Clinical trial results:
Study of CYD Dengue Vaccine in Healthy Children and Adolescents in South America

Summary

EudraCT number	2014-001715-39
Trial protocol	Outside EU/EEA
Global end of trial date	15 May 2012

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	CYD30

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01187433
WHO universal trial number (UTN)	U1111-1111-6073

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Inc
Sponsor organisation address	1 Discovery Drive, Swiftwater, United States, 18370
Public contact	Director, Clinical Development, Sanofi Pasteur Inc, 52 55 5484 4891, enrique.rivas@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur Inc, 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	12 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Humoral immune response to dengue before and after each vaccination with dengue vaccine
Safety and reactogenicity

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	20 August 2010
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	Brazil: 150
Worldwide total number of subjects	150
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)	0
Children (2-11 years)	59
Adolescents (12-17 years)	91
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 20 August 2010 to 8 December 2011 at 1 clinical site in Brazil.

Pre-assignment

Screening details:

A total of 150 subjects who met all of the inclusion criteria and none 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 procedure was implemented for all three injections. The blind-observer Investigator, Sponsor, and subjects/parents did not know which vaccine was administered. To maintain the blind, the vaccinator prepared and administered the vaccine(s) in a separate room away from the blind-observer Investigator who was in charge of the assessment of safety.

Arms

Are arms mutually exclusive?	Yes
Arm title	CYD Dengue vaccine group

Arm description:

Subjects received 3 injections of the CYD dengue vaccine, 1 injection each at 0, 6, and 12 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, 1 injection each at 0, 6, and 12 months.

Arm title	Control group

Arm description:

Subjects received 3 injections of placebo, 1 injection each at 0, 6, and 12 months.

Arm type	Placebo
Investigational medicinal product name	Placebo (NaCl 0.9%)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, 1 injection each at 0, 6, and 12 months.

Number of subjects in period 1	CYD Dengue vaccine group	Control group
Started	100	50
Completed	89	46
Not completed	11	4
Consent withdrawn by subject	5	2
Protocol deviation	6	2

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue vaccine group
Reporting group description:	
Subjects received 3 injections of the CYD dengue vaccine, 1 injection each at 0, 6, and 12 months.	
Reporting group title	Control group
Reporting group description:	
Subjects received 3 injections of placebo, 1 injection each at 0, 6, and 12 months.	

Reporting group values	CYD Dengue vaccine group	Control group	Total
Number of subjects	100	50	150
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)	0	0	0
Children (2-11 years)	40	19	59
Adolescents (12-17 years)	60	31	91
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	12.7	12.7	
standard deviation	± 2.1	± 2.2	-
Gender categorical Units: Subjects			
Female	59	23	82
Male	41	27	68

End points

End points reporting groups

Reporting group title	CYD Dengue vaccine group
Reporting group description:	
Subjects received 3 injections of the CYD dengue vaccine, 1 injection each at 0, 6, and 12 months.	
Reporting group title	Control group
Reporting group description:	
Subjects received 3 injections of placebo, 1 injection each at 0, 6, and 12 months.	

Primary: Percentage of Subjects With Seropositivity Against Each Serotype with the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Subjects With Seropositivity Against Each Serotype with the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[1]
End point description:	
Seropositivity was defined as subjects achieving neutralizing antibody titers ≥10 (1/dil) against each serotype and was assessed using the Dengue Plaque Reduction Neutralization Test (PRNT).	
End point type	Primary
End point timeframe:	
Pre-Injections 1, 2, and 3 and Post-Injections 1,2, and 3	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	49		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	59.6	63.3		
Serotype 1; Post-Injection 1	79.8	69.4		
Serotype 1; Pre-Injection 2	80.9	72.3		
Serotype 1; Post-Injection 2	95.7	72.3		
Serotype 1; Pre-Injection 3	78.9	69.6		
Serotype 1; Post-Injection 3	96.6	69.6		
Serotype 2; Pre-Injection 1	65.7	67.3		
Serotype 2; Post-Injection 1	80.8	67.3		
Serotype 2; Pre-Injection 2	80.9	74.5		
Serotype 2; Post-Injection 2	98.9	72.3		
Serotype 2; Pre-Injection 3	85.6	76.1		
Serotype 2; Post-Injection 3	98.9	76.1		
Serotype 3; Pre-Injection 1	62.6	65.3		
Serotype 3; Post-Injection 1	92.9	67.3		
Serotype 3; Pre-Injection 2	89.4	72.3		
Serotype 3; Post-Injection 2	100	72.3		

Serotype 3; Pre-Injection 3	94.4	71.7		
Serotype 3; Post-Injection 3	100	73.9		
Serotype 4; Pre-Injection 1	47.5	51		
Serotype 4; Post-Injection 1	89.9	58.3		
Serotype 4; Pre-Injection 2	92.6	57.4		
Serotype 4; Post-Injection 2	100	59.6		
Serotype 4; Pre-Injection 3	97.7	69.6		
Serotype 4; Post-Injection 3	100	73.9		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavivirus-immune Subjects With Seropositivity Against Each Serotype with the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Flavivirus-immune Subjects With Seropositivity Against Each Serotype with the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[2]

End point description:

Seropositivity was defined as subjects achieving neutralizing antibody titers ≥10 (1/dil) against each serotype and was assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-immune subjects at baseline are defined as those subjects with ≥10 (1/dil) for at least 1 serotype with the parental dengue virus strain or for the yellow fever titer.

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	41		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	73.8	75.6		
Serotype 1; Post-Injection 1	88.8	82.9		
Serotype 1; Pre-Injection 2	91	87.2		
Serotype 1; Post-Injection 2	100	87.2		
Serotype 1; Pre-Injection 3	87.8	81.6		
Serotype 1; Post-Injection 3	98.6	81.6		
Serotype 2; Pre-Injection 1	81.3	80.5		
Serotype 2; Post-Injection 1	93.8	80.5		
Serotype 2; Pre-Injection 2	92.3	89.7		
Serotype 2; Post-Injection 2	100	87.2		
Serotype 2; Pre-Injection 3	91.9	89.5		
Serotype 2; Post-Injection 3	100	89.5		

Serotype 3; Pre-Injection 1	77.5	78		
Serotype 3; Post-Injection 1	95	80.5		
Serotype 3; Pre-Injection 2	93.6	87.2		
Serotype 3; Post-Injection 2	100	87.2		
Serotype 3; Pre-Injection 3	97.3	84.2		
Serotype 3; Post-Injection 3	100	86.8		
Serotype 4; Pre-Injection 1	58.8	61		
Serotype 4; Post-Injection 1	95	70		
Serotype 4; Pre-Injection 2	94.9	69.2		
Serotype 4; Post-Injection 2	100	71.8		
Serotype 4; Pre-Injection 3	98.6	81.6		
Serotype 4; Post-Injection 3	100	84.2		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavivirus-naïve Subjects With Seropositivity Against Each Serotype with the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Flavivirus-naïve Subjects With Seropositivity Against Each Serotype with the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[3]

End point description:

Seropositivity was defined as subjects achieving neutralizing antibody titers ≥10 (1/dil) against each serotype and was assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-naïve subjects at baseline are defined as those subjects with <10 (1/dil) for all serotypes with parental dengue virus strains and for yellow fever titer.

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	8		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	0	0		
Serotype 1; Post-Injection 1	42.1	0		
Serotype 1; Pre-Injection 2	31.3	0		
Serotype 1; Post-Injection 2	75	0		
Serotype 1; Pre-Injection 3	37.5	12.5		
Serotype 1; Post-Injection 3	87.5	12.5		
Serotype 2; Pre-Injection 1	0	0		
Serotype 2; Post-Injection 1	26.3	0		

Serotype 2; Pre-Injection 2	25	0		
Serotype 2; Post-Injection 2	93.8	0		
Serotype 2; Pre-Injection 3	56.3	12.5		
Serotype 2; Post-Injection 3	93.8	12.5		
Serotype 3; Pre-Injection 1	0	0		
Serotype 3; Post-Injection 1	84.2	0		
Serotype 3; Pre-Injection 2	68.8	0		
Serotype 3; Post-Injection 2	100	0		
Serotype 3; Pre-Injection 3	80	12.5		
Serotype 3; Post-Injection 3	100	12.5		
Serotype 4; Pre-Injection 1	0	0		
Serotype 4; Post-Injection 1	68.4	0		
Serotype 4; Pre-Injection 2	81.3	0		
Serotype 4; Post-Injection 2	100	0		
Serotype 4; Pre-Injection 3	93.3	12.5		
Serotype 4; Post-Injection 3	100	25		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Seropositivity Against At Least 1, 2, 3, or 4 Parental Dengue Virus Serotypes Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Subjects With Seropositivity Against At Least 1, 2, 3, or 4 Parental Dengue Virus Serotypes Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[4]

End point description:

Seropositivity was defined as subjects achieving neutralizing antibody titers ≥10 (1/dil) against each serotype and was assessed using the Dengue Plaque Reduction Neutralization Test (PRNT).

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	49		
Units: Percentage of subjects				
number (not applicable)				
At least 1 serotype; Pre-Injection 1	68.7	71.4		
At least 1 serotype; Post-Injection 1	97	71.4		
At least 1 serotype; Pre-Injection 2	94.7	74.5		
At least 1 serotype; Post-Injection 2	100	74.5		
At least 1 serotype; Pre-Injection 3	98.9	78.3		
At least 1 serotype; Post-Injection 3	100	78.3		
At least 2 serotypes; Pre-Injection 1	62.6	67.3		

At least 2 serotypes; Post-Injection 1	91.9	71.4		
At least 2 serotypes; Pre-Injection 2	92.6	74.5		
At least 2 serotypes; Post-Injection 2	100	72.3		
At least 2 serotypes; Pre-Injection 3	91.1	73.9		
At least 2 serotypes; Post-Injection 3	100	76.1		
At least 3 serotypes; Pre-Injection 1	56.6	61.2		
At least 3 serotypes; Post-Injection 1	81.8	65.3		
At least 3 serotypes; Pre-Injection 2	81.9	72.3		
At least 3 serotypes; Post-Injection 2	98.9	70.2		
At least 3 serotypes; Pre-Injection 3	86.7	71.7		
At least 3 serotypes; Post-Injection 3	98.9	71.7		
All 4 serotypes; Pre-Injection 1	47.5	46.9		
All 4 serotypes; Post-Injection 1	72.7	53.1		
All 4 serotypes; Pre-Injection 2	74.5	55.3		
All 4 serotypes; Post-Injection 2	95.7	59.6		
All 4 serotypes; Pre-Injection 3	76.7	63		
All 4 serotypes; Post-Injection 3	96.6	67.4		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavivirus-immune Subjects With Seropositivity Against At Least 1, 2, 3, or 4 Parental Dengue Virus Serotypes Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Flavivirus-immune Subjects With Seropositivity Against At Least 1, 2, 3, or 4 Parental Dengue Virus Serotypes Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[5]

End point description:

Seropositivity was defined as subjects achieving neutralizing antibody titers ≥10 (1/dil) against each serotype and was assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-immune subjects at baseline are defined as those subjects with ≥10 (1/dil) for at least 1 serotype with the parental dengue virus strain or for the yellow fever titer.

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	41		
Units: Percentage of subjects				
number (not applicable)				
At least 1 serotype; Pre-Injection 1	85	85.4		
At least 1 serotype; Post-Injection 1	97.5	85.4		
At least 1 serotype; Pre-Injection 2	97.4	89.7		

At least 1 serotype; Post-Injection 2	100	89.7		
At least 1 serotype; Pre-Injection 3	100	92.1		
At least 1 serotype; Post-Injection 3	100	89.5		
At least 2 serotypes; Pre-Injection 1	77.5	80.5		
At least 2 serotypes; Post-Injection 1	95	85.4		
At least 2 serotypes; Pre-Injection 2	97.4	89.7		
At least 2 serotypes; Post-Injection 2	100	87.2		
At least 2 serotypes; Pre-Injection 3	95.9	86.8		
At least 2 serotypes; Post-Injection 3	100	89.5		
At least 3 serotypes; Pre-Injection 1	70	73.2		
At least 3 serotypes; Post-Injection 1	92.5	78		
At least 3 serotypes; Pre-Injection 2	91	87.2		
At least 3 serotypes; Post-Injection 2	100	84.6		
At least 3 serotypes; Pre-Injection 3	93.2	84.2		
At least 3 serotypes; Post-Injection 3	100	84.2		
All 4 serotypes; Pre-Injection 1	58.8	56.1		
All 4 serotypes; Post-Injection 1	87.5	63.4		
All 4 serotypes; Pre-Injection 2	85.9	66.7		
All 4 serotypes; Post-Injection 2	100	71.8		
All 4 serotypes; Pre-Injection 3	85.1	73.7		
All 4 serotypes; Post-Injection 3	98.6	78.9		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavivirus-naïve Subjects With Seropositivity Against At Least 1, 2, 3, or 4 Parental Dengue Virus Serotypes Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Flavivirus-naïve Subjects With Seropositivity Against At Least 1, 2, 3, or 4 Parental Dengue Virus Serotypes Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[6]

End point description:

Seropositivity was defined as subjects achieving neutralizing antibody titers ≥10 (1/dil) against each serotype and was assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-naïve subjects at baseline are defined as those subjects with <10 (1/dil) for all serotypes with parental dengue virus strains and for yellow fever titer.

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	8		
Units: Percentage of subjects				
number (not applicable)				
At least 1 serotype; Pre-Injection 1	0	0		
At least 1 serotype; Post-Injection 1	94.7	0		
At least 1 serotype; Pre-Injection 2	81.3	0		
At least 1 serotype; Post-Injection 2	100	0		
At least 1 serotype; Pre-Injection 3	93.8	12.5		
At least 1 serotype; Post-Injection 3	100	25		
At least 2 serotypes; Pre-Injection 1	0	0		
At least 2 serotypes; Post-Injection 1	78.9	0		
At least 2 serotypes; Pre-Injection 2	68.8	0		
At least 2 serotypes; Post-Injection 2	100	0		
At least 2 serotypes; Pre-Injection 3	68.8	12.5		
At least 2 serotypes; Post-Injection 3	100	12.5		
At least 3 serotypes; Pre-Injection 1	0	0		
At least 3 serotypes; Post-Injection 1	36.8	0		
At least 3 serotypes; Pre-Injection 2	37.5	0		
At least 3 serotypes; Post-Injection 2	93.8	0		
At least 3 serotypes; Pre-Injection 3	56.3	12.5		
At least 3 serotypes; Post-Injection 3	93.8	12.5		
All 4 serotypes; Pre-Injection 1	0	0		
All 4 serotypes; Post-Injection 1	10.5	0		
All 4 serotypes; Pre-Injection 2	18.8	0		
All 4 serotypes; Post-Injection 2	75	0		
All 4 serotypes; Pre-Injection 3	37.5	12.5		
All 4 serotypes; Post-Injection 3	87.5	12.5		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios (GMTRs) Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Geometric Mean Titer Ratios (GMTRs) Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[7]

End point description:

Geometric mean titer ratios of antibodies against the dengue virus serotypes were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT).

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	49		
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Serotype 1; Post-Injection 1/Pre-Injection 1	4.67 (3.37 to 6.47)	0.834 (0.699 to 0.994)		
Serotype 1; Post-Injection 2/Pre-Injection 1	7.26 (5.51 to 9.57)	2.11 (1.12 to 4)		
Serotype 1; Post-Injection 2/Pre-Injection 2	1.66 (1.31 to 2.1)	1.25 (0.801 to 1.94)		
Serotype 1; Post-Injection 3/Pre-Injection 1	4.92 (3.71 to 6.52)	1.36 (0.797 to 2.31)		
Serotype 1; Post-Injection 3/Pre-Injection 2	1.07 (0.828 to 1.39)	0.793 (0.508 to 1.24)		
Serotype 1; Post-Injection 3/Pre-Injection 3	1.48 (1.25 to 1.74)	0.706 (0.607 to 0.821)		
Serotype 2; Post-Injection 1/Pre-Injection 1	4.15 (3.07 to 5.59)	0.733 (0.639 to 0.84)		
Serotype 2; Post-Injection 2/Pre-Injection 1	6.8 (5.46 to 8.45)	1.75 (0.956 to 3.21)		
Serotype 2; Post-Injection 2/Pre-Injection 2	1.97 (1.56 to 2.5)	0.981 (0.66 to 1.46)		
Serotype 2; Post-Injection 3/Pre-Injection 1	6.21 (4.96 to 7.78)	1.68 (1.06 to 2.66)		
Serotype 2; Post-Injection 3/Pre-Injection 2	1.78 (1.39 to 2.28)	0.944 (0.646 to 1.38)		
Serotype 2; Post-Injection 3/Pre-Injection 3	1.4 (1.16 to 1.69)	0.851 (0.734 to 0.986)		
Serotype 3; Post-Injection 1/Pre-Injection 1	6.5 (5.01 to 8.45)	0.916 (0.673 to 1.25)		
Serotype 3; Post-Injection 2/Pre-Injection 1	8.57 (6.79 to 10.8)	1.85 (1.03 to 3.32)		
Serotype 3; Post-Injection 2/Pre-Injection 2	2.03 (1.58 to 2.61)	1.02 (0.701 to 1.47)		
Serotype 3; Post-Injection 3/Pre-Injection 1	6.26 (4.82 to 8.13)	1.24 (0.815 to 1.9)		
Serotype 3; Post-Injection 3/Pre-Injection 2	1.46 (1.11 to 1.91)	0.673 (0.489 to 0.925)		
Serotype 3; Post-Injection 3/Pre-Injection 3	1.53 (1.27 to 1.86)	0.8 (0.681 to 0.94)		
Serotype 4; Post-Injection 1/Pre-Injection 1	17.7 (12.1 to 26)	0.806 (0.665 to 0.976)		
Serotype 4; Post-Injection 2/Pre-Injection 1	15.4 (12.3 to 19.2)	1.27 (0.795 to 2.04)		
Serotype 4; Post-Injection 2/Pre-Injection 2	1.84 (1.5 to 2.26)	0.835 (0.587 to 1.19)		
Serotype 4; Post-Injection 3/Pre-Injection 1	20.2 (15.4 to 26.3)	1.4 (0.939 to 2.1)		
Serotype 4; Post-Injection 3/Pre-Injection 2	2.26 (1.74 to 2.93)	0.912 (0.606 to 1.37)		
Serotype 4; Post-Injection 3/Pre-Injection 3	1.68 (1.38 to 2.05)	0.723 (0.564 to 0.927)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) of Flavivirus-immune Subjects Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Geometric Mean Titers (GMTs) of Flavivirus-immune Subjects Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[8]

End point description:

Geometric mean titers of antibodies against the dengue virus serotypes were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-immune subjects at baseline are defined as those subjects with ≥10 (1/dil) for at least 1 serotype with the parental dengue virus strain or for the yellow fever titer.

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	41		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	68.5 (44.5 to 105)	73.1 (40.9 to 131)		
Serotype 1; Post-Injection 1	549 (328 to 918)	79.8 (46.1 to 138)		
Serotype 1; Pre-Injection 2	430 (261 to 709)	154 (78.5 to 303)		
Serotype 1; Post-Injection 2	661 (442 to 987)	253 (116 to 553)		
Serotype 1; Pre-Injection 3	268 (164 to 435)	143 (73.7 to 278)		
Serotype 1; Post-Injection 3	381 (256 to 566)	126 (67.6 to 236)		
Serotype 2; Pre-Injection 1	124 (81.9 to 188)	114 (59.7 to 217)		
Serotype 2; Post-Injection 1	816 (517 to 1290)	103 (54.8 to 193)		
Serotype 2; Pre-Injection 2	591 (376 to 928)	224 (112 to 446)		
Serotype 2; Post-Injection 2	978 (697 to 1374)	271 (120 to 610)		
Serotype 2; Pre-Injection 3	648 (400 to 1048)	240 (122 to 471)		
Serotype 2; Post-Injection 3	835 (584 to 1193)	242 (126 to 463)		
Serotype 3; Pre-Injection 1	159 (93.5 to 271)	168 (74.3 to 380)		
Serotype 3; Post-Injection 1	1263 (764 to 2088)	202 (89.3 to 455)		
Serotype 3; Pre-Injection 2	879 (531 to 1455)	387 (170 to 878)		

Serotype 3; Post-Injection 2	1426 (950 to 2141)	497 (204 to 1210)		
Serotype 3; Pre-Injection 3	776 (481 to 1251)	272 (122 to 606)		
Serotype 3; Post-Injection 3	1031 (700 to 1519)	266 (125 to 566)		
Serotype 4; Pre-Injection 1	19.5 (14.6 to 26.1)	22.4 (14.6 to 34.3)		
Serotype 4; Post-Injection 1	467 (325 to 672)	25.2 (17.1 to 37.1)		
Serotype 4; Pre-Injection 2	220 (164 to 295)	39.5 (23.1 to 67.6)		
Serotype 4; Post-Injection 2	377 (303 to 470)	45.3 (25.1 to 81.8)		
Serotype 4; Pre-Injection 3	313 (231 to 424)	53.9 (31.7 to 91.8)		
Serotype 4; Post-Injection 3	485 (374 to 628)	46.5 (29.3 to 73.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios (GMTRs) of Flavivirus-naïve Subjects Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Geometric Mean Titer Ratios (GMTRs) of Flavivirus-naïve Subjects Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[9]

End point description:

Geometric mean titer ratios of antibodies against the dengue virus serotypes were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-naïve subjects at baseline are defined as those subjects with <10 (1/dil) for all serotypes with parental dengue virus strains and for yellow fever titer.

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	8		
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Serotype 1; Post-Injection 1/Pre-Injection 1	1.03 (0.639 to 1.67)	0.5 (0.5 to 0.5)		
Serotype 1; Post-Injection 2/Pre-Injection 1	5.73 (1.89 to 17.3)	0.5 (0.5 to 0.5)		
Serotype 1; Post-Injection 2/Pre-Injection 2	3.25 (1.18 to 8.93)	0.5 (0.5 to 0.5)		

Serotype 1; Post-Injection 3/Pre-Injection 1	5.34 (2.25 to 12.7)	0.861 (0.238 to 3.11)		
Serotype 1; Post-Injection 3/Pre-Injection 2	3.03 (1.35 to 6.8)	0.861 (0.238 to 3.11)		
Serotype 1; Post-Injection 3/Pre-Injection 3	2.19 (1.37 to 3.48)	0.446 (0.342 to 0.584)		
Serotype 2; Post-Injection 1/Pre-Injection 1	1.02 (0.527 to 1.99)	0.5 (0.5 to 0.5)		
Serotype 2; Post-Injection 2/Pre-Injection 1	8.62 (3.49 to 21.3)	0.5 (0.5 to 0.5)		
Serotype 2; Post-Injection 2/Pre-Injection 2	6.02 (2.37 to 15.3)	0.5 (0.5 to 0.5)		
Serotype 2; Post-Injection 3/Pre-Injection 1	7.67 (4.19 to 14)	0.737 (0.294 to 1.85)		
Serotype 2; Post-Injection 3/Pre-Injection 2	5.36 (2.73 to 10.5)	0.737 (0.294 to 1.85)		
Serotype 2; Post-Injection 3/Pre-Injection 3	2.37 (1.35 to 4.17)	0.538 (0.453 to 0.639)		
Serotype 3; Post-Injection 1/Pre-Injection 1	5.41 (2.8 to 10.5)	0.5 (0.5 to 0.5)		
Serotype 3; Post-Injection 2/Pre-Injection 1	21.2 (10.5 to 42.9)	0.5 (0.5 to 0.5)		
Serotype 3; Post-Injection 2/Pre-Injection 2	7.58 (3.12 to 18.4)	0.5 (0.5 to 0.5)		
Serotype 3; Post-Injection 3/Pre-Injection 1	16.3 (9.65 to 27.7)	0.678 (0.33 to 1.39)		
Serotype 3; Post-Injection 3/Pre-Injection 2	5.83 (3.17 to 10.7)	0.678 (0.33 to 1.39)		
Serotype 3; Post-Injection 3/Pre-Injection 3	3.35 (1.92 to 5.84)	0.524 (0.469 to 0.587)		
Serotype 4; Post-Injection 1/Pre-Injection 1	16.5 (4.58 to 59.1)	0.5 (0.5 to 0.5)		
Serotype 4; Post-Injection 2/Pre-Injection 1	22.7 (12.8 to 40.3)	0.5 (0.5 to 0.5)		
Serotype 4; Post-Injection 2/Pre-Injection 2	3.15 (1.63 to 6.09)	0.5 (0.5 to 0.5)		
Serotype 4; Post-Injection 3/Pre-Injection 1	25.5 (11.6 to 55.9)	0.701 (0.414 to 1.19)		
Serotype 4; Post-Injection 3/Pre-Injection 2	3.53 (1.71 to 7.26)	0.701 (0.414 to 1.19)		
Serotype 4; Post-Injection 3/Pre-Injection 3	2.55 (1.37 to 4.75)	0.578 (0.401 to 0.832)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following Any and Each Vaccination With Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following Any and Each Vaccination With Either CYD Dengue Vaccine or a Placebo[10]

End point description:

Injection site reactions: Pain, Erythema, and Swelling. Systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 Injection site reactions (9-11 yrs): Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥5 cm. Grade 3 Injection site reactions (≥12 yrs): Pain, Significant; prevents daily activity; Erythema and Swelling, >10 cm. Grade 3 Systemic reactions:

Fever, ≥39°C; Headache, Malaise, Myalgia, and Asthenia, Significant; prevents daily activity.

End point type	Primary

End point timeframe:

Day 0 up to Day 14 post-any and each vaccination

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	50		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; Post-Any Injection	40	40.8		
Gr 3 Injection site Pain; Post-Any Injection	0	4.1		
Injection site Erythema; Post-Any Injection	4	2		
Gr 3 Injection site Erythema; Post-Any Injection	0	0		
Injection site Swelling; Post-Any Injection	5	4.1		
Gr 3 Injection site Swelling; Post-Any Injection	0	0		
Injection site Pain; Post-Injection 1	26.3	30.6		
Gr 3 Injection site Pain; Post-Injection 1	0	2		
Injection site Erythema; Post-Injection 1	1	2		
Gr 3 Injection site Erythema; Post-Injection 1	0	0		
Injection site Swelling; Post-Injection 1	2	4.1		
Gr 3 Injection site Swelling; Post-Injection 1	0	0		
Injection site Pain; Post-Injection 2	21.5	14.9		
Gr 3 Injection site Pain; Post-Injection 2	0	2.1		
Injection site Erythema; Post-Injection 2	3.2	0		
Gr 3 Injection site Erythema; Post-Injection 2	0	0		
Injection site Swelling; Post-Injection 2	2.2	0		
Gr 3 Injection site Swelling; Post-Injection 2	0	0		
Injection site Pain; Post-Injection 3	16.9	15.6		
Gr 3 Injection site Pain; Post-Injection 3	0	2.2		
Injection site Erythema; Post-Injection 3	0	0		
Gr 3 Injection site Erythema; Post-Injection 3	0	0		
Injection site Swelling; Post-Injection 3	1.1	0		
Gr 3 Injection site Swelling; Post-Injection 3	0	0		
Fever; Post-Any Injection	30	18.4		
Gr 3 Fever; Post-Any Injection	8	6.1		
Headache; Post-Any Injection	61	51		
Gr 3 Headache; Post-Any Injection	15	20.4		
Malaise; Post-Any Injection	40	32.7		

Gr 3 Malaise; Post-Any Injection	11	6.1		
Myalgia; Post-Any Injection	42	42.9		
Gr 3 Myalgia; Post-Any Injection	6	8.2		
Asthenia; Post-Any Injection	35	20.4		
Gr 3 Asthenia; Post-Any Injection	8	4.1		
Fever; Post-Injection 1	15.3	10.4		
Gr 3 Fever; Post-Injection 1	3.1	2.1		
Headache; Post-Injection 1	48.5	40.8		
Gr 3 Headache; Post-Injection 1	8.1	10.2		
Malaise; Post-Injection 1	31.3	18.4		
Gr 3 Malaise; Post-Injection 1	3	2		
Myalgia; Post-Injection 1	32.3	30.6		
Gr 3 Myalgia; Post-Injection 1	2	6.1		
Asthenia; Post-Injection 1	22.2	10.2		
Gr 3 Asthenia; Post-Injection 1	4	4.1		
Fever; Post-Injection 2	8.7	4.3		
Gr 3 Fever; Post-Injection 2	2.2	0		
Headache; Post-Injection 2	28.7	34		
Gr 3 Headache; Post-Injection 2	5.3	6.4		
Malaise; Post-Injection 2	18.1	17		
Gr 3 Malaise; Post-Injection 2	6.4	4.3		
Myalgia; Post-Injection 2	20.2	21.3		
Gr 3 Myalgia; Post-Injection 2	3.2	4.3		
Asthenia; Post-Injection 2	12.8	14.9		
Gr 3 Asthenia; Post-Injection 2	3.2	0		
Fever; Post-Injection 3	11	7		
Gr 3 Fever; Post-Injection 3	3.7	7		
Headache; Post-Injection 3	27	20		
Gr 3 Headache; Post-Injection 3	5.6	8.9		
Malaise; Post-Injection 3	15.7	11.1		
Gr 3 Malaise; Post-Injection 3	2.2	0		
Myalgia; Post-Injection 3	20.2	11.1		
Gr 3 Myalgia; Post-Injection 3	2.2	0		
Asthenia; Post-Injection 3	14.6	4.4		
Gr 3 Asthenia; Post-Injection 3	2.2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo

End point title	Geometric Mean Titers (GMTs) Against Each Serotype with the Parental of Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[11]

End point description:

Geometric mean titers of antibodies against the dengue virus serotypes were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT).

End point type	Primary

End point timeframe:

Pre-Injections 1, 2, and 3 and Post-Injections 1, 2, and 3

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	49		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	41.4 (27.7 to 62.1)	47.2 (26.9 to 82.7)		
Serotype 1; Post-Injection 1	256 (151 to 433)	50.7 (29.5 to 87.3)		
Serotype 1; Pre-Injection 2	230 (138 to 384)	86 (43.8 to 169)		
Serotype 1; Post-Injection 2	436 (287 to 662)	130 (59.7 to 283)		
Serotype 1; Pre-Injection 3	162 (99.8 to 262)	90.8 (46.6 to 177)		
Serotype 1; Post-Injection 3	267 (181 to 394)	79.2 (42.4 to 148)		
Serotype 2; Pre-Injection 1	67 (44 to 102)	68.3 (36.3 to 129)		
Serotype 2; Post-Injection 1	352 (210 to 592)	62.8 (33.9 to 116)		
Serotype 2; Pre-Injection 2	287 (173 to 475)	117 (57.6 to 238)		
Serotype 2; Post-Injection 2	647 (449 to 932)	137 (61.4 to 306)		
Serotype 2; Pre-Injection 3	360 (219 to 592)	131 (65.7 to 262)		
Serotype 2; Post-Injection 3	544 (378 to 782)	132 (67 to 259)		
Serotype 3; Pre-Injection 1	81.9 (49.3 to 136)	94.7 (43.6 to 206)		
Serotype 3; Post-Injection 1	690 (423 to 1125)	110 (50.3 to 242)		
Serotype 3; Pre-Injection 2	471 (282 to 787)	184 (80.3 to 424)		
Serotype 3; Post-Injection 2	1031 (704 to 1512)	227 (92.8 to 556)		
Serotype 3; Pre-Injection 3	481 (300 to 772)	144 (65.8 to 316)		
Serotype 3; Post-Injection 3	741 (516 to 1062)	140 (66 to 298)		
Serotype 4; Pre-Injection 1	15 (11.6 to 19.4)	17.5 (11.9 to 25.8)		
Serotype 4; Post-Injection 1	383 (262 to 559)	19.2 (13.3 to 27.7)		
Serotype 4; Pre-Injection 2	178 (134 to 238)	27.8 (16.9 to 45.8)		
Serotype 4; Post-Injection 2	346 (281 to 425)	31.2 (18.1 to 53.7)		
Serotype 4; Pre-Injection 3	258 (192 to 347)	37.4 (22.6 to 62.1)		

Serotype 4; Post-Injection 3	432 (335 to 556)	33.4 (21.5 to 51.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from Day 0 (post-vaccination) up to Day 14 post-Injection 3.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	CYD Dengue vaccine group
Reporting group description:	
Subjects received 3 injections of the CYD dengue vaccine, 1 injection each at 0, 6, and 12 months.	
Reporting group title	Control group
Reporting group description:	
Subjects received 3 injections of placebo, 1 injection each at 0, 6, and 12 months.	

Serious adverse events	CYD Dengue vaccine group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 100 (5.00%)	3 / 50 (6.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	0 / 100 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Intra-uterine death			
subjects affected / exposed	1 / 100 (1.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 100 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			

subjects affected / exposed	1 / 100 (1.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 100 (1.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 100 (1.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 100 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 50 (2.00%)	
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	CYD Dengue vaccine group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 100 (61.00%)	25 / 50 (50.00%)	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	6 / 100 (6.00%)	4 / 50 (8.00%)	
occurrences (all)	6	4	
Wound			
subjects affected / exposed	0 / 100 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Nervous system disorders			

Headache			
subjects affected / exposed	6 / 100 (6.00%)	7 / 50 (14.00%)	
occurrences (all)	7	8	
Headache; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[1]	61 / 100 (61.00%)	25 / 49 (51.02%)	
occurrences (all)	61	25	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	9 / 100 (9.00%)	1 / 50 (2.00%)	
occurrences (all)	9	2	
General disorders and administration site conditions			
Injection site Pain; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[2]	40 / 100 (40.00%)	20 / 49 (40.82%)	
occurrences (all)	40	20	
Injection site Swelling; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[3]	5 / 100 (5.00%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Fever; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[4]	30 / 100 (30.00%)	9 / 49 (18.37%)	
occurrences (all)	30	9	
Malaise; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[5]	40 / 100 (40.00%)	16 / 49 (32.65%)	
occurrences (all)	40	16	
Asthenia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[6]	35 / 100 (35.00%)	10 / 49 (20.41%)	
occurrences (all)	35	10	
Eye disorders			

Conjunctivitis			
subjects affected / exposed	11 / 100 (11.00%)	7 / 50 (14.00%)	
occurrences (all)	11	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 100 (12.00%)	4 / 50 (8.00%)	
occurrences (all)	16	6	
Nausea			
subjects affected / exposed	8 / 100 (8.00%)	0 / 50 (0.00%)	
occurrences (all)	11	0	
Vomiting			
subjects affected / exposed	7 / 100 (7.00%)	2 / 50 (4.00%)	
occurrences (all)	7	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 100 (6.00%)	4 / 50 (8.00%)	
occurrences (all)	7	4	
Musculoskeletal and connective tissue disorders			
Myalgia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[7]	42 / 100 (42.00%)	21 / 49 (42.86%)	
occurrences (all)	42	21	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 100 (12.00%)	6 / 50 (12.00%)	
occurrences (all)	12	6	
Rhinitis			
subjects affected / exposed	6 / 100 (6.00%)	2 / 50 (4.00%)	
occurrences (all)	7	2	
Tonsillitis			
subjects affected / exposed	5 / 100 (5.00%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
Upper respiratory tract infection			
subjects affected / exposed	18 / 100 (18.00%)	3 / 50 (6.00%)	
occurrences (all)	19	3	

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 any 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 any 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 any 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 14 days after any 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 7 days after any 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 any 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 any 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
11 September 2009	Replaced Principal Investigators and Sponsor's Regional Clinical Trial Managers in Venezuela as well as updated the site name.
15 November 2009	Revised trial dates, replaced the meningococcal A+C vaccine (in Brazil) or ADACEL (in Venezuela) as third vaccination by placebo injection, updated the "Product Logistics" section accordingly, clarified the minimum timeline between two febrile episodes to consider two separate episodes, replaced control products 2 and 3 with placebo, modified the inclusion and exclusion criteria, offered a licensed, commercial vaccine meningococcal A+C vaccine for Brazil and ADACEL for Brazil after the completion of the safety surveillance period, implemented a temperature monitoring card, adapted a second temporary contraindication in the context of future pandemic influenza vaccination campaigns, revised contraindications accordingly, modified the text describing blood collection, revised the text regarding the use of unused stored serum samples, added a full description of the enzyme-linked immunosorbent assay with all acute samples collected from suspected dengue cases having been tested with the wild-type dengue reverse transcriptase-polymerase chain reaction.
31 March 2010	Updated the trial personnel (including the Principal Investigator in Brazil and Sanofi Pasteur personnel)
22 July 2010	Reworded to confirm that it was a monocenter trial conducted in Brazil, updated number of enrolled subjects to 150 instead of 300, statistical methods were revised, updated the methodology to the dengue screen reverse transcriptase-polymerase chain reaction assay and dengue plaque reduction neutralization test.
09 February 2011	Expanded the description of events to be reviewed by the Independent Data Monitoring Committee, increased the number of visits to 10, changed the last study contact to a clinic visit to allow for the optional administration of the vaccine, clarified subject benefits, quantity of blood drawn was no longer specified to give more flexibility due to differences in the amount of blood collected, added a description of the optional administration of the vaccine at the last study contact, reworded clinical supplies section, revised text in the assessment method section in addition to updating text to wild-type dengue reverse transcriptase-polymerase chain reaction for technical accuracy, modified the interim analysis and statistical methods, revised the immunogenicity methods, modified the description of the flavivirus serology, updated study violations, and reworded the description of the handling of missing data and outliers.
20 October 2011	Updated the study design such that it clarified all three vaccinations were handled in the same way, updated personnel information on the cover page, updated the statistical analyses sections, updated text regarding the status of the phase II trials at the time of the writing of this amendment, updated the date and version number of the Investigator's Brochure, updated text regarding the current status of the clinical trials and current available document, replaced meningococcal A+C vaccine with influenza vaccine since meningococcal A+C vaccine was no longer licensed in Brazil, updated current information on Principal Investigator, updated text to delete the interim analysis after the second vaccination, modified the description of the yellow fever dengue plaque reduction neutralization test assay, updated the description of the Per Protocol Analysis Set, Full Analysis Set, and Safety Analysis Set, and revised the handling of missing data and outliers section to incorporate statistical standard text.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24189367