Clinical trial results:
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

Summary

EudraCT number	2014-001736-11
Trial protocol	Outside EU/EEA
Global end of trial date	04 February 2014

Results information

Result version number	v1 (current)
This version publication date	08 February 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	CYD33

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01411241
WHO universal trial number (UTN)	U1111-1115-6290

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, 69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 52 55 5484 4891, enrique.rivas@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 52 55 5484 4891, enrique.rivas@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001201-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the antibody (Ab) response against all antigens (diphtheria, tetanus, pertussis, polio and Haemophilus influenzae type b [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

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	18 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Mexico: 720
Worldwide total number of subjects	720
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	720
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 18 July 2011 to 31 July 2012 at 3 clinical sites in Mexico.

Pre-assignment

Screening details:

The study planned for 732 subjects; however, recruitment was stopped when 720 subjects were enrolled due to the difficulty in enrolling subjects. Therefore, a total of 720 subjects who met all of the inclusion criteria and non of the exclusion criteria were enrolled and randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

An observer-blind design was chosen since the products were visually different. For the second dose of CYD dengue vaccine, the person who administered the injections knew which product was administered while the subject/parent and Investigator were blinded. The first and third doses of CYD dengue vaccine were administered according to an open-label procedure. A placebo dose was administered at Month 7 (Group 1) and concomitantly with Pentaxim vaccine at Month 6 (Group 2) to maintain the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), a booster dose of Pentaxim vaccine was administered concomitantly with the second injection of CYD dengue vaccine at Month 6 (15 to 18 months of age), placebo at Month 7 (16 to 19 months of age) to maintain the blind, and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).

Arm type	Experimental
Investigational medicinal product name	CYD Dengue vaccine
Investigational medicinal product code	323
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous in the deltoid region of the upper arm, 3 injections of the CYD Dengue vaccine, 1 injection each at Months 0, 6, and 12.

Investigational medicinal product name	DTap-IPV/Hib vaccine (Pentaxim™)
Investigational medicinal product code	283
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the anterolateral aspect of the thigh, 1 booster injection administered concomitantly with the second injection of the CYD dengue vaccine at Month 6.

Investigational medicinal product name	Placebo (NaCl)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous in the deltoid region of the upper arm, 1 injection at Month 7.

Arm title	Group 2

Arm description:

Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), the Pentaxim vaccine was administered concomitantly with placebo at Month 6 (15 to 18 months of age) to maintain the blind, a second injection of CYD dengue vaccine at Month 7 (16 to 19 months of age), and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).

Arm type	Experimental
Investigational medicinal product name	CYD Dengue vaccine
Investigational medicinal product code	323
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous in the deltoid region of the upper arm, 3 injections of the CYD Dengue vaccine, 1 injection each at Months 0, 7, and 12.

Investigational medicinal product name	DTap-IPV/Hib vaccine (Pentaxim™)
Investigational medicinal product code	283
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the anterolateral aspect of the thigh, 1 injection administered concomitantly with placebo at Month 6.

Investigational medicinal product name	Placebo (NaCl)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous in the deltoid region of the upper arm, 1 injection at Month 6.

Number of subjects in period 1[1]	Group 1	Group 2
Started	309	315
Completed	298	293
Not completed	11	22
Consent withdrawn by subject	9	10
Serious adverse event	-	3
Lost to follow-up	2	4
Protocol deviation	-	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Although the study planned for the enrollment of 732 subjects, the recruitment was stopped when 720 subjects were enrolled due to the difficulty in enrolling subjects. Of the 720 subjects, 309 subjects were randomized to Group 1, 315 to Group 2, and 96 subjects were not randomized at Month 6. The data reported reflect those patients who were enrolled and randomized to Group 1 and Group 2.

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), a booster dose of Pentaxim vaccine was administered concomitantly with the second injection of CYD dengue vaccine at Month 6 (15 to 18 months of age), placebo at Month 7 (16 to 19 months of age) to maintain the blind, and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).	
Reporting group title	Group 2
Reporting group description:	
Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), the Pentaxim vaccine was administered concomitantly with placebo at Month 6 (15 to 18 months of age) to maintain the blind, a second injection of CYD dengue vaccine at Month 7 (16 to 19 months of age), and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).	

Reporting group values	Group 1	Group 2	Total
Number of subjects	309	315	624
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	309	315	624
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
arithmetic mean	10.7	10.7	
standard deviation	± 1.12	± 1.17	-
Gender categorical Units: Subjects			
Female	146	139	285
Male	163	176	339

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), a booster dose of Pentaxim vaccine was administered concomitantly with the second injection of CYD dengue vaccine at Month 6 (15 to 18 months of age), placebo at Month 7 (16 to 19 months of age) to maintain the blind, and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).

Reporting group title	Group 2

Reporting group description:

Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), the Pentaxim vaccine was administered concomitantly with placebo at Month 6 (15 to 18 months of age) to maintain the blind, a second injection of CYD dengue vaccine at Month 7 (16 to 19 months of age), and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).

Primary: Percentage of Subjects with Seroprotection or Booster Response After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point title	Percentage of Subjects with Seroprotection or Booster Response After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point description:

Antibodies (Ab) against diphtheria, tetanus toxoid, pertussis toxoid (PT), and filamentous hemagglutinin (FHA) were measured by enzyme-linked immunosorbent assay (ELISA), polyribosylribitol phosphate (PRP) by Farr-type radioimmunoassay, and poliovirus types 1, 2, and 3 by seroneutralization assay. Seroprotection was defined as ≥0.1 International Unit (IU)/mL for diphtheria toxoid and tetanus toxoid, ≥8 1/dil for poliovirus types 1, 2, and 3, and ≥1.0 µg/mL for PRP. Booster response to PT and FHA: subjects whose pre-vaccination Ab titers were < lower limit of quantitation (LLOQ), a booster response occurred if they had post-vaccination levels ≥4X LLOQ; subjects whose pre-vaccination Ab concentrations were ≥LLOQ but <4X LLOQ, a booster response occurred if they had a 4-fold increase (post/pre-vaccination levels ≥4); for subjects whose pre-vaccination Ab concentrations were ≥4X LLOQ, a booster response occurred if they had a 2-fold increase (post/pre-vaccination ≥2).

End point type	Primary

End point timeframe:

28 days post-injection

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	270		
Units: Percentage of subjects				
number (not applicable)				
Anti-diphtheria	100	100		
Anti-tetanus	100	99.6		
Anti-polio 1	100	99.6		
Anti-polio 2	100	100		
Anti-polio 3	100	99.6		

Anti-PRP	100	100		
Anti-PT	96.5	97		
Anti-FHA	93	93.3		

Statistical analyses

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-diphtheria

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 2 v Group 1
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	1.4

Notes:

[1] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-tetanus

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	2.07

Notes:

[2] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-polio 1

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2

Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	2.08

Notes:

[3] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-polio 2

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	1.4

Notes:

[4] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-polio 3

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	2.09

Notes:

[5] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-PRP

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	1.4

Notes:

[6] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-PT

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	2.69

Notes:

[7] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Statistical analysis title	Non-inferiority (Grp 1 - Grp 2); Anti-FHA

Statistical analysis description:

Non-inferiority of Pentaxim booster dose based on seroprotection/booster response was assessed 28 days after injection.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	-0.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.87
upper limit	4.06

Notes:

[8] - The non-inferiority will be demonstrated if the lower limit of all the 95% CI of the difference is greater than -10% for all antigens. Wilson score (without continuity adjustment) 95% two-sided confidence intervals used for the difference of seroprotection/booster rates.

Secondary: Geometric Mean Titers Against Each Serotype with the Parental of Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point title	Geometric Mean Titers Against Each Serotype with the Parental of Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point description:

Dengue neutralizing antibody levels were measured by dengue plaque reduction neutralization test (PRNT).

End point type	Secondary

End point timeframe:

Pre-injection 1 and post-injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	107		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-injection 1	5.28 (4.82 to 5.78)	5.35 (4.85 to 5.91)		
Serotype 1; Post-injection 2	39.8 (30.5 to 51.9)	62.8 (48.1 to 82)		
Serotype 1; Post-injection 3	93.1 (76.6 to 113)	97 (78.8 to 120)		
Serotype 2; Pre-injection 1	5.22 (4.89 to 5.57)	5.53 (5.04 to 6.07)		
Serotype 2; Post-injection 2	109 (80.2 to 149)	121 (89.3 to 164)		
Serotype 2; Post-injection 3	189 (156 to 228)	208 (166 to 261)		
Serotype 3; Pre-injection 1	5.26 (4.93 to 5.62)	5.38 (4.95 to 5.84)		
Serotype 3; Post-injection 2	92.8 (75.7 to 114)	116 (91.1 to 149)		
Serotype 3; Post-injection 3	196 (168 to 229)	217 (183 to 256)		
Serotype 4; Pre-injection 1	5.11 (4.94 to 5.28)	5 (5 to 5)		
Serotype 4; Post-injection 2	57.8 (44.5 to 75.2)	104 (81.7 to 131)		
Serotype 4; Post-injection 3	121 (103 to 142)	127 (103 to 155)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios Against Each Serotype with the Parental of Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point title	Geometric Mean Titer Ratios Against Each Serotype with the Parental of Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point description:

Dengue neutralizing antibody levels were measured by dengue plaque reduction neutralization test (PRNT).

End point type	Secondary

End point timeframe:

Pre-injection 1 and post-injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	107		
Units: Titer ratio				
geometric mean (confidence interval 95%)				
Serotype 1; Post-injection 2/pre-injection 1	3.81 (2.95 to 4.93)	5.97 (4.64 to 7.68)		
Serotype 1; Post-injection 3/pre-injection 1	8.91 (7.4 to 10.7)	9.2 (7.55 to 11.2)		
Serotype 2; Post-injection 2/pre-injection 1	10.6 (7.77 to 14.5)	11.5 (8.5 to 15.4)		
Serotype 2; Post-injection 3/pre-injection 1	18.3 (15.1 to 22.1)	19.6 (15.6 to 24.7)		
Serotype 3; Post-injection 2/pre-injection 1	8.97 (7.33 to 11)	11.1 (8.73 to 14.1)		
Serotype 3; Post-injection 3/pre-injection 1	19.1 (16.4 to 22.2)	20.6 (17.4 to 24.4)		
Serotype 4; Post-injection 2/pre-injection 1	5.73 (4.4 to 7.45)	10 (7.96 to 12.6)		
Serotype 4; Post-injection 3/pre-injection 1	12 (10.2 to 14.1)	12.6 (10.3 to 15.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Titer ≥ 10 (1/dil) Against Each Serotype With the Parental Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point title	Percentage of Subjects With a Titer ≥ 10 (1/dil) Against Each Serotype With the Parental Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Tetravalent Dengue Vaccine

End point description:

Dengue neutralizing antibody levels were measured by dengue plaque reduction neutralization test (PRNT). Seropositivity was defined as antibody titers ≥10 (1/dil).

End point type	Secondary

End point timeframe:

Pre-injection 1 and post-injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	107		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-injection 1	1.8	2.8		
Serotype 1; Post-injection 2	84.8	92.2		
Serotype 1; Post-injection 3	100	100		
Serotype 2; Pre-injection 1	1.8	4.7		
Serotype 2; Post-injection 2	98.1	96.1		
Serotype 2; Post-injection 3	100	100		
Serotype 3; Pre-injection 1	2.8	3.7		
Serotype 3; Post-injection 2	100	98.1		
Serotype 3; Post-injection 3	100	100		
Serotype 4; Pre-injection 1	1.8	0		
Serotype 4; Post-injection 2	90.5	96.1		
Serotype 4; Post-injection 3	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Titer ≥ 10 (1/dil) for at Least One, Two, Three, or Four Serotypes With the Parental Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered With Tetravalent Dengue Vaccine

End point title	Percentage of Subjects With a Titer ≥ 10 (1/dil) for at Least One, Two, Three, or Four Serotypes With the Parental Dengue Virus Strains Before and After a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered With Tetravalent Dengue Vaccine

End point description:

Dengue neutralizing antibody levels were measured by dengue plaque reduction neutralization test (PRNT). Seropositivity was defined as antibody titers ≥10 (1/dil).

End point type	Secondary

End point timeframe:

Pre-injection 1 and post-injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	107		
Units: Percentage of subjects				
number (not applicable)				
At least 1 serotype; Pre-injection 1	4.6	8.4		
At least 1 serotype; Post-injection 2	100	100		
At least 1 serotype; Post-injection 3	100	100		
At least 2 serotypes; Pre-injection 1	1.8	1.9		
At least 2 serotypes; Post-injection 2	100	98.1		
At least 2 serotypes; Post-injection 3	100	100		
At least 3 serotypes; Pre-injection 1	0.9	0.9		
At least 3 serotypes; Post-injection 2	94.3	95.1		
At least 3 serotypes; Post-injection 3	100	100		
All 4 serotypes; Pre-injection 1	0.9	0		
All 4 serotypes; Post-injection 2	79	89.3		
All 4 serotypes; Post-injection 3	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following the First Injection with Tetravalent Dengue Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following the First Injection with Tetravalent Dengue Vaccine

End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 Solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Solicited systemic reactions: Fever, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to Day 14 post-first injection

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	315		
Units: Percentage of subjects				
number (not applicable)				
Injection site Tenderness	29.9	33.3		
Grade 3 Injection site Tenderness	0.3	0		
Injection site Erythema	14	15.7		
Grade 3 Injection site Erythema	0	0		
Injection site Swelling	4.9	10.9		
Grade 3 Injection site Swelling	0	0.3		
Fever	25.1	28.1		
Grade 3 Fever	1.6	0		
Vomiting	18.8	17.6		
Grade 3 Vomiting	1.3	0.6		
Crying abnormal	36.4	38.5		
Grade 3 Crying abnormal	2.3	2.2		
Drowsiness	24	23.4		
Grade 3 Drowsiness	1.9	1.6		
Appetite lost	32.5	34.7		
Grade 3 Appetite lost	4.5	4.5		
Injection site Irritability	47.1	45.5		
Grade 3 Injection site Irritability	3.2	4.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Either Tetravalent Dengue Vaccine or a Placebo Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following a Booster Injection of DTaP-IPV//Hib (Pentaxim™) Administered Concomitantly with Either Tetravalent Dengue Vaccine or a Placebo Vaccine

End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 Solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Solicited systemic reactions: Fever, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable; and Extensive swelling, severe.

End point type	Secondary

End point timeframe:

Day 0 up to Day 14 post-booster injection

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	314		
Units: Percentage of subjects				
number (not applicable)				
Injection site Tenderness	43.2	42.3		
Grade 3 Injection site Tenderness	1	0.7		
Injection site Tenderness; Post-Pentaxim	37.5	37.7		
Grade 3 Injection site Tenderness; Post-Pentaxim	1	0.7		
Injection site Tenderness; Post-CYD dengue/placebo	33.2	30.5		
Grd 3 Inj. site Tenderness;Post-CYD dengue/placebo	0	0.3		
Injection site Erythema	15	20.3		
Grade 3 Injection site Erythema	0.3	0		
Injection site Erythema; Post-Pentaxim	13	17.8		
Grade 3 Injection site Erythema; Post-Pentaxim	0.3	0		
Injection site Erythema; Post-CYD dengue/placebo	8.3	13.1		
Grd 3 Inj. site Erythema; Post-CYD dengue/placebo	0	0		
Injection site Swelling	11.6	17		
Grade 3 Injection site Swelling	0.3	0		
Injection site Swelling; Post-Pentaxim	9.4	16.1		
Grade 3 Injection site Swelling; Post-Pentaxim	0.3	0		
Injection site Swelling; Post-CYD dengue/placebo	5	7.2		
Grd 3 Inj. site Swelling; Post-CYD dengue/placebo	0	0		
Injection site extensive swelling; Post-Pentaxim	0	0		
Grd 3 Inj. site extensive swelling; Post-Pentaxim	0	0		
Fever	29.1	24.3		
Grade 3 Fever	1	0		
Vomiting	11.7	11.8		
Grade 3 Vomiting	1	0		
Crying abnormal	33.7	30.8		
Grade 3 Crying abnormal	0.7	1.6		
Drowsiness	19.7	17		
Grade 3 Drowsiness	1	0.7		
Appetite lost	23.3	23		
Grade 3 Appetite lost	3.7	3		
Irritability	37.7	39.7		
Grade 3 Irritability	1	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following a Second Injection of Tetravalent Dengue Vaccine or a Placebo Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following a Second Injection of Tetravalent Dengue Vaccine or a Placebo Vaccine

End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 Solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Solicited systemic reactions: Fever, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to Day 14 post-second injection

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	302		
Units: Percentage of subjects				
number (not applicable)				
Injection site Tenderness	24.5	25.7		
Grade 3 Injection site Tenderness	0	0		
Injection site Erythema	8.2	10.1		
Grade 3 Injection site Erythema	0	0		
Injection site Swelling	4.4	5.1		
Grade 3 Injection site Swelling	0	0.3		
Fever	16.7	18.1		
Grade 3 Fever	0	0.7		
Vomiting	6.8	8.8		
Grade 3 Vomiting	0.3	0		
Crying abnormal	21.2	24.3		
Grade 3 Crying abnormal	0	0.3		
Drowsiness	11.9	14.9		
Grade 3 Drowsiness	0	0		
Appetite lost	17.7	20.9		
Grade 3 Appetite lost	1.7	1.7		
Irritability	23.9	25.3		
Grade 3 Irritability	0.3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following a Third Injection of Tetravalent Dengue Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following a Third Injection of Tetravalent Dengue Vaccine

End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 Solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Solicited systemic reactions: Fever, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to Day 14 post-third injection

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	297		
Units: Percentage of subjects				
number (not applicable)				
Injection site Tenderness	19.8	25.4		
Grade 3 Injection site Tenderness	0	0		
Injection site Erythema	6.7	5.8		
Grade 3 Injection site Erythema	0	0		
Injection site Swelling	2	2.7		
Grade 3 Injection site Swelling	0	0		
Fever	16	15.2		
Grade 3 Fever	1	0		
Vomiting	4.4	7.2		
Grade 3 Vomiting	0.7	1		
Crying abnormal	21.5	18.9		
Grade 3 Crying abnormal	0.7	0.3		
Drowsiness	10.4	10		
Grade 3 Drowsiness	0.7	0.7		
Appetite lost	18.8	18.6		
Grade 3 Appetite lost	1.3	2.4		
Irritability	23.8	20.6		
Grade 3 Irritability	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to Day 14 post-third injection.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), a booster dose of Pentaxim vaccine was administered concomitantly with the second injection of CYD dengue vaccine at Month 6 (15 to 18 months of age), placebo at Month 7 (16 to 19 months of age) to maintain the blind, and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).

Reporting group title	Group 2

Reporting group description:

Subjects received the first injection of CYD dengue vaccine at Month 0 (9 to 12 months of age), a measles, mumps, rubella (MMR) vaccine and pneumococcal conjugate vaccine at Month 1 (10 to 13 months of age), the Pentaxim vaccine was administered concomitantly with placebo at Month 6 (15 to 18 months of age) to maintain the blind, a second injection of CYD dengue vaccine at Month 7 (16 to 19 months of age), and the third injection of CYD dengue vaccine at Month 12 (21 to 24 months).

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 309 (5.50%)	21 / 315 (6.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myelomonocytic leukaemia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Accidental exposure			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			

subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	5 / 309 (1.62%)	7 / 315 (2.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenic purpura			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 309 (0.32%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	2 / 309 (0.65%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Amoebic dysentery			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascariasis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 309 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 309 (0.32%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 309 (46.93%)	142 / 315 (45.08%)	
Nervous system disorders			
Drowsiness; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[1]	74 / 308 (24.03%)	73 / 312 (23.40%)	
occurrences (all)	74	73	
General disorders and administration site conditions			
Injection site Tenderness; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[2]	92 / 308 (29.87%)	104 / 312 (33.33%)	
occurrences (all)	92	104	
Injection site Erythema; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[3]	43 / 308 (13.96%)	49 / 312 (15.71%)	
occurrences (all)	43	49	
Injection site Swelling; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[4]	15 / 308 (4.87%)	34 / 312 (10.90%)	
occurrences (all)	15	34	
Fever; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[5]	77 / 307 (25.08%)	88 / 313 (28.12%)	
occurrences (all)	77	88	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	34 / 309 (11.00%)	34 / 315 (10.79%)	
occurrences (all)	41	37	
Vomiting; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[6]	58 / 308 (18.83%)	55 / 312 (17.63%)	
occurrences (all)	58	55	
Psychiatric disorders			

Crying abnormal; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[7]	112 / 308 (36.36%)	120 / 312 (38.46%)	
occurrences (all)	112	120	
Irritability; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[8]	145 / 308 (47.08%)	142 / 312 (45.51%)	
occurrences (all)	145	142	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	55 / 309 (17.80%)	47 / 315 (14.92%)	
occurrences (all)	61	51	
Nasopharyngitis			
subjects affected / exposed	109 / 309 (35.28%)	104 / 315 (33.02%)	
occurrences (all)	147	132	
Pharyngitis			
subjects affected / exposed	50 / 309 (16.18%)	57 / 315 (18.10%)	
occurrences (all)	60	69	
Pharyngotonsillitis			
subjects affected / exposed	24 / 309 (7.77%)	33 / 315 (10.48%)	
occurrences (all)	28	33	
Rhinitis			
subjects affected / exposed	25 / 309 (8.09%)	22 / 315 (6.98%)	
occurrences (all)	26	26	
Metabolism and nutrition disorders			
Appetite lost; Post-injection 1			
alternative assessment type: Systematic			
subjects affected / exposed[9]	100 / 308 (32.47%)	108 / 311 (34.73%)	
occurrences (all)	100	108	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after the first injection; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2011	Investigator was made responsible for communicating procedural benefits and risks, clarified subject randomization at Month 0 and the 2 vaccine groups at Month 6, confirmed that first and second injection of CYD dengue vaccine were blind and the third injection was open, added safety information regarding potential patient risks, specified that there were 3 clinical sites in Mexico, confirmed the addition of a Pentaxim dose at the end of the trial to subjects who were not protected in the the combination vaccine, the 6-month follow-up call could be replaced with a site visit to accommodate re-vaccination of Pentaxim, clarified the purpose and updated the wording of the interim analysis post-injection 2, clarified that certain contraindications were specific for measles, mumps, and rubella (MMR) and pneumococcal conjugate vaccinations at Month 1 and were not contraindications for subsequent CYD dengue vaccinations or Pentaxim vaccination, added the definition of suspected serious dengue disease and blood sample collection and testing, added key biological parameters that must be checked in cases of hospitalized suspected dengue cases, added methodologies for dengue, updated blind review of data, and clarified that subjects who did not receive the MMR of pneumococcal conjugate vaccine were not to be excluded from any analyses sets nor considered protocol deviations.
26 August 2011	Vaccination schedule for pentavalent vaccine was modified to be administered at 6 weeks, eligibility criteria were made more flexible to the site for recruitment, and time window for assessment of viscerotropism was updated from 10 to 30 days after vaccination.
19 February 2013	Corrected planned trial calendar dates, clarified a first interim analysis may be done if necessary, clarified definitive contraindications to differentiate the conditions for which the Investigator will withdraw the subject but continue safety follow up, clarified conditions in which the subject did not receive the MMR vaccine and/or pneumococcal conjugate vaccine and continued the trial, revised the "Blinding and Code-Breaking Procedures", clarified that Category 2 concomitant medication are treatments used to define protocol-restricted medications, updated the Per Protocol Analysis Set definition for the Pentaxim vaccine immune response and clarified the vaccination schedule, contraindications, acceptable time windows for vaccination, exclusion criteria, and the data sets to be used for the primary objective (Per Protocol Analysis Set and confirmed on the Full Analysis Set).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported