Clinical trial results:
Immunogenicity and Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Viet Nam

Summary

EudraCT number	2014-001709-41
Trial protocol	Outside EU/EEA
Global end of trial date	12 July 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	CYD22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00875524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, 69367
Public contact	Senior Director, Clinical Development, Sanofi Pasteur SA, +65 6431 2358, Anh.Wartel-Tram@sanofipasteur.com
Scientific contact	Senior Director, Clinical Development, Sanofi Pasteur SA, +65 6431 2358, Anh.Wartel-Tram@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	10 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 July 2014
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 CYD dengue vaccine
Persistence of antibodies (Abs) against dengue during 5 years after the first vaccination with CYD 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	14 March 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	Vietnam: 180
Worldwide total number of subjects	180
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)	120
Adolescents (12-17 years)	30

Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 18 March 2009 to 01 July 2010 at 1 clinical center in Vietnam.

Pre-assignment

Screening details:

A total of 180 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

Blinding implementation details:

The first and second vaccinations were administered in a blind-observer manner. The third vaccination was planned to be administered in a single-blind manner; however, due to the cancellation of the statistical analysis after the second vaccination, the third vaccination was also administered in a blind-observer manner. To ensure the blind-observer design of the 3 vaccinations, the product was prepared in a separate room whether neither the Investigator nor subject had access.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dengue Group

Arm description:

Subjects who received CYD dengue vaccine as first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations.

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, 3 injections at Day 0, Day 0 + 6 months, and Day 0 + 12 months.

Arm title	Control group

Arm description:

Subjects who received the Meningococcal Polysaccharide Vaccine A + C, placebo, and Typhoid Vi polysaccharide vaccine as the first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations, respectively.

Arm type	Active comparator
Investigational medicinal product name	Meningococcal Polysaccharide Vaccine A+C
Investigational medicinal product code	
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 at Day 0.

Investigational medicinal product name	Placebo (NaCl containing human serum albumin)
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneoous, 1 injection at Day 0 + 6 months.

Investigational medicinal product name	Typhoid Vi polysaccharide vaccine (Typhim Vi Vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, 1 injection at Day 0 + 12 months.

Number of subjects in period 1	Dengue Group	Control group
Started	120	60
Completed	112	54
Not completed	8	6
Consent withdrawn by subject	3	5
Serious adverse event	-	1
Lost to follow-up	1	-
Protocol deviation	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Dengue Group
Reporting group description:	
Subjects who received CYD dengue vaccine as first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations.	
Reporting group title	Control group
Reporting group description:	
Subjects who received the Meningococcal Polysaccharide Vaccine A + C, placebo, and Typhoid Vi polysaccharide vaccine as the first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations, respectively.	

Reporting group values	Dengue Group	Control group	Total
Number of subjects	120	60	180
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)	80	40	120
Adolescents (12-17 years)	20	10	30
Adults (18-64 years)	20	10	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	10.9	11.8	
standard deviation	± 8.6	± 9.6	-
Gender categorical Units: Subjects			
Female	62	25	87
Male	58	35	93

End points

End points reporting groups

Reporting group title	Dengue Group
Reporting group description:	
Subjects who received CYD dengue vaccine as first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations.	
Reporting group title	Control group
Reporting group description:	
Subjects who received the Meningococcal Polysaccharide Vaccine A + C, placebo, and Typhoid Vi polysaccharide vaccine as the first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations, respectively.	

Primary: Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain Before and Following Injection with ChimeriVax™ Dengue Tetravalent Vaccine

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain Before and Following Injection with ChimeriVax™ Dengue Tetravalent Vaccine[1]
End point description:	
Geometric mean titers against each serotype of the Parental Dengue Virus strains were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT).	
End point type	Primary
End point timeframe:	
Pre-dose 1, 2, and 3 and 28 days Post-dose 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	Dengue Group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	60		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Dengue Parental Serotype 1; Pre-dose 1	32.7 (21.6 to 49.5)	19.6 (12 to 31.8)		
Dengue Parental Serotype 1; Post-dose 1	70.9 (44.3 to 113)	18.8 (11.4 to 30.8)		
Dengue Parental Serotype 1; Pre-dose 2	52.2 (33.3 to 81.6)	19.8 (11.4 to 34.3)		
Dengue Parental Serotype 1; Post-dose 2	100 (65.1 to 155)	20.6 (11.8 to 36)		
Dengue Parental Serotype 1; Pre-dose 3	70.9 (45.5 to 110)	24.6 (13.7 to 44)		
Dengue Parental Serotype 1; Post-dose 3	129 (90.5 to 183)	25.3 (13.7 to 46.8)		
Dengue Parental Serotype 2; Pre-dose 1	33.1 (22.5 to 48.7)	27.2 (15.3 to 48.1)		
Dengue Parental Serotype 2; Post-dose 1	92.3 (58.5 to 145)	25 (13.8 to 45.4)		

Dengue Parental Serotype 2; Pre-dose 2	74.8 (47.7 to 117)	29.5 (16 to 54.4)		
Dengue Parental Serotype 2; Post-dose 2	195 (139 to 274)	29.3 (16 to 53.8)		
Dengue Parental Serotype 2; Pre-dose 3	111 (74.4 to 165)	32.3 (17.4 to 59.8)		
Dengue Parental Serotype 2; Post-dose 3	216 (163 to 286)	30.4 (16.7 to 55.1)		
Dengue Parental Serotype 3; Pre-dose 1	31.9 (23.3 to 43.8)	20.5 (13.2 to 31.9)		
Dengue Parental Serotype 3; Post-dose 1	95.6 (67.2 to 136)	18.4 (12 to 28.2)		
Dengue Parental Serotype 3; Pre-dose 2	60.4 (41.9 to 87.2)	19.1 (12.1 to 30.3)		
Dengue Parental Serotype 3; Post-dose 2	152 (115 to 203)	21.9 (14.1 to 34)		
Dengue Parental Serotype 3; Pre-dose 3	87.2 (62.5 to 122)	26.8 (17.1 to 42.1)		
Dengue Parental Serotype 3; Post-dose 3	169 (134 to 214)	25.2 (16.3 to 39.1)		
Dengue Parental Serotype 4; Pre-dose 1	17 (12.8 to 22.5)	13.9 (9.28 to 20.9)		
Dengue Parental Serotype 4; Post-dose 1	104 (71 to 153)	15.4 (10.2 to 23.3)		
Dengue Parental Serotype 4; Pre-dose 2	51.7 (37 to 72.2)	14.1 (9.29 to 21.4)		
Dengue Parental Serotype 4; Post-dose 2	120 (89.2 to 160)	14.3 (9.44 to 21.6)		
Dengue Parental Serotype 4; Pre-dose 3	70.1 (52.2 to 94.1)	17.1 (10.9 to 26.9)		
Dengue Parental Serotype 4; Post-dose 3	146 (115 to 184)	17.4 (11.2 to 27)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Antibody titers ≥ 10 (1/dil) Against Each Serotypes with the Parental Dengue Virus Strains Following Injection with ChimeriVax™ Dengue Tetravalent Vaccine

End point title	Percentage of Subjects with Antibody titers ≥ 10 (1/dil) Against Each Serotypes with the Parental Dengue Virus Strains Following Injection with ChimeriVax™ Dengue Tetravalent Vaccine[2]

End point description:

Neutralizing antibody levels against each serotype of the Parental Dengue Virus strains were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT).

End point type	Primary

End point timeframe:

Pre-dose 1, 2, and 3 and 28 days Post-dose 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	Dengue Group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	60		
Units: Percentage of subjects				
number (not applicable)				
Dengue Parental Serotype 1; Pre-dose 1	50.4	43.3		
Dengue Parental Serotype 1; Post-dose 1	62.2	41.7		
Dengue Parental Serotype 1; Pre-dose 2	58.3	39.7		
Dengue Parental Serotype 1; Post-dose 2	79.1	41.4		
Dengue Parental Serotype 1; Pre-dose 3	68.4	46.6		
Dengue Parental Serotype 1; Post-dose 3	93	41.4		
Dengue Parental Serotype 2; Pre-dose 1	49.6	41.7		
Dengue Parental Serotype 2; Post-dose 1	66.4	35.6		
Dengue Parental Serotype 2; Pre-dose 2	63.5	39.7		
Dengue Parental Serotype 2; Post-dose 2	93.9	41.4		
Dengue Parental Serotype 2; Pre-dose 3	80.7	43.1		
Dengue Parental Serotype 2; Post-dose 3	99.1	43.1		
Dengue Parental Serotype 3; Pre-dose 1	63	52.5		
Dengue Parental Serotype 3; Post-dose 1	84.9	47.5		
Dengue Parental Serotype 3; Pre-dose 2	73	46.6		
Dengue Parental Serotype 3; Post-dose 2	94.8	53.4		
Dengue Parental Serotype 3; Pre-dose 3	85.1	62.1		
Dengue Parental Serotype 3; Post-dose 3	99.1	58.6		
Dengue Parental Serotype 4; Pre-dose 1	44.5	37.3		
Dengue Parental Serotype 4; Post-dose 1	77.3	41.7		
Dengue Parental Serotype 4; Pre-dose 2	73	39.7		
Dengue Parental Serotype 4; Post-dose 2	89.6	40.4		
Dengue Parental Serotype 4; Pre-dose 3	84.2	43.1		
Dengue Parental Serotype 4; Post-dose 3	95.6	43.1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Solicited Injection-site and Systemic Reactions Following Any and Each Injection with CYD Dengue Tetravalent Vaccine

End point title	Percentage of Subjects with Solicited Injection-site and Systemic Reactions Following Any and Each Injection with CYD Dengue Tetravalent Vaccine[3]

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Grade 3 solicited injection site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥5 cm. Solicited

systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 solicited systemic reactions: Fever, >39.0°C; Headache, Malaise, Myalgia, and Asthenia, Prevents daily activities.

End point type	Primary

End point timeframe:

Day 0 up to Day 14 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	Dengue Group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Percentage of subjects				
number (not applicable)				
Inj. site Pain; Post-Any Inj.	28.3	80		
Grade 3 Inj. site Pain; Post-Any Inj.	0	0		
Inj. site Erythema; Post-Any Inj.	6.7	21.7		
Grade 3 Inj. site Erythema; Post-Any Inj.	0	1.7		
Inj. site Swelling; Post-Any Inj.	4.2	15		
Grade 3 Inj. site Swelling; Post-Any Inj.	0	1.7		
Inj. site Pain; Post-Inj. 1	15.8	73.3		
Grade 3 Inj. site Pain; Post-Inj. 1	0	0		
Inj. site Erythema; Post-Inj. 1	4.2	16.7		
Grade 3 Inj. site Erythema; Post-Inj. 1	0	1.7		
Inj. site Swelling; Post-Inj. 1	1.7	6.7		
Grade 3 Inj. site Swelling; Post-Inj. 1	0	1.7		
Inj. site Pain; Post-Inj. 2	15.5	15.5		
Grade 3 Inj. site Pain; Post-Inj. 2	0	0		
Inj. site Erythema; Post-Inj. 2	4.3	5.2		
Grade 3 Inj. site Erythema; Post-Inj. 2	0	0		
Inj. site Swelling; Post-Inj. 2	2.6	3.4		
Grade 3 Inj. site Swelling; Post-Inj. 2	0	0		
Inj. site Pain; Post-Inj. 3	11.4	41.4		
Grade 3 Inj. site Pain; Post-Inj. 3	0	0		
Inj. site Erythema; Post-Inj. 3	2.6	5.2		
Grade 3 Inj. site Erythema; Post-Inj. 3	0	0		
Inj. site Swelling; Post-Inj. 3	0	6.9		
Grade 3 Inj. site Swelling; Post-Inj. 3	0	0		
Fever; Post-Any Inj.	27.5	26.7		
Grade 3 Fever; Post-Any Inj.	0.8	3.3		
Headache; Post-Any Inj.	35.3	30		
Grade 3 Headache; Post-Any Inj.	0.8	0		
Malaise; Post-Any Inj.	29.4	23.3		
Grade 3 Malaise; Post-Any Inj.	0	0		
Myalgia; Post-Any Inj.	20.2	23.3		
Grade 3 Myalgia; Post-Any Inj.	0	0		
Asthenia; Post-Any Inj.	13.4	5		
Grade 3 Asthenia; Post-Any Inj.	1.7	0		
Fever; Post-Inj. 1	19.2	15		
Grade 3 Fever; Post-Inj. 1	0.8	3.3		

Headache; Post-Inj. 1	29.4	28.3		
Grade 3 Headache; Post-Inj. 1	0.8	0		
Malaise; Post-Inj. 1	21.8	16.7		
Grade 3 Malaise; Post-Inj. 1	0	0		
Myalgia; Post-Inj. 1	15.1	20		
Grade 3 Myalgia; Post-Inj. 1	0	0		
Asthenia; Post-Inj. 1	8.4	0		
Grade 3 Asthenia; Post-Inj. 1	0.8	0		
Fever; Post-Inj. 2	12.1	6.9		
Grade 3 Fever; Post-Inj. 2	0	0		
Headache; Post-Inj. 2	15.7	8.6		
Grade 3 Headache; Post-Inj. 2	0	0		
Malaise; Post-Inj. 2	13	8.6		
Grade 3 Malaise; Post-Inj. 2	0	0		
Myalgia; Post-Inj. 2	9.6	5.2		
Grade 3 Myalgia; Post-Inj. 2	0	0		
Asthenia; Post-Inj. 2	6.1	1.7		
Grade 3 Asthenia; Post-Inj. 2	0.9	0		
Fever; Post-Inj. 3	3.5	8.6		
Grade 3 Fever; Post-Inj. 3	0	0		
Headache; Post-Inj. 3	8.8	10.3		
Grade 3 Headache; Post-Inj. 3	0	0		
Malaise; Post-Inj. 3	5.3	8.6		
Grade 3 Malaise; Post-Inj. 3	0	0		
Myalgia; Post-Inj. 3	4.4	10.3		
Grade 3 Myalgia; Post-Inj. 3	0	0		
Asthenia; Post-Inj. 3	0.9	3.4		
Grade 3 Asthenia; Post-Inj. 3	0	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 6 months after the last vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Dengue Group

Reporting group description:

Subjects who received CYD dengue vaccine as first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations.

Reporting group title	Control group

Reporting group description:

Subjects who received the Meningococcal Polysaccharide Vaccine A + C, placebo, and Typhoid Vi polysaccharide vaccine as the first (Day 0), second (Day 0 + 6 months), and third (Day 0 + 12 months) vaccinations, respectively.

Serious adverse events	Dengue Group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 120 (2.50%)	3 / 60 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (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			
Dengue fever			
subjects affected / exposed	1 / 120 (0.83%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (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	Dengue Group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 120 (35.00%)	48 / 60 (80.00%)	
Nervous system disorders			
Headache; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[1]	42 / 119 (35.29%)	18 / 60 (30.00%)	
occurrences (all)	63	28	
General disorders and administration site conditions			
Injection site Pain; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 120 (28.33%)	48 / 60 (80.00%)	
occurrences (all)	50	77	
Injection site Erythema; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 120 (6.67%)	13 / 60 (21.67%)	
occurrences (all)	13	16	
Injection site Swelling; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[2]	5 / 119 (4.20%)	9 / 60 (15.00%)	
occurrences (all)	5	10	
Fever; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	33 / 120 (27.50%)	16 / 60 (26.67%)	
occurrences (all)	41	18	
Malaise; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[3]	35 / 119 (29.41%)	14 / 60 (23.33%)	
occurrences (all)	47	20	
Asthenia; Post-Any Injection			
alternative assessment type: Systematic			

subjects affected / exposed[4]	16 / 119 (13.45%)	3 / 60 (5.00%)	
occurrences (all)	18	3	
Musculoskeletal and connective tissue disorders			
Myalgia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[5]	24 / 119 (20.17%)	14 / 60 (23.33%)	
occurrences (all)	34	21	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 120 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Pharyngitis			
subjects affected / exposed	9 / 120 (7.50%)	7 / 60 (11.67%)	
occurrences (all)	9	7	

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 vaccination; 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 vaccination; 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 14 days after any vaccination; 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 vaccination; 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 any vaccination; 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
08 April 2008	Refined methods used for diagnosis of symptomatic dengue cases, implemented third vaccination blind-observer procedures, clarified exclusion criteria, deleted the fingerprint system for identification, modified the category designations of the intensity scales, avoided the use of the trade name ChimeriVax™, and aligned the informed consent form and assent form with the modifications of the protocol.
23 July 2008	Updated the protocol in response to comments from the Vietnamese Ministry of Health Ethic Committee and added the possibility to perform safety surveillance on the 4-year follow-up in all subjects with at least 1 dose of dengue vaccine, including subjects who discontinued for any reason, except those discontinued due to consent withdrawal.
04 November 2008	Changed the name of the Coordinating Investigator, identified the trial organization for laboratory analyses, and updated the planned trial calendar.
15 June 2009	Updated time period for assay analyses, updated information reviewed by the Safety Review Committee, revised and updated the inclusion and exclusion criteria, and modified follow-up phone call procedures.
10 June 2010	Replaced the Pan reverse transcriptase-polymerase chain reaction (RT-PCR) assay with the dengue screen RT-PCR and the microneutralization assay with the Dengue Plaque Reduction Neutralization Test (PRNT), and cancelled the post-dose 2 analysis of safety and immunogenicity.
17 October 2013	Changed the name of the Sponsor's responsible medical officer and regional clinical trial manager, added a database lock and interim analysis on follow-up unblinded data, updated the Institutional Review Board section regarding the Joint Research Ethics Committee, updated the pharmacovigilance email address, and exploratory analyses about natural booster infections were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported