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Sponsor: Sanofi Pasteur **Drug substance:** CYD Dengue Vaccine	**Study Identifiers:** U1111-1115-6290, NCT01411241 **Study code:** CYD33
Title of the study: Immunogenicity and Safety of a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine in Healthy Toddlers Aged 15 to 18 Months in Mexico	
Study center(s): This was a multi-center trial involving 3 investigators over 1 country.	
Study period: Date first subject/patient enrolled: 18/Jul/2011 Date last subject/patient completed: 04/Feb/2014	
Phase of development: Phase III	

Objectives:

Primary Objective:

Immunogenicity

To demonstrate the non-inferiority of the antibody (Ab) response against all antigens (diphtheria, tetanus, pertussis, polio and Hib) in subjects receiving one booster dose of Pentaxim vaccine administered concomitantly with the second dose of CYD dengue vaccine compared to subjects receiving one booster dose of Pentaxim vaccine administered concomitantly with placebo.

Secondary Objective:

Safety (All Subjects):

1. To describe the safety of Pentaxim vaccine administered concomitantly with the second dose of CYD dengue vaccine, or administered concomitantly with placebo.
2. To describe the safety of CYD dengue vaccine after the second dose of CYD dengue vaccine administered concomitantly with Pentaxim vaccine (at V05) or administered alone (at V06).
3. To describe the safety of the CYD dengue vaccine in all subjects after each dose.

Immunogenicity (Dengue Immunogenicity Subset):

1. To describe the Ab response to each dengue virus serotype (post-Dose 2 and post-Dose 3) after the second dose of CYD dengue vaccine administered concomitantly with Pentaxim vaccine (at V05) or administered alone (at V06).
2. To describe the Ab response to each dengue virus serotype post-Dose 2 and post-Dose 3.

Methodology:

Randomized, observer-blind (for the second dose of tetravalent dengue vaccine), open-label (for the first and third doses of tetravalent dengue vaccine), multi-center, Phase III trial in 732 healthy toddlers in Mexico administered a booster injection of Pentaxim vaccine concomitantly with the second dose of tetravalent dengue vaccine at 15 to 18 months of age. Subjects were to be randomized into a 1:1 ratio into 2 groups to receive 7 injections:

Table S1: Vaccination schedule

V01 M0	V04* M1	V05† M6	V06 M7	V08 M12
9-12	**10-13**	**15-18**	**16-19**	**21-24**
CYD dengue vaccine Dose 1	MMR + pneumococcal conjugate vaccine	Pentaxim + CYD dengue vaccine Dose 2	Placebo	CYD dengue vaccine Dose 3
CYD dengue vaccine Dose 1	MMR + pneumococcal conjugate vaccine	Pentaxim + Placebo	CYD dengue vaccine Dose 2	CYD dengue vaccine Dose 3

MMR: measles, mumps, rubella vaccine; Pentaxim: diphtheria, tetanus, acellular pertussis, polio and *Haemophilus influenzae* type b (Hib) vaccine

*Vaccines were to be administered according to manufacturer's instruction but in 2 different injection sites.

†At M6 the 2 vaccines were to be administered in separate limbs (the Pentaxim intramuscular [IM] vaccination was to be in the thigh and the dengue vaccine/placebo subcutaneous (SC) vaccination was to be in the deltoid)

All subjects were to provide one blood sample (BL) for baseline dengue immune status before the first vaccination (BL1 at visit (V) 01); one pre-co-administration blood sample for assessment of baseline pertussis antigens (pertussis toxoid [PT] and filamentous hemagglutinin [FHA]) (BL3 at V05); and one post-vaccination blood sample for Pentaxim vaccine immunogenicity (BL4 at V06).

The **viremia subset** consisted of the first 100 subjects enrolled in the trial and vaccinal viremia was assessed at Day 8 (BL2 at V02).

The **dengue immunogenicity subset** consisted of a randomized subset of 250 subjects (125 subjects from each group) and CYD dengue vaccine immunogenicity was assessed in this subset 28 days after Dose 2 (BL4 at V06 and BL5 at V07) and after Dose 3 (BL6 at V09).

Note: the sampling and testing was to be performed for each vaccine group for BL4 (in all subjects) and BL5 (in subjects randomized in the dengue immunogenicity subset) in order to maintain the blind.

An interactive voice response system (IVRS) / interactive web response system (IWRS) was used for the randomization to the dengue immunogenicity subset at V01, for the allocation of the first 100 subjects to the viremia subset at V01 and for the randomization into the vaccine group at V05. Note: subjects were only allocated to one of the two subsets at V01 (not both).

Reactogenicity data were collected in all subjects after each dose. Serious adverse events (SAEs) were reported throughout the study and adverse events of special interest (AESIs) were collected in defined time-windows. There was to be a 6-month safety follow-up after the last CYD dengue vaccination for all subjects.

Number of subjects/patients: Planned: 732

Randomized: 720

Evaluated:

Immunogenicity: 244

Safety: 714

Diagnosis and criteria for inclusion:

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

1) Aged 9 to 12 months on the day of inclusion.

2) Born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 2.5 kg.

3) Subject in good health, based on medical history and physical examination.

4) Documentation of completion of the primary vaccination series with Pentaxim vaccine with 3 doses received between 2 and 8 months of age.

5) Informed consent form has been signed and dated by both parents or other legally acceptable representative (and by 2 mandatory witnesses as required by local regulations).

6) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures.

Study treatments

Investigational product 1: CYD Dengue Vaccine

Formulation: Powder and solvent for suspension for injection

Composition: Each 0.5 mL dose of reconstituted vaccine contains:

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%, Batch Number D1148

Route of administration: Subcutaneous (SC) in the deltoid region of the upper arm

Investigational product 2: DTaP-IPV//Hib vaccine (Pentaxim™)

Formulation: Powder and suspension for injection

Composition: Each 0.5 mL dose of reconstituted vaccine contains:

- Diphtheria toxoid	≥ 30 IU
- Tetanus toxoid	≥ 40 IU
- *Bordetella pertussis* antigens:	
Toxoid	25 µg
Filamentous haemagglutinin	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 antigen unit

† or equivalent antigenic quantity determined by a suitable immunochemical method

The other ingredients are: saccharose, trometamol, aluminium hydroxide, Hank's medium without phenol red, acetic acid and/or sodium hydroxide for pH adjustment, formaldehyde, phenoxyethanol and water for injections

Route of administration: Intramuscular (IM) in the anterolateral aspect of the thigh

Investigational product 3: Placebo (NaCl)

Formulation: Solution

Composition: NaCl 0.9%

Route of administration: SC in the deltoid region of the upper arm

Duration of participation: The duration of each subject's participation in the trial was approximately 18 months including 6-month safety follow-up.

Criteria for evaluation:

Primary Endpoints:

Immunogenicity :

Levels of Abs 28 days post-Pentaxim booster vaccination to each of the following antigens were measured: diphtheria toxoid, tetanus toxoid, PT, FHA, polyribosylribitol phosphate (PRP) and polio. In addition the levels of Abs to pertussis antigens (PT and FHA) on the day of Pentaxim vaccination were measured.

Seroprotection 28 days post-Pentaxim vaccination to each of the following antigens:

- Diphtheria toxoid (at the level of ≥ 0.1 International unit [IU]/milliliter [mL])
- Tetanus toxoid (at the level of ≥ 0.1 IU/mL)
- Poliovirus types 1, 2 and 3 (at a titer of ≥ 8 1/ dilution [dil])
- PRP (at the level of ≥ 1.0 μg/mL)

The long-term seroprotection thresholds were chosen for diphtheria, tetanus, and Hib antigens as they are more relevant for the booster vaccination.

Booster response 28 days post-Pentaxim vaccination to each of the following pertussis antigens:

- PT
- FHA

The "booster response" was based on the comparison of the pre- and post-booster titers and defined as follows:

- For subjects whose pre-vaccination Ab titers were less than the lower limit of quantitation (< LLOQ), these subjects demonstrated the booster response if they had post-vaccination levels ≥ 4 x LLOQ;
- For subjects whose pre-vaccination Ab concentrations were ≥ LLOQ but < 4 x LLOQ, these subjects demonstrated the booster response if they had a 4-fold increase (i.e., post/pre-vaccination ≥ 4);
- For subjects whose pre-vaccination Ab concentrations were ≥ 4 x LLOQ, these subjects demonstrated the booster response if they had a 2-fold increase (i.e., post/pre-vaccination ≥ 2)

Secondary Endpoints:

Safety (All Subjects):

- Occurrence, intensity, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each dose.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity, of solicited, i.e., pre-listed in the subject's diary and CRF, injection site reactions occurring up to 7 days after each dose.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited systemic reactions occurring up to 14 days after each dose.
- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each dose.
- Occurrence of SAEs, including serious AESIs, throughout the trial period.
- Occurrence, nature (MedDRA preferred term), time to onset, intensity, and relationship to vaccination of non-serious AESIs occurring up to 7 days after each dose.

Immunogenicity (Dengue Immunogenicity Subset):

Neutralizing Ab levels against each of the 4 dengue virus serotype strains contained in the CYD dengue vaccine were measured in sera collected from a randomized subset of 250 subjects 28 days post-Dose 2 and post-Dose 3 (dengue plaque reduction neutralization test [PRNT]).

Statistical methods:

Hypothesis and Statistical Method for the Primary Objective

Individual hypotheses for each antigen and endpoints:

The difference in terms of proportion of subjects reaching each antigen specific endpoint (seroprotection, or booster response for pertussis antigens), between test Group 1 (Pentaxim administered concomitantly with CYD dengue vaccine Dose 2) and reference Group 2 (Pentaxim administered concomitantly with placebo), ≤ the clinically relevant limit for non-inferiority (-δi).

Thus the eight individual hypotheses, one for each antigen i were as follows:

$$H_0^i : P^i_{Tested} - P^i_{Reference} \leq -\delta^i$$

$$H_1^i : P^i_{Tested} - P^i_{Reference} > -\delta^i$$

where δi is the non-inferiority limit that is set at 10% for all antigens.

Overall immunogenicity hypothesis:

For at least one antigen i, the non-inferiority between Group 1 (Pentaxim administered concomitantly with CYD dengue vaccine Dose 2) and Reference Group 2 (Pentaxim administered concomitantly with placebo) is not demonstrated.

$$H_0^G : \text{at least one } H_0^i \textit{ not rejected}$$

$$H_1^G : \text{all } H_0^i \textit{ are rejected}$$

For each antigen, a non-inferiority test was performed using the 95% two-sided confidence interval (CI) of the difference Ptest-Preference between the seroprotection rates (α=2.5%). The two-sided 95% CI was calculated based on the Wilson score method without continuity correction. For each antigen, non-inferiority for valence i was demonstrated if the lower limit of the two-sided 95% CI was greater than -δi. This is equivalent to testing and rejecting hypothesis Hi^0.

The per-protocol analysis set (PPAS) was used for the primary objective, i.e., the analyses on humoral immunogenicity pre- and post-Pentaxim booster vaccination and confirmed on the full analysis set (FAS).

Hypotheses and Statistical Methods for Secondary and Additional Objectives

There were no hypotheses tested for the secondary or additional objectives. All analyses were descriptive.

The FAS was used for the Pentaxim immunogenicity analyses, the full analysis set for dengue immunogenicity (FASDI) was used for the dengue immunogenicity analyses, the safety analysis set (SafAS) was used for the safety analyses, and the viremia subset was used for viremia analyses.

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

Statistical Analysis

A blinded analysis was performed by an internal SMT on safety data following the first dengue vaccination.

A statistical analysis of safety and immunogenicity was performed after database lock post-Dose 3. Data were unblinded at that time. A final statistical analysis was produced after the 6 month safety follow-up.

Summary:

Population characteristics:

A total of 720 subjects were enrolled in the study. At V05, 309 subjects were randomized to Group 1, 315 subjects were randomized to Group 2, and 96 subjects (including 90 subjects not present) were not randomized to Group 1 or Group 2. A total of 194 subjects (26.9%) reported at least one deviation to the protocol and were therefore excluded from the PPAS.

Overall, there were slightly more male (54.6%) than female subjects (45.4%); these proportions were similar in each treatment group. The mean age (± standard deviation) at enrollment was 10.7 ± 1.12 months in Group 1 and 10.7 ± 1.17 months in Group 2. The majority of subjects (81.9%) were Hispanic. There were 226 subjects (31.4%) reporting at least one past and current significant medical history. Among those, 157 subjects (21.8%) reported at least one still ongoing at inclusion.

The proportion of dengue immune subjects at baseline was low (58 subjects in the FAS [9.6%], with 24 subjects [8.0%] in Group 1 and 34 subjects [11.3%] in Group 2).

Immunogenicity results:

Primary Objective: Non-inferiority of Pentaxim Booster Dose

Table S4: Non-inferiority of Pentaxim booster dose based on seroprotection / booster response 28 days after injection – Per Protocol Analysis Set

		Group 1 (N=256)			Group 2 (N=270)			Group 1 – Group 2	
		n/M	%	(95% CI)	n/M	%	(95% CI)	%	(95% CI)
Anti-Diphtheria	≥ 0.1 IU/mL	255/255	100.0	(98.6; 100.0)	270/270	100.0	(98.6; 100.0)	0.0	(-1.48; 1.40)
Anti-Tetanus	≥ 0.1 IU/mL	255/255	100.0	(98.6; 100.0)	269/270	99.6	(98.0; 100.0)	0.37	(-1.14; 2.07)
Anti-Polio 1	≥ 8 (1/dil)	256/256	100.0	(98.6; 100.0)	268/269	99.6	(97.9; 100.0)	0.37	(-1.14; 2.08)
Anti-Polio 2	≥ 8 (1/dil)	256/256	100.0	(98.6; 100.0)	270/270	100.0	(98.6; 100.0)	0.0	(-1.48; 1.40)
Anti-Polio 3	≥ 8 (1/dil)	254/254	100.0	(98.6; 100.0)	266/267	99.6	(97.9; 100.0)	0.37	(-1.15; 2.09)
Anti-PRP	≥ 1 µg/mL	256/256	100.0	(98.6; 100.0)	270/270	100.0	(98.6; 100.0)	0.0	(-1.48; 1.40)
Anti-PT	booster response	246/255	96.5	(93.4; 98.4)	261/269	97.0	(94.2; 98.7)	-0.56	(-3.93; 2.69)
Anti-FHA	booster response	238/256	93.0	(89.1; 95.8)	252/270	93.3	(89.7; 96.0)	-0.36	(-4.87; 4.06)

Twenty-eight days after vaccination, the Ab response against all antigens (diphtheria, tetanus, pertussis, polio, and Hib) in subjects who received one booster dose of Pentaxim vaccine administered concomitantly with the second dose of CYD dengue vaccine was non inferior to the Ab response against all antigens (diphtheria, tetanus, pertussis, polio, and Hib) in subjects who received one booster dose of Pentaxim vaccine concomitantly with placebo. The lower limit of all of the 2-sided 95% CIs for the difference between the seroprotection / booster rates was > -10% for all of the antigens. The range for the lower limit of the differences in the 95% CIs was from -4.87 (for anti-FHA) to 1.14 (for anti-tetanus and anti-polio 1).

The percentage of subjects with seroprotection against diphtheria toxoid, tetanus toxoid, polioviruses types 1, 2, and 3, and PRP was 100.0% in Group 1 and ranged from 99.6% to 100.0% in Group 2. The percentage of subjects with a booster response to PT and FHA was about 97% and 93%, respectively, in both groups.

Secondary Objectives: Immunogenicity (Dengue Immunogenicity Subset)

After the second CYD dengue vaccine dose, GMT levels were similar for serotype 1, serotype 2, and serotype 3 in both groups with a trend to lower GMT levels observed for serotype 4 in Group 1 with the concomitant administration of CYD dengue vaccine with Pentaxim vaccine (57.8 [1/dil]) compared to Group 2 when CYD dengue vaccine was administered alone (104 [1/dil]). Concomitant Pentaxim vaccine administration did not seem to have a lasting impact on the dengue immune response in terms of GMTs and GMTRs, as these were similar for all 4 serotypes in both groups 28 days after the third CYD dengue vaccine dose.

After the second CYD dengue vaccine dose, the percentages of seropositive subjects were similar in Group 1 and Group 2 for all 4 serotypes. After the third CYD dengue vaccine dose, the percentage of seropositive subjects for all 4 serotypes was 100.0% in both groups. Concomitant Pentaxim vaccine administration with Dose 2 of CYD dengue vaccine did not have any effect on the percentages of subjects who were seropositive after the second and third dose of CYD dengue vaccine.

Overall in both groups, the percentage of seropositive subjects against at least 1, 2, 3, or all 4 serotypes increased 28 days after each dengue injection compared to baseline and previous injection and was similar. Concomitant Pentaxim vaccine administration did not have an effect on the percentage of subjects seropositive against at least 1, 2, 3, and 4 serotypes, as all subjects were seropositive against all 4 serotypes 28 days after the third CYD dengue vaccine dose.

Safety results:

Immediate AEs

There were no immediate unsolicited AEs (i.e., within the 30-minute observation period) reported in any subject following any injection.

Solicited Reactions

The percentage of subjects reporting at least 1 solicited reaction after any vaccine injections (including both solicited injection site and solicited systemic reactions) was similar in Group 1 (91.9%) compared to Group 2 (90.2%). After any injections, at least 1 solicited injection site reaction was reported by 61.8% of subjects in Group 1 and 62.9% of subjects in Group 2; whereas at least 1 solicited systemic reaction was reported by 85.4% of subjects in Group 1 and 86.0% of subjects in Group 2. Generally, these reactions were Grade 1 reactions occurring within 3 days after any injection.

Grade 3 solicited reactions occurred at similar frequencies in Group 1 (18.8%) and Group 2 (16.2%). There were 5 subjects (1.6%) in Group 1 and 4 subjects (1.3%) in Group 2 who reported at least 1 Grade 3 solicited injection site reaction and 55 subjects (17.8%) in Group 1 and 48 subjects (15.2%) in Group 2 who reported at least 1 Grade 3 solicited systemic reaction.

Injection Site Reactions

After vaccine injection at V01 (first dose of CYD dengue vaccine), the percentage of subjects reporting an injection site reaction was 31.4% for tenderness, 14.6% for erythema, and 7.3% for swelling. Generally, these reactions were Grade 1 reactions that occurred within 3 days and spontaneously resolved after a few days.

After vaccine injections at V05, the percentages of subjects reporting injection site reactions when Pentaxim vaccine and CYD dengue vaccine were administered concomitantly were similar to the percentages of subjects reporting injection site reactions when Pentaxim vaccine was concomitantly administered with placebo.

After vaccine injection at V06, the percentages of subjects reporting tenderness, erythema, and swelling in both groups were similar, demonstrating good safety of the CYD dengue vaccine in terms of solicited injection site reactions.

The frequency of each injection site reaction for CYD dengue vaccine concomitantly administered with Pentaxim vaccine in Group 1 at V05 was similar to the frequency of each injection site reaction for CYD dengue vaccine administered alone in Group 2 at V06.

In general the frequency of subjects who reported injection site reactions was lowest after the third CYD dengue vaccine dose (at V08) in both groups. Tenderness was the most frequently reported injection site reaction, reported by 19.8% of subjects in Group 1 and 25.4% of subjects in Group 2, followed by erythema (6.7% of subjects in Group 1 and 5.8% of subjects in Group 2), and swelling (2.0% of subjects in Group 1 and 2.7% of subjects in Group 2).

Systemic Reactions

Irritability was the most frequently reported solicited systemic reaction within 14 days after vaccine injection at V01 (i.e., the first CYD dengue vaccine dose), reported by 45.9% of subjects followed by crying abnormal (37.1% of subjects). The percentage of subjects reporting appetite lost, fever, and drowsiness was 33.0%, 26.9%, and 23.7%, respectively. Vomiting was the least frequently reported (18.5% of subjects).

Concomitant administration of Pentaxim vaccine with the second CYD dengue vaccine dose did not have an impact on solicited systemic reactions as compared to when Pentaxim vaccine was administered with placebo. The percentage of subjects who reported at least 1 solicited systemic reaction within 14 days after vaccine injections at V05 was 60.1% after concomitant administration of the second CYD dengue vaccine dose with Pentaxim vaccine and was 55.6% after Pentaxim vaccine administered with placebo. The percentages of subjects reporting each of the solicited systemic reactions were similar in both groups and ranged from 11.7% to 37.7% in Group 1 and 11.8% to 39.7% in Group 2.

The percentages of subjects reporting each solicited systemic reaction within 14 days after vaccine injection at V06 were fairly similar in both groups, demonstrating good safety of the CYD dengue vaccine in terms of solicited systemic reactions.

The percentage of subjects who reported a solicited systemic reaction was higher after administration of vaccines at V05 in Group 1 (i.e., the second CYD dengue vaccine dose administered concomitantly with Pentaxim vaccine [60.1% of subjects]) than after the administration of vaccine at V06 in Group 2 (i.e., the second dose of CYD dengue vaccine administered alone [42.8% of subjects]). The percentages of subjects who reported irritability and fever were slightly higher in Group 1 (37.7% and 29.1%, respectively) than in Group 2 (25.3% and 18.1%, respectively).

The percentage of subjects who reported a solicited systemic reaction within 14 days after vaccine injection at V08 was approximately 40% in both groups. In both groups, irritability, crying abnormal, and appetite lost were each reported by approximately 20% of subjects (ranging from 18.8% to 23.8% in Group 1 and from 18.6% to 20.6% in Group 2).

In general, the percentage of subjects who reported solicited systemic reactions was highest after the first CYD dengue vaccine dose (approaching approximately 70%) in both groups.

Unsolicited Non-serious AEs

The percentages of subjects reporting at least 1 unsolicited non-serious AE after any injections were similar in Group 1 (72.2%) and Group 2 (75.6%) and most were common medical conditions. Most of the unsolicited AEs were Infections and Infestations considered non-serious in both treatment groups. In Group 1, the most common unsolicited AEs were nasopharyngitis, gastroenteritis, and pharyngitis, reported by 109 subjects (35.3%), 55 subjects (17.8%), and 50 subjects (16.2%), respectively. In Group 2, the most common unsolicited AEs were the same, reported by 104 subjects (33.0%), 47 subjects (14.9%), and 57 subjects (18.1%), respectively. Generally, AEs were reported as Grade 1 AEs that resolved within 4 to 14 days with health care provider contact and medication

Grade 3 unsolicited non-serious AEs were not frequent: 5 subjects (1.6%) in Group 1 and 6 subjects (1.9%) in Group 2 reported at least 1 Grade 3 unsolicited reaction. Unsolicited non-serious ARs (i.e., AEs related to vaccination) were reported by 2 subjects (0.6%) in Group 1 and 4 subjects (1.3%) in Group 2. The most common AR reported was injection site swelling reported by 2 subjects (0.6%) in Group 2.

There was no impact on the frequency of non-serious AEs following Pentaxim vaccine whether administered with CYD dengue vaccine concomitantly or not. The percentage of subjects reporting at least 1 non-serious AE after the Pentaxim vaccine was similar for subjects in Group 1 (33.7%) and Group 2 (35.0%).

There was no impact on the frequency of non-serious AEs following CYD dengue vaccine whether administered with Pentaxim vaccine concomitantly or not. The percentage of subject reporting at least 1 non-serious AE after the second dose of CYD dengue vaccine was similar in Group 1 (33.7%) and Group 2 (33.1%).

AEs Leading to Discontinuation:

No subjects were discontinued due to a non-serious AE.

SAEs

Overall, a total of 41 subjects reported 48 SAEs that occurred at any time during the study: 17 subjects (5.5%) in Group 1, 21 subjects (6.7%) in Group 2, and 3 subjects (3.3%) who were not randomized at V05 reported 18, 26, and 4 SAEs, respectively. A total of 6 subjects experienced SAEs that led to study discontinuation: 3 subjects in Group 2 and 3 subjects who were not randomized at V05. There were no SAEs related to the trial vaccines as per the Investigator. Three SAEs were considered as related to the trial vaccines as per the Sponsor: a subject in Group 1 with no medical history of seizures reported febrile seizure 1 day after CYD dengue vaccine and Pentaxim vaccine injection; a subject in Group 2 with a family history of seizures reported febrile seizure 1 day after the second dose of CYD dengue vaccine; and a subject (not randomized at V05) with no medical history of seizure reported febrile seizure 36 hours after receiving the first dose of CYD dengue vaccine. Two non-related deaths were reported (complex congenital cyanogen cardiopathy and post-operative complications in a subject not-randomized at V05 and a death in a subject in Group 2). There were no safety concerns raised following the report of 17 episodes of febrile convulsions during the entire clinical trial. No serious immediate allergic reactions and no serious neurotropic of viscerotropic events were reported during the trial.

AESI

One subject in Group 1 experienced a serious AESI that was also considered significant (hemorrhagic dengue requiring hospitalization that was non-severe). Only 5 subjects reported non-serious AESIs: 2 subjects (0.6%) in Group 1 and 3 subjects (1.0%) in Group 2. All, except for 1 episode of urticaria, were considered as not related to the study vaccines.

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