were neither immediate unsolicited AEs nor ARs in any vaccine group.

The incidence of unsolicited AEs within 28 days after the first injection was the highest in Group 2 (Control) (63.3%), lower in Group 1 (DV) (58.3%), even lower in Group 3 (Co-ad) (42.4%), and the lowest in Group 4 (Seq) (26.7%). There were as many unsolicited AEs in Group 3 (Co-ad) within 28 days after the concomitant administration of MMR and CYD dengue vaccine as in pooled Group 1+4 (DV+Seq) within 28 days after the administration CYD dengue vaccine (with or without placebo). There were much more unsolicited AEs reported in Group 2 (Control) within 28 days after the Varicella vaccination than in pooled Group 1+3+4 (CYD dengue vaccine) within 28 days after the administration CYD dengue vaccine.

In all 4 vaccine groups, the incidence of unsolicited AEs within 28 days after the second injection was markedly lower than after the first injection. The incidence was the highest in Group 2 (Control) (23.3%), and between 5.0% and 8.6% in Groups 1, 3 and 4. There were as many unsolicited AEs in Group 3 (Co-ad) as in pooled Group 1+4 (DV+Seq) and substantially more unsolicited AEs in Group 2 (Control) as in pooled Group 1+3+4 (CYD dengue vaccine) within 28 days after the second injection.

The incidence of unsolicited AEs within 28 days after the third injection was relatively similar between all 4 vaccine groups (ranging from 10.0% in Group 2 to 20.0% in Group 4). It was substantially higher than after the second injection in Groups 1, 3 and 4, and lower in Group 2 (Control). Still, the incidence was lower in all 4 vaccine groups than after the first injection. There were as many unsolicited AEs in Group 3 (Co-ad) as in pooled Group 1+4 (DV+Seq) and nearly twice as many unsolicited AEs in pooled Group 1+3+4 (CYD dengue vaccine) as in Group 2 (Control) within 28 days after the third injection.

Viremia

There was no safety issue regarding the vaccine viremia.

Eight days after the first injection, non-serotype specific and serotype specific dengue vaccinal viremia was detected in only 3 subjects who received CYD dengue vaccine (1 subject in each of the 3 vaccine groups). They had a quantified non-serotype specific dengue vaccinal viremia but at low levels ranging from 5.29 to 5.72 log10 Geq/mL or a quantified serotype 4 specific dengue vaccinal viremia still at low levels ranging from 5.55 to 5.98 log10 Geq/mL.

Clinical Laboratory Evaluation

There was no safety issue regarding the biological safety data.

The most common biological abnormalities at baseline were not clinically significant based on the Investigator's judgment and did not prevent any subject from being enrolled in the study. There was no Grade 3 abnormality at baseline.

The most common biological abnormalities eight days after the first injection were not different from baseline and there was a slight increase of hematological parameter abnormalities compared to baseline for all vaccine groups. There were five subjects with at least one Grade 3 abnormality eight days after the first injection: 1 subject in Group 3 (Co-ad) and 3 subjects in Group 4 (Seq) with Grade 3 ALT increase, and 1 subject in Group 4 (Seq) with Grade 3 hemoglobin abnormality.

Immunogenicity:

Seropositivity Against Each Parental Dengue Virus Serotype

Table 6: **Summary of seropositivity (%, 95% CI) for parental dengue virus serotypes – Full Analysis Set**

Component	Timepoint	Group 1 (N=60)	Group 2 (N=30)	Group 3 (N=58)	Group 4 (N=60)	Group 1+4 (N=120)	Group 1+3+4 (N=178)
Serotype 1	Pre-Inj 1 (SC)	10.0 (3.8; 20.5)	3.3 (0.1; 17.2)	6.9 (1.9; 16.7)	10.0 (3.8; 20.5)	10.0 (5.3; 16.8)	9.0 (5.2; 14.2)
	Post- Inj 3 (V10)	94.8 (85.6; 98.9)	20.0 (7.7; 38.6)	94.7 (85.4; 98.9)	96.7 (88.5; 99.6)	95.8 (90.4; 98.6)	95.4 (91.2; 98.0)
Serotype 2	Pre-Inj 1 (SC)	18.3 (9.5; 30.4)	16.7 (5.6; 34.7)	13.8 (6.1; 25.4)	10.0 (3.8; 20.5)	14.2 (8.5; 21.7)	14.0 (9.3; 20.0)
	Post- Inj 3 (V10)	96.6 (88.1; 99.6)	33.3 (17.3; 52.8)	96.5 (87.9; 99.6)	100.0 (94.0; 100.0)	98.3 (94.0; 99.8)	97.7 (94.3; 99.4
Serotype 3	Pre-Inj 1 (SC)	26.7 (16.1; 39.7)	23.3 (9.9; 42.3)	37.9 (25.5; 51.6)	40.7 (28.1; 54.3)	33.6 (25.2; 42.8)	35.0 (28.0; 42.5
	Post- Inj 3 (V10)	100.0 (93.8; 100.0	36.7 (19.9; 56.1)	100.0 (93.7; 100.0	100.0 (94.0; 100.0)	100.0 (96.9; 100.0)	100.0 (97.9; 100.0)
Serotype 4	Pre-Inj 1 (SC)	25.0 (14.7; 37.9)	21.4 (8.3; 41.0)	5.2 (1.1; 14.4)	16.7 (8.3; 28.5)	20.8 (14.0; 29.2)	15.7 (10.7; 21.9)
	Post- Inj 3 (V10)	98.3 (90.8; 100.0)	23.3 (9.9; 42.3)	96.5 (87.9; 99.6)	100.0 (94.0; 100.0)	99.2 (95.4; 100.0)	98.3 (95.1; 99.6)

In the groups that received the CYD dengue vaccine (Groups 1, 3, and 4), there was an increase in seropositivity rates after each injection till post-injection 3 (V10), regardless of the FV-immune status. There was no substantial change from baseline in seropositivity rates after any injection in Group 2 (Control), regardless of the FV-immune status.

After completion of the three dose vaccination regimen, seropositivity rates against each parental dengue virus serotype were similar in pooled Group 1+4 (DV+Seq) and in Group 3 (Co-ad). Co-administration with MMR vaccine had no impact on the seropositivity rates obtained with the CYD dengue vaccine.

At post-injection 3 (V10), the seropositivity rates against each parental dengue virus serotype ranged from 94.7% to 100.0% in Groups 1, 3 and 4 compared to 20.0% to 36.7% in Group 2 (Control).

Seropositivity Against At Least 1, 2, 3 and 4 Serotypes

Table 7: **Summary of seropositivity (%, 95% CI) for at least 1, 2, 3 or 4 parental dengue virus serotypes – Full Analysis Set**

Component	Timepoint	Group 1 (N=60)	Group 2 (N=30)	Group 3 (N=58)	Group 4 (N=60)	Group 1+4 (N=120)	Group 1+3+4 (N=178)
At least 1 serotype	Pre-Inj 1 (SC)	38.3 (26.1; 51.8)	43.3 (25.5; 62.6)	46.6 (33.3; 60.1)	46.7 (33.7; 60.0)	42.5 (33.5; 51.9)	43.8 (36.4; 51.4)
	Post- Inj 3 (V10)	100.0 (93.8; 100.0)	43.3 (25.5; 62.6)	100.0 (93.7; 100.0)	100.0 (94.0; 100.0)	100.0 (96.9; 100.0)	100.0 (97.9; 100.0)
At least 2 serotypes	Pre-Inj 1 (SC)	21.7 (12.1; 34.2)	13.3 (3.8; 30.7)	12.1 (5.0; 23.3)	15.0 (7.1; 26.6)	18.3 (11.9; 26.4)	16.3 (11.2; 22.6)
	Post- Inj 3 (V10)	100.0 (93.8; 100.0)	30.0 (14.7; 49.4)	100.0 (93.7; 100.0)	100.0 (94.0; 100.0)	100.0 (96.9; 100.0)	100.0 (97.9; 100.0)
At least 3 serotypes	Pre-Inj 1 (SC)	11.7 (4.8; 22.6)	3.3 (0.1; 17.2)	3.4 (0.4; 11.9)	8.3 (2.8; 18.4)	10.0 (5.3; 16.8)	7.9 (4.4; 12.8)
	Post- Inj 3 (V10)	96.6 (88.1; 99.6)	26.7 (12.3; 45.9)	100.0 (93.7; 100.0)	100.0 (94.0; 100.0)	98.3 (94.0; 99.8)	97.7 (94.3; 99.4)
At least 4 serotypes	Pre-Inj 1 (SC)	8.3 (2.8; 18.4)	3.3 (0.1; 17.2)	1.7 (0.0; 9.2)	6.7 (1.8; 16.2)	7.5 (3.5; 13.8)	5.6 (2.7; 10.1)
	Post- Inj 3 (V10)	93.1 (83.3; 98.1)	13.3 (3.8; 30.7)	91.2 (80.7; 97.1)	96.7 (88.5; 99.6)	94.9 (89.3; 98.1)	93.7 (89.0; 96.8)

In the groups that received the CYD dengue vaccine (Groups 1, 3, and 4):

- There was an increase in seropositivity rates after each injection
- At post-injection 3 (V10), all of the subjects were seropositive for at least 2 serotypes.
- The seropositivity rates for all 4 serotypes at post-injection 3 were high ranging from 91.2% (Group 3) to 96.7% (Group 4).

There was no substantial change in seropositivity rates after any injection in the Group 2 (Control). At post-injection 3, the seropositivity rate ranged from 13.3% (for all 4 serotypes) to 43.3% (for at least 1 serotype), similar to baseline.

Seropositivity rates for at least 1, 2, 3 or 4 serotypes were similar in pooled Group 1+4 (DV+Seq) and in Group 3 (Co-ad).

At post-injection 3, seropositivity rates for at least 1, 2, 3 or 4 serotypes were largely higher in pooled Group 1+3+4 (CYD dengue vaccine) compared to Group 2 (Control).

Dengue Neutralizing Antibody Levels

Table 8: **Summary of geometric mean titers of antibodies against parental dengue virus serotypes – Full Analysis Set**

Component	Timepoint	Group 1 (N=60)	Group 2 (N=30)	Group 3 (N=58)	Group 4 (N=60)	Group 1+4 (N=120)	Group 1+3+4 (N=178)
Serotype 1	Pre-Inj 1 (SC)	6.39 (5.21; 7.85)	5.31 (4.69; 6.02)	5.59 (4.94; 6.33)	6.18 (5.16; 7.41)	6.29 (5.50; 7.19)	6.05 (5.48; 6.68)
	Post- Inj 3 (V10)	105 (73.8; 148)	11.5 (5.77; 22.8)	108 (80.7; 144)	124 (90.9; 169)	114 (90.6; 143)	112 (93.5; 134)
Serotype 2	Pre-Inj 1 (SC)	10.0 (6.54; 15.4)	9.73 (5.18; 18.3)	7.20 (5.30; 9.77)	7.46 (5.25; 10.6)	8.66 (6.58; 11.4)	8.15 (6.62; 10.0)
	Post- Inj 3 (V10)	147 (99.2; 219)	15.7 (7.70; 32.0)	213 (146; 311)	176 (121; 254)	161 (123; 210)	176 (142; 219)
Serotype 3	Pre-Inj 1 (SC)	10.1 (6.99; 14.5)	9.05 (5.80; 14.1)	13.8 (9.49; 20.0)	14.8 (9.50; 23.1)	12.2 (9.17; 16.2)	12.7 (10.1; 15.9)
	Post- Inj 3 (V10)	311 (222; 436)	13.4 (7.63; 23.5)	358 (277; 464)	387 (284; 527)	347 (277; 436)	351 (295; 417)
Serotype 4	Pre-Inj 1 (SC)	8.25 (6.40; 10.7)	6.98 (5.41; 9.01)	5.60 (4.90; 6.40)	6.99 (5.66; 8.63)	7.59 (6.45; 8.95)	6.88 (6.10; 7.75)
	Post- Inj 3 (V10)	143 (107; 192)	8.16 (5.66; 11.8)	127 (96.0; 169)	160 (131; 195)	152 (127; 180)	143 (123; 166)

Geometric means of individual titers (GMTs) increased after each CYD dengue vaccine injection for Groups 1, 3, and 4 (CYD dengue vaccine groups) to reach global levels of 112 (serotype 1) to 351 (serotype 3) after completion of the three dose vaccination regimen. For Group 2 (Control), GMTs remained low (< 16), similar to baseline values.

GMTs were slightly lower in Group 3 (Co-ad) than in pooled Group 1+4 (DV+Seq) after the first vaccination. At post-injection 3, GMTs were similar in both Group 3 (Co-ad) and pooled Group 1+4 (DV+Seq) for serotype 1 (108 versus 114), and serotype 3 (358 versus 347), lower in Group 3 (Co-ad) than in pooled Group 1+4 (DV+Seaq) for serotype 4 (127 versus 152), and higher in Group 3 (Co-ad) than in pooled Group 1+4 (DV+Seq) for serotype 2 (213 versus 161).

At post-injection 3, GMTs were largely higher in pooled Group 1+3+4 (CYD dengue vaccine) (ranging from 112 to 351) than in Group 2 (Control) (ranging from 8.16 to 15.7) for all 4 serotypes.

Response Rates for Measles, Mumps and Rubella

Measles, mumps and rubella status at screening visit was similar between Group 3 (Co-ad) and Group 4 (Seq) in terms of GMTs and percentages of seroprotected subjects. For measles, the seroprotection rate was low before MMR vaccination in both groups (14.0% and 8.3% respectively). For rubella, only one subject in Group 3 (Co-ad) and none in Group 4 (Seq) was seroprotected for rubella before MMR vaccination.

After MMR vaccination, 100.0% and 96.7% of the subjects in, respectively, Group 3 (Co-ad) and Group 4 (Seq) were seroprotected for measles, at least 95% of the subjects in both Groups 3 and 4 were seroprotected for mumps (regardless of the administration with the CYD dengue vaccine), and 98.3% of the subjects in both Groups 3 and 4 were seroprotected for rubella (regardless of the administration with the CYD dengue vaccine).

For all 3 Ags, there was no difference in the seroprotection rates or increase of Ab levels after vaccination when the MMR vaccine was co-administered with the CYD dengue vaccine or when the administration was sequential.

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