Clinical trial results:
Immunogenicity and Safety of Sanofi Pasteur's CYD Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Latin America

Summary

EudraCT number	2014-001707-53
Trial protocol	Outside EU/EEA
Global end of trial date	29 August 2011

Results information

Result version number	v1 (current)
This version publication date	08 February 2016
First version publication date	06 December 2014

Trial information

Trial identification

Sponsor protocol code	CYD13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00993447
WHO universal trial number (UTN)	U1111-1111-5511

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	1541, Avenue Marcel Mérieux, Marcy L'Etoile, France, 69280
Public contact	Clinical Team Leader, Sanofi Pasteur SA, +1 570-957-2952, Gustavo.Dayan@sanofipasteur.com
Scientific contact	Clinical Team Leader, Sanofi Pasteur SA, +1 570-957-2952, Gustavo.Dayan@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	25 June 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-Humoral immune response to each dengue serotype before and after each injection
-Safety and reactogenicity

Protection of trial subjects:

Only subjects that met all of 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 were 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	09 October 2009
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	Honduras: 158
Country: Number of subjects enrolled	Colombia: 159
Country: Number of subjects enrolled	Mexico: 177
Country: Number of subjects enrolled	Puerto Rico: 106
Worldwide total number of subjects	600
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)	243
Adolescents (12-17 years)	357
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 09 October 2009 to 25 February 2010 in 3 clinic centers in Colombia, 1 in Honduras, 3 in Mexico, and 1 in Puerto Rico.

Pre-assignment

Screening details:

A total of 600 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

Period 1

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

Blinding implementation details:

The investigator (blind observer or assessor) and subject’s parents or guardians did not know the vaccine administered. For the first 2 injections, the vaccinator prepared and administered the vaccine(s) in a separate room, away from the Investigator who was in charge of safety assessment. The third injection was done in a single-blind-manner. The blind was broken by the Sponsor after the third injection at the time of the first planned analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	CYD Dengue Vaccine Group

Arm description:

Subjects who received the 5555 formulation of Sanofi Pasteur's CYD dengue vaccine as first (Day 0), second (Month 6), and third (Month 12) injections.

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, one dose each at Day 0, Day 0 + 6 months, and Day 0 + 12 months.

Arm title	Control Group

Arm description:

Subjects who received a placebo (NaCl) as first (Day 0) and second (Month 6) injections and ADACEL vaccine as a third (Month 12) injection.

Arm type	Active comparator
Investigational medicinal product name	ADACEL, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, one dose at Day 0 + 12 months

Number of subjects in period 1	CYD Dengue Vaccine Group	Control Group
Started	401	199
Completed	364	180
Not completed	37	19
Consent withdrawn by subject	23	8
Adverse event, non-fatal	1	-
Lost to follow-up	1	3
Protocol deviation	12	8

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue Vaccine Group
Reporting group description:	
Subjects who received the 5555 formulation of Sanofi Pasteur's CYD dengue vaccine as first (Day 0), second (Month 6), and third (Month 12) injections.	
Reporting group title	Control Group
Reporting group description:	
Subjects who received a placebo (NaCl) as first (Day 0) and second (Month 6) injections and ADACEL vaccine as a third (Month 12) injection.	

Reporting group values	CYD Dengue Vaccine Group	Control Group	Total
Number of subjects	401	199	600
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)	169	74	243
Adolescents (12-17 years)	232	125	357
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	12.6	12.5	
standard deviation	± 2.1	± 2.1	-
Gender categorical Units: Subjects			
Female	204	108	312
Male	197	91	288

End points

End points reporting groups

Reporting group title	CYD Dengue Vaccine Group
Reporting group description:	
Subjects who received the 5555 formulation of Sanofi Pasteur's CYD dengue vaccine as first (Day 0), second (Month 6), and third (Month 12) injections.	
Reporting group title	Control Group
Reporting group description:	
Subjects who received a placebo (NaCl) as first (Day 0) and second (Month 6) injections and ADACEL vaccine as a third (Month 12) injection.	

Primary: Percentage of Subjects With Antibody Titers of ≥10 1/dil Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Percentage of Subjects With Antibody Titers of ≥10 1/dil Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[1]
End point description:	
Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured using the dengue plaque reduction neutralization test (PRNT).	
End point type	Primary
End point timeframe:	
Day 0 (pre-each vaccination) and Day 28 post-each vaccination	

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	401	199		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	64.9	68.1		
Serotype 1; Post-Injection 1	73.1	67		
Serotype 1; Pre-Injection 2	75.6	67.8		
Serotype 1; Post-Injection 2	85	69		
Serotype 1; Pre-Injection 3	79.7	73.6		
Serotype 1; Post-Injection 3	94.6	75.5		
Serotype 2; Pre-Injection 1	69.9	74.3		
Serotype 2; Post-Injection 1	85.2	72.8		
Serotype 2; Pre-Injection 2	87.3	71.8		
Serotype 2; Post-Injection 2	96.9	73		
Serotype 2; Pre-Injection 3	91.9	76.7		
Serotype 2; Post-Injection 3	99.1	78.5		
Serotype 3; Pre-Injection 1	69.9	73.3		
Serotype 3; Post-Injection 1	90.8	74.3		

Serotype 3; Pre-Injection 2	90.9	72.4		
Serotype 3; Post-Injection 2	98.6	73.6		
Serotype 3; Pre-Injection 3	96.4	74.8		
Serotype 3; Post-Injection 3	100	76.7		
Serotype 4; Pre-Injection 1	63.1	68.1		
Serotype 4; Post-Injection 1	92.6	62.3		
Serotype 4; Pre-Injection 2	92.4	66.7		
Serotype 4; Post-Injection 2	96.6	70.1		
Serotype 4; Pre-Injection 3	95.8	69.9		
Serotype 4; Post-Injection 3	98.8	69.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavi-Virus Immune Subjects at Baseline With Antibody Titers ≥10 1/dil Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Percentage of Flavi-Virus Immune Subjects at Baseline With Antibody Titers ≥10 1/dil Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[2]

End point description:

Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured using the dengue plaque reduction neutralization test (PRNT). Flavi-virus (FV) immune subjects at baseline are defined as those subjects with ≥ 10 1/dil for at least one serotype with the parental dengue virus strain or for Yellow Fever titer.

End point type	Primary

End point timeframe:

Day 0 (pre-each vaccination) and Day 28 post-each vaccination

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	316	160		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	81.3	84.4		
Serotype 1; Post-Injection 1	90.8	82.3		
Serotype 1; Pre-Injection 2	90.5	82.4		
Serotype 1; Post-Injection 2	95.6	84.4		
Serotype 1; Pre-Injection 3	92	87.4		
Serotype 1; Post-Injection 3	97.6	88.8		
Serotype 2; Pre-Injection 1	88	91.9		
Serotype 2; Post-Injection 1	96.4	89.9		
Serotype 2; Pre-Injection 2	96.6	89.2		
Serotype 2; Post-Injection 2	98.6	90.5		

Serotype 2; Pre-Injection 3	96.5	90.9		
Serotype 2; Post-Injection 3	99.7	92.3		
Serotype 3; Pre-Injection 1	88.3	90.6		
Serotype 3; Post-Injection 1	96.7	89.9		
Serotype 3; Pre-Injection 2	96.6	87.8		
Serotype 3; Post-Injection 2	99	88.4		
Serotype 3; Pre-Injection 3	97.9	89.5		
Serotype 3; Post-Injection 3	100	89.5		
Serotype 4; Pre-Injection 1	79.4	84.4		
Serotype 4; Post-Injection 1	97.4	76.6		
Serotype 4; Pre-Injection 2	96.9	81.1		
Serotype 4; Post-Injection 2	98	84.4		
Serotype 4; Pre-Injection 3	99.3	84.6		
Serotype 4; Post-Injection 3	100	84.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavi-Virus Naive Subjects at Baseline With Antibody Titers ≥10 1/dil Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Percentage of Flavi-Virus Naive Subjects at Baseline With Antibody Titers ≥10 1/dil Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[3]

End point description:

Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured using the dengue plaque reduction neutralization test (PRNT). Flavi-virus (FV) naïve subjects 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:

Day 0 (pre-each vaccination) and Day 28 post-each vaccination

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	85	38		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	0	0		
Serotype 1; Post-Injection 1	7.1	2.7		
Serotype 1; Pre-Injection 2	17.9	5.6		
Serotype 1; Post-Injection 2	44.9	5.6		
Serotype 1; Pre-Injection 3	33.8	16.7		
Serotype 1; Post-Injection 3	81.8	19.4		

Serotype 2; Pre-Injection 1	0	0		
Serotype 2; Post-Injection 1	42.9	0		
Serotype 2; Pre-Injection 2	51.3	2.8		
Serotype 2; Post-Injection 2	89.7	5.6		
Serotype 2; Pre-Injection 3	70.1	16.7		
Serotype 2; Post-Injection 3	96.1	19.4		
Serotype 3; Pre-Injection 1	0	0		
Serotype 3; Post-Injection 1	67.9	10.8		
Serotype 3; Pre-Injection 2	66.7	8.3		
Serotype 3; Post-Injection 2	94.9	8.3		
Serotype 3; Pre-Injection 3	89.6	5.6		
Serotype 3; Post-Injection 3	100	16.7		
Serotype 4; Pre-Injection 1	0	0		
Serotype 4; Post-Injection 1	73.8	2.7		
Serotype 4; Pre-Injection 2	73.1	5.6		
Serotype 4; Post-Injection 2	91	8.3		
Serotype 4; Pre-Injection 3	80.5	8.3		
Serotype 4; Post-Injection 3	94.8	5.6		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Geometric Mean Titers (GMTs) of Antibodies Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Summary of Geometric Mean Titers (GMTs) of Antibodies Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[4]

End point description:

Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured using the dengue plaque reduction neutralization test (PRNT).

End point type	Primary

End point timeframe:

Day 0 (pre-each vaccination) and Day 28 post-each vaccination

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	401	199		
Units: Titers				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	74.2 (58.8 to 93.6)	81.9 (59.2 to 113)		

Serotype 1; Post-Injection 1	221 (167 to 292)	77.1 (55.8 to 106)		
Serotype 1; Pre-Injection 2	193 (149 to 251)	96.6 (67.1 to 139)		
Serotype 1; Post-Injection 2	276 (215 to 355)	102 (70.9 to 147)		
Serotype 1; Pre-Injection 3	204 (159 to 262)	113 (80 to 159)		
Serotype 1; Post-Injection 3	320 (258 to 396)	106 (75.4 to 149)		
Serotype 2; Pre-Injection 1	92.6 (73.9 to 116)	100 (73.5 to 136)		
Serotype 2; Post-Injection 1	409 (320 to 520)	90.4 (66.6 to 123)		
Serotype 2; Pre-Injection 2	326 (320 to 524)	117 (82.2 to 166)		
Serotype 2; Post-Injection 2	504 (414 to 613)	114 (80.8 to 160)		
Serotype 2; Pre-Injection 3	300 (245 to 368)	133 (95.6 to 186)		
Serotype 2; Post-Injection 3	486 (414 to 572)	133 (96.2 to 185)		
Serotype 3; Pre-Injection 1	85 (68.1 to 106)	88.8 (65.9 to 120)		
Serotype 3; Post-Injection 1	442 (352 to 554)	93.2 (69.1 to 126)		
Serotype 3; Pre-Injection 2	301 (243 to 372)	107 (77 to 149)		
Serotype 3; Post-Injection 2	502 (421 to 599)	108 (76.8 to 151)		
Serotype 3; Pre-Injection 3	379 (313 to 458)	123 (87.3 to 172)		
Serotype 3; Post-Injection 3	594 (511 to 692)	121 (86.6 to 168)		
Serotype 4; Pre-Injection 1	37.2 (31.1 to 44.5)	40.1 (31.2 to 51.5)		
Serotype 4; Post-Injection 1	416 (347 to 498)	34.1 (26.5 to 43.9)		
Serotype 4; Pre-Injection 2	200 (171 to 233)	43.8 (33.2 to 57.8)		
Serotype 4; Post-Injection 2	305 (265 to 352)	43.9 (33.5 to 57.5)		
Serotype 4; Pre-Injection 3	182 (158 to 210)	47.7 (36.4 to 62.6)		
Serotype 4; Post-Injection 3	273 (241 to 309)	42.8 (33 to 55.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Geometric Mean Titers (GMTs) of Antibodies in Flavivirus-Immune Subjects at Baseline Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Summary of Geometric Mean Titers (GMTs) of Antibodies in Flavivirus-Immune Subjects at Baseline Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[5]

End point description:

Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured using the dengue plaque reduction neutralization test (PRNT). Flavi-virus (FV) immune subjects at baseline are defined as those subjects with ≥ 10 1/dil for at least one serotype with the parental dengue virus strain or for Yellow Fever titer.

End point type	Primary

End point timeframe:

Day 0 (pre-each vaccination) and Day 28 post-each vaccination

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	316	160		
Units: Titers				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	153 (121 to 194)	162 (117 to 224)		
Serotype 1; Post-Injection 1	604 (468 to 780)	148 (107 to 205)		
Serotype 1; Pre-Injection 2	447 (352 to 567)	192 (133 to 279)		
Serotype 1; Post-Injection 2	607 (483 to 764)	199 (138 to 287)		
Serotype 1; Pre-Injection 3	435 (344 to 550)	225 (161 to 315)		
Serotype 1; Post-Injection 3	580 (471 to 715)	205 (146 to 287)		
Serotype 2; Pre-Injection 1	203 (164 to 252)	207 (156 to 275)		
Serotype 2; Post-Injection 1	1001 (811 to 1236)	181 (136 to 242)		
Serotype 2; Pre-Injection 2	673 (555 to 817)	251 (179 to 351)		
Serotype 2; Post-Injection 2	888 (738 to 1067)	232 (167 to 321)		
Serotype 2; Pre-Injection 3	554 (461 to 667)	265 (195 to 361)		
Serotype 2; Post-Injection 3	741 (631 to 869)	266 (196 to 359)		
Serotype 3; Pre-Injection 1	182 (147 to 225)	179 (136 to 237)		
Serotype 3; Post-Injection 1	863 (700 to 1064)	180 (135 to 239)		
Serotype 3; Pre-Injection 2	556 (456 to 679)	221 (161 to 304)		
Serotype 3; Post-Injection 2	782 (654 to 936)	215 (155 to 297)		
Serotype 3; Pre-Injection 3	615 (510 to 743)	265 (193 to 362)		
Serotype 3; Post-Injection 3	827 (704 to 972)	248 (181 to 340)		
Serotype 4; Pre-Injection 1	63.8 (52.9 to 76.9)	66.5 (51.4 to 86.1)		
Serotype 4; Post-Injection 1	549 (465 to 649)	53.4 (40.8 to 69.8)		

Serotype 4; Pre-Injection 2	278 (239 to 322)	73.7 (55.2 to 98.5)		
Serotype 4; Post-Injection 2	395 (341 to 456)	70.4 (53.3 to 92.8)		
Serotype 4; Pre-Injection 3	259 (227 to 296)	81.8 (62.1 to 108)		
Serotype 4; Post-Injection 3	341 (299 to 388)	72.5 (55.8 to 94.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Geometric Mean Titers (GMTs) of Antibodies in Flavivirus-Naive Subjects at Baseline Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Summary of Geometric Mean Titers (GMTs) of Antibodies in Flavivirus-Naive Subjects at Baseline Against Each Parental Dengue Virus Serotype Strain Before and Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[6]

End point description:

Neutralizing antibody levels against each of the 4 parental dengue virus strains of Sanofi Pasteur's CYD dengue vaccine constructs were measured using the dengue plaque reduction neutralization test (PRNT). Flavi-virus (FV) naïve subjects 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:

Day 0 (pre-each vaccination) and Day 28 post-each vaccination

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	85	38		
Units: Titers				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 1; Post-Injection 1	5.72 (5.1 to 6.42)	5.15 (4.85 to 5.47)		
Serotype 1; Pre-Injection 2	8.16 (5.98 to 11.1)	6.18 (4.2 to 9.11)		
Serotype 1; Post-Injection 2	14.3 (10 to 20.3)	7.29 (4.27 to 12.5)		
Serotype 1; Pre-Injection 3	12 (8.48 to 16.9)	7.93 (5.05 to 12.5)		
Serotype 1; Post-Injection 3	34.6 (25 to 48.1)	8.36 (5.31 to 13.2)		
Serotype 2; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 2; Post-Injection 1	15.9 (11.4 to 22.3)	5 (5 to 5)		

Serotype 2; Pre-Injection 2	21 (14.2 to 31.1)	5.5 (4.54 to 6.66)		
Serotype 2; Post-Injection 2	60 (43.3 to 83)	6.79 (4.37 to 10.6)		
Serotype 2; Pre-Injection 3	30.3 (21.4 to 42.7)	9.48 (5.6 to 16.1)		
Serotype 2; Post-Injection 3	101 (77.2 to 133)	9.45 (5.78 to 15.4)		
Serotype 3; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 3; Post-Injection 1	38.8 (25.6 to 59.1)	6.1 (4.89 to 7.6)		
Serotype 3; Pre-Injection 2	28.6 (20 to 41.1)	5.97 (4.75 to 7.5)		
Serotype 3; Post-Injection 2	94.9 (70.7 to 127)	7.07 (4.41 to 11.3)		
Serotype 3; Pre-Injection 3	61.9 (44.4 to 86.1)	6.18 (4.58 to 8.34)		
Serotype 3; Post-Injection 3	174 (136 to 221)	7.53 (5.32 to 10.7)		
Serotype 4; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 4; Post-Injection 1	151 (89.3 to 255)	5.3 (4.71 to 5.96)		
Serotype 4; Pre-Injection 2	57.5 (38.8 to 85.1)	5.48 (4.8 to 6.26)		
Serotype 4; Post-Injection 2	117 (84.8 to 161)	6.77 (4.64 to 9.88)		
Serotype 4; Pre-Injection 3	48.3 (35.5 to 65.6)	5.97 (4.87 to 7.32)		
Serotype 4; Post-Injection 3	119 (92 to 153)	5.63 (4.76 to 6.65)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine

End point title	Number of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following each Injection with Sanofi Pasteur's CYD Dengue Vaccine[7]

End point description:

Solicited Injection Site Reactions: Injection site Pain, Injection site Erythema, and Injection site Swelling. Solicited Systemic Reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 Solicited Injection Site Reactions: Injection site Pain, Incapacitating, unable to perform usual activities; Injection site Erythema and Injection site Swelling, ≥5 cm. Grade 3 Solicited 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 after each injection

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	401	199		
Units: Subjects				
number (not applicable)				
Injection site Pain (Any dose)	192	132		
Grade 3 Injection site Pain (Any dose)	13	7		
Injection site Erythema (Any dose)	26	18		
Grade 3 Injection site Erythema (Any dose)	0	1		
Injection site Swelling (Any dose)	20	16		
Grade 3 Injection site Swelling (Any dose)	1	1		
Injection site Pain (Post-dose 1)	121	54		
Grade 3 Injection site Pain (Post-dose 1)	6	2		
Injection site Erythema (Post-dose 1)	11	6		
Grade 3 Injection site Erythema (Post-dose 1)	0	0		
Injection site Swelling (Post-dose 1)	8	5		
Grade 3 Injection site Swelling (Post-dose 1)	1	0		
Injection site Pain (Post-dose 2)	101	31		
Grade 3 Injection site Pain (Post-dose 2)	7	0		
Injection site Erythema (Post-dose 2)	12	5		
Grade 3 Injection site Erythema (Post-dose 2)	0	0		
Injection site Swelling (Post-dose 2)	8	2		
Grade 3 Injection site Swelling (Post-dose 2)	1	0		
Injection site Pain (Post-dose 3)	88	118		
Grade 3 Injection site Pain (Post-dose 3)	2	5		
Injection site Erythema (Post-dose 3)	8	16		
Grade 3 Injection site Erythema (Post-dose 3)	0	1		
Injection site Swelling (Post-dose 3)	6	14		
Grade 3 Injection site Swelling (Post-dose 3)	0	1		
Fever (Any dose)	84	36		
Grade 3 Fever (Any dose)	13	3		
Headache (Any dose)	237	116		
Grade 3 Headache (Any dose)	40	11		
Malaise (Any dose)	157	82		
Grade 3 Malaise (Any dose)	21	8		
Myalgia (Any dose)	171	90		
Grade 3 Myalgia (Any dose)	22	10		
Asthenia (Any dose)	119	51		
Grade 3 Asthenia (Any dose)	14	5		
Fever (Post-dose 1)	43	13		
Grade 3 Fever (Post-dose 1)	11	0		
Headache (Post-dose 1)	173	80		
Grade 3 Headache (Post-dose 1)	26	5		
Malaise (Post-dose 1)	102	45		
Grade 3 Malaise (Post-dose 1)	14	0		
Myalgia (Post-dose 1)	121	52		

Grade 3 Myalgia (Post-dose 1)	15	3		
Asthenia (Post-dose 1)	77	30		
Grade 3 Asthenia (Post-dose 1)	7	2		
Fever (Post-dose 2)	29	16		
Grade 3 Fever (Post-dose 2)	2	0		
Headache (Post-dose 2)	131	69		
Grade 3 Headache (Post-dose 2)	14	4		
Malaise (Post-dose 2)	68	36		
Grade 3 Malaise (Post-dose 2)	6	4		
Myalgia (Post-dose 2)	80	45		
Grade 3 Myalgia (Post-dose 2)	8	3		
Asthenia (Post-dose 2)	51	24		
Grade 3 Asthenia (Post-dose 2)	5	1		
Fever (Post-dose 3)	17	14		
Grade 3 Fever (Post-dose 3)	0	3		
Headache (Post-dose 3)	106	62		
Grade 3 Headache (Post-dose 3)	10	4		
Malaise (Post-dose 3)	60	41		
Grade 3 Malaise (Post-dose 3)	2	4		
Myalgia (Post-dose 3)	66	51		
Grade 3 Myalgia (Post-dose 3)	3	5		
Asthenia (Post-dose 3)	42	23		
Grade 3 Asthenia (Post-dose 3)	2	2		

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 28 after each vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	CYD Dengue Vaccine Group

Reporting group description:

Subjects who received the 5555 formulation of Sanofi Pasteur's CYD dengue vaccine as first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) injections.

Reporting group title	Control Group

Reporting group description:

Subjects who received a placebo (NaCl) as first (Day 0) and second (Day 0 + 6 months) injections and ADACEL vaccine as a third (Day 0 + 12 months) injection.

Serious adverse events	CYD Dengue Vaccine Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 401 (2.49%)	15 / 199 (7.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental poisoning			
subjects affected / exposed	1 / 401 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
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	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			

subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 401 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 401 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 401 (0.75%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 401 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dengue fever			
subjects affected / exposed	3 / 401 (0.75%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 401 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 401 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 401 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	237 / 401 (59.10%)	132 / 199 (66.33%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			

subjects affected / exposed	237 / 401 (59.10%)	116 / 199 (58.29%)	
occurrences (all)	237	116	
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	192 / 401 (47.88%)	132 / 199 (66.33%)	
occurrences (all)	192	132	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 401 (6.48%)	18 / 199 (9.05%)	
occurrences (all)	26	18	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	20 / 401 (4.99%)	16 / 199 (8.04%)	
occurrences (all)	20	16	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	84 / 401 (20.95%)	36 / 199 (18.09%)	
occurrences (all)	84	36	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	157 / 401 (39.15%)	82 / 199 (41.21%)	
occurrences (all)	157	82	
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	119 / 401 (29.68%)	51 / 199 (25.63%)	
occurrences (all)	119	51	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	17 / 401 (4.24%)	12 / 199 (6.03%)	
occurrences (all)	19	12	
Diarrhoea			
subjects affected / exposed	30 / 401 (7.48%)	9 / 199 (4.52%)	
occurrences (all)	30	10	
Respiratory, thoracic and mediastinal			

disorders Cough subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	 24 / 401 (5.99%) 26 14 / 401 (3.49%) 16	 23 / 199 (11.56%) 24 10 / 199 (5.03%) 10	
Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 171 / 401 (42.64%) 171	 90 / 199 (45.23%) 90	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 105 / 401 (26.18%) 124	 51 / 199 (25.63%) 61	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2009	Frequency of follow-up phone calls and home visits, inclusion criteria, and Involved Personnel List were updated.
13 July 2010	Dengue assays and Involved Personnel List were updated.
28 January 2011	Updates to the protocol included, description of events reviewed by the IDMC, interim statistical analysis, last follow-up contact and blood collection procedures, applying the most recent standards and the involved personnel list for the study.

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/24067553