Clinical trial results:
Study of a Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 11 Years in Malaysia

Summary

EudraCT number	2014-001717-11
Trial protocol	Outside EU/EEA
Global end of trial date	14 August 2012

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	CYD32

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01254422
WHO universal trial number (UTN)	U1111-1115-6579

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, 69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 65 6431 2600, Josemund.menezes@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 65 6431 2600, Josemund.menezes@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	26 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety and reactogenicity
Humoral immune response to dengue after the second and third injections

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	02 December 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	Malaysia: 250
Worldwide total number of subjects	250
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)	250
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 02 December 2010 to 10 February 2011 at 4 clinical sites in Malaysia.

Pre-assignment

Screening details:

A total of 250 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 design was chosen since the products had different aspects and could be recognized. The person who administered the study vaccines knew which product had been administered while neither the subject/parent nor the Investigator in charge of the safety evaluation knew which product was administered to the subjects.

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	Placebo 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)
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	Placebo Group
Started	199	51
Completed	196	50
Not completed	3	1
Adverse event, non-fatal	1	-
Serious adverse event	-	1
Lost to follow-up	1	-
Protocol deviation	1	-

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	Placebo 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	Placebo Group	Total
Number of subjects	199	51	250
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)	199	51	250
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	6.4	6.5	
standard deviation	± 2.8	± 3	-
Gender categorical Units: Subjects			
Female	103	19	122
Male	96	32	128

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	Placebo Group
Reporting group description:	
Subjects received 3 injections of placebo, 1 injection each at 0, 6, and 12 months.	

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[1]
End point description:	
Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 Solicited injection site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥50 mm. 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 post-any and 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	51		
Units: Percentage of subjects				
number (not applicable)				
Inj. site Pain; Post-Any Inj.	69.3	56.9		
Grade 3 Inj. site Pain; Post-Any Inj.	1	0		
Inj. site Erythema; Post-Any Inj.	46.7	49		
Grade 3 Inj. site Erythema; Post-Any Inj.	0.5	0		
Inj. site Swelling; Post-Any Inj.	38.7	35.3		
Grade 3 Inj. site Swelling; Post-Any Inj.	0.5	0		
Inj. site Pain; Post-Inj. 1	41.4	27.5		
Grade 3 Inj. site Pain; Post-Inj. 1	0.5	0		
Inj. site Erythema; Post-Inj. 1	22.2	23.5		
Grade 3 Inj. site Erythema; Post-Inj. 1	0.5	0		
Inj. site Swelling; Post-Inj. 1	18.7	21.6		
Grade 3 Inj. site Swelling; Post-Inj. 1	0	0		
Inj. site Pain; Post-Inj. 2	48.2	26		
Grade 3 Inj. site Pain; Post-Inj. 2	0.5	0		

Inj. site Erythema; Post-Inj. 2	33	32		
Grade 3 Inj. site Erythema; Post-Inj. 2	0	0		
Inj. site Swelling; Post-Inj. 2	15.2	10		
Grade 3 Inj. site Swelling; Post-Inj. 2	0	0		
Inj. site Pain; Post-Inj. 3	40	38		
Grade 3 Inj. site Pain; Post-Inj. 3	0.5	0		
Inj. site Erythema; Post-Inj. 3	23.6	24		
Grade 3 Inj. site Erythema; Post-Inj. 3	0	0		
Inj. site Swelling; Post-Inj. 3	20	24		
Grade 3 Inj. site Swelling; Post-Inj. 3	0.5	0		
Asthenia; Post-Any Inj.	47.2	33.3		
Grade 3 Asthenia; Post-Any Inj.	3	0		
Fever; Post-Any Inj.	29.3	19.6		
Grade 3 Fever; Post-Any Inj.	6.6	3.9		
Headache; Post-Any Inj.	52.3	39.2		
Grade 3 Headache; Post-Any Inj.	2	2		
Malaise; Post-Any Inj.	54.3	41.2		
Grade 3 Malaise; Post-Any Inj.	3.5	0		
Myalgia; Post-Any Inj.	37.7	31.4		
Grade 3 Myalgia; Post-Any Inj.	2.5	0		
Asthenia; Post-Inj. 1	28.1	19.6		
Grade 3 Asthenia; Post-Inj. 1	2	0		
Fever; Post-Inj. 1	12.6	8.2		
Grade 3 Fever; Post-Inj. 1	2	4.1		
Headache; Post-Inj. 1	37.2	27.5		
Grade 3 Headache; Post-Inj. 1	1.5	0		
Malaise; Post-Inj. 1	36.4	29.4		
Grade 3 Malaise; Post-Inj. 1	2.5	0		
Myalgia; Post-Inj. 1	22.7	23.5		
Grade 3 Myalgia; Post-Inj. 1	2	0		
Asthenia; Post-Inj. 2	23.9	6		
Grade 3 Asthenia; Post-Inj. 2	0.5	0		
Fever; Post-Inj. 2	15.2	10.2		
Grade 3 Fever; Post-Inj. 2	2.5	0		
Headache; Post-Inj. 2	31	16		
Grade 3 Headache; Post-Inj. 2	0.5	2		
Malaise; Post-Inj. 2	27.9	6		
Grade 3 Malaise; Post-Inj. 2	0.5	0		
Myalgia; Post-Inj. 2	18.8	8		
Grade 3 Myalgia; Post-Inj. 2	0.5	0		
Asthenia; Post-Inj. 3	19	12		
Grade 3 Asthenia; Post-Inj. 3	1.5	0		
Fever; Post-Inj. 3	9.5	2		
Grade 3 Fever; Post-Inj. 3	3.7	0		
Headache; Post-Inj. 3	22.6	14		
Grade 3 Headache; Post-Inj. 3	1.5	0		
Malaise; Post-Inj. 3	20.5	12		
Grade 3 Malaise; Post-Inj. 3	1.5	0		
Myalgia; Post-Inj. 3	17.4	10		
Grade 3 Myalgia; Post-Inj. 3	1	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Flavivirus-immune Subjects Reporting Solicited Injection-site and Systemic Reactions Following Each Vaccination With CYD Dengue Vaccine or a Placebo Vaccine[2]

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 Solicited injection site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥5 cm. Grade 3 Solicited systemic reactions: Fever, >39°C; Headache, Malaise, Myalgia, and Asthenia, Prevents daily activity. Flavivirus-immune is defined as subjects with quantified antibodies against Japanese encephalitis and/or against at least 1 serotype with parental dengue virus strains in the baseline sample.

End point type	Primary

End point timeframe:

Day 0 up to Day 14 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	31		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; Post-Injection 1	44.5	29		
Injection site Erythema; Post-Injection 1	14.5	29		
Injection site Swelling; Post-Injection 1	13.6	22.6		
Asthenia; Post-Injection 1	27.9	25.8		
Fever; Post-Injection 1	12.7	13.3		
Malaise; Post-Injection 1	38.2	38.7		
Myalgia; Post-Injection 1	22.7	25.8		
Headache; Post-Injection 1	36.9	29		
Injection site Pain; Post-Injection 2	48.2	32.3		
Injection site Erythema; Post-Injection 2	25.5	29		
Injection site Swelling; Post-Injection 2	9.1	16.1		
Asthenia; Post-Injection 2	21.8	9.7		
Fever; Post-Injection 2	18.2	9.7		
Malaise; Post-Injection 2	29.1	3.2		
Myalgia; Post-Injection 2	19.1	12.9		
Headache; Post-Injection 2	31.8	12.9		
Injection site Pain; Post-Injection 3	34.3	41.9		

Injection site Erythema; Post-Injection 3	21.3	22.6		
Injection site Swelling; Post-Injection 3	15.7	22.6		
Asthenia; Post-Injection 3	13.9	16.1		
Fever; Post-Injection 3	10.5	0		
Malaise; Post-Injection 3	18.5	16.1		
Myalgia; Post-Injection 3	14.8	16.1		
Headache; Post-Injection 3	19.4	19.4		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Flavivirus-naïve Subjects Reporting Solicited Injection-site and Systemic Reactions Following Each Vaccination With CYD Dengue Vaccine or a Placebo Vaccine[3]

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 Solicited injection site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥5 cm. Grade 3 Solicited systemic reactions: Fever, >39°C; Headache, Malaise, Myalgia, and Asthenia, Prevents daily activity. Flavivirus-naive is defined as subjects without quantified antibodies against Japanese encephalitis and without antibody quantified against all serotypes with parental dengue virus strains in the baseline sample.

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	CYD Dengue vaccine group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	20		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; Post-Injection 1	37.5	25		
Injection site Erythema; Post-Injection 1	31.8	15		
Injection site Swelling; Post-Injection 1	25	20		
Asthenia; Post-Injection 1	28.4	10		
Fever; Post-Injection 1	12.5	0		
Malaise; Post-Injection 1	34.1	15		
Myalgia; Post-Injection 1	22.7	20		
Headache; Post-Injection 1	37.5	25		
Injection site Pain; Post-Injection 2	48.3	15.8		
Injection site Erythema; Post-Injection 2	42.5	36.8		
Injection site Swelling; Post-Injection 2	23	0		
Asthenia; Post-Injection 2	26.4	0		

Fever; Post-Injection 2	11.5	11.1		
Malaise; Post-Injection 2	26.4	10.5		
Myalgia; Post-Injection 2	18.4	0		
Headache; Post-Injection 2	29.9	21.1		
Injection site Pain; Post-Injection 3	47.1	31.6		
Injection site Erythema; Post-Injection 3	26.4	26.3		
Injection site Swelling; Post-Injection 3	25.3	26.3		
Asthenia; Post-Injection 3	25.3	5.3		
Fever; Post-Injection 3	8.2	5.3		
Malaise; Post-Injection 3	23	5.3		
Myalgia; Post-Injection 3	20.7	0		
Headache; Post-Injection 3	26.4	5.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With a Titer ≥ 10 (1/dil) 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 a Titer ≥ 10 (1/dil) Against Each Serotype With the Parental Dengue Virus Strains 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-Injection 1 and Post-Injections 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	50		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	31.1	32		
Serotype 1; Post-Injection 2	90.3	34		
Serotype 1; Post-Injection 3	96.4	30		
Serotype 2; Pre-Injection 1	27.6	30		
Serotype 2; Post-Injection 2	94.9	34		
Serotype 2; Post-Injection 3	96.9	34		
Serotype 3; Pre-Injection 1	36.7	36.7		
Serotype 3; Post-Injection 2	98.5	32		
Serotype 3; Post-Injection 3	99	34		
Serotype 4; Pre-Injection 1	24	30		

Serotype 4; Post-Injection 2	91.8	32		
Serotype 4; Post-Injection 3	98	28		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With a Titer ≥ 10 (1/dil) for at Least One, Two, Three, or the Four 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 a Titer ≥ 10 (1/dil) for at Least One, Two, Three, or the Four Serotype With the Parental Dengue Virus Strains 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).

End point type	Primary

End point timeframe:

Pre-Injection 1 and Post-Injections 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	50		
Units: Percentage of subjects				
number (not applicable)				
At least 1 serotype; Pre-Injection 1	44.9	48		
At least 1 serotype; Post-Injection 2	100	46		
At least 1 serotype; Post-Injection 3	100	42		
At least 2 serotypes; Pre-Injection 1	29.1	28		
At least 2 serotypes; Post-Injection 2	99	34		
At least 2 serotypes; Post-Injection 3	100	32		
At least 3 serotypes; Pre-Injection 1	25.5	28		
At least 3 serotypes; Post-Injection 2	96.4	28		
At least 3 serotypes; Post-Injection 3	98.5	30		
All 4 serotypes; Pre-Injection 1	19.9	24		
All 4 serotypes; Post-Injection 2	80.1	24		
All 4 serotypes; Post-Injection 3	91.8	22		

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[6]

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-Injection 1 and Post-Injections 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	50		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	15.3 (11.5 to 20.4)	18.6 (9.69 to 35.8)		
Serotype 1; Post-Injection 2	119 (90.7 to 155)	21 (10.6 to 41.9)		
Serotype 1; Post-Injection 3	151 (121 to 188)	18.9 (9.94 to 35.8)		
Serotype 2; Pre-Injection 1	15.9 (11.8 to 21.3)	18.6 (10 to 34.5)		
Serotype 2; Post-Injection 2	160 (127 to 203)	17.9 (9.91 to 32.2)		
Serotype 2; Post-Injection 3	180 (146 to 221)	16.3 (9.59 to 27.7)		
Serotype 3; Pre-Injection 1	15.6 (12.3 to 19.9)	15.9 (9.57 to 26.5)		
Serotype 3; Post-Injection 2	196 (163 to 235)	15.9 (9.27 to 27.4)		
Serotype 3; Post-Injection 3	193 (161 to 231)	16.3 (9.81 to 27)		
Serotype 4; Pre-Injection 1	9.92 (8.17 to 12)	12.3 (7.96 to 19)		
Serotype 4; Post-Injection 2	110 (88.9 to 136)	13.3 (7.94 to 22.1)		
Serotype 4; Post-Injection 3	114 (97 to 134)	10.9 (7.34 to 16.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavivirus-immune Subjects With a Titer ≥ 10 (1/dil) 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 a Titer ≥ 10 (1/dil) Against Each Serotype With the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[7]

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 is defined as subjects with quantified antibodies against Japanese encephalitis and/or against at least 1 serotype with parental dengue virus strains in the baseline sample.

End point type	Primary

End point timeframe:

Pre-Injection 1 and Post-Injections 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	31		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	56	51.6		
Serotype 1; Post-Injection 2	96.3	48.4		
Serotype 1; Post-Injection 3	97.2	41.9		
Serotype 2; Pre-Injection 1	49.5	48.4		
Serotype 2; Post-Injection 2	96.3	54.8		
Serotype 2; Post-Injection 3	97.2	48.4		
Serotype 3; Pre-Injection 1	66.1	60		
Serotype 3; Post-Injection 2	100	51.6		
Serotype 3; Post-Injection 3	99.1	48.4		
Serotype 4; Pre-Injection 1	43.1	48.4		
Serotype 4; Post-Injection 2	97.2	45.2		
Serotype 4; Post-Injection 3	100	41.9		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Flavivirus Naïve Subjects With a Titer ≥ 10 (1/dil) 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 a Titer ≥ 10 (1/dil) Against Each Serotype With the Parental Dengue Virus Strains Before and After Vaccinations With Either CYD Dengue Vaccine or a Placebo[8]

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-naive is defined as subjects without quantified antibodies against Japanese encephalitis and without quantified antibodies against all serotypes with parental dengue virus strains in the baseline sample.

End point type	Primary

End point timeframe:

Pre-Injection 1 and Post-Injections 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	19		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1; Pre-Injection 1	0	0		
Serotype 1; Post-Injection 2	82.8	10.5		
Serotype 1; Post-Injection 3	95.4	10.5		
Serotype 2; Pre-Injection 1	0	0		
Serotype 2; Post-Injection 2	93.1	0		
Serotype 2; Post-Injection 3	96.6	10.5		
Serotype 3; Pre-Injection 1	0	0		
Serotype 3; Post-Injection 2	96.6	0		
Serotype 3; Post-Injection 3	98.9	10.5		
Serotype 4; Pre-Injection 1	0	0		
Serotype 4; Post-Injection 2	85.1	10.5		
Serotype 4; Post-Injection 3	95.4	5.3		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers 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 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[9]

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 is defined as subjects with quantified antibodies against Japanese encephalitis and/or against at least 1 serotype with parental dengue virus strains in the baseline sample.

End point type	Primary

End point timeframe:

Pre-Injection 1 and Post-Injections 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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	31		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	37.5 (24 to 58.6)	41.7 (16 to 109)		
Serotype 1; Post-Injection 2	248 (171 to 361)	45.4 (16.3 to 127)		
Serotype 1; Post-Injection 3	247 (178 to 343)	33.5 (13.3 to 84.4)		
Serotype 2; Pre-Injection 1	39.9 (25.2 to 63.1)	41.6 (17 to 102)		
Serotype 2; Post-Injection 2	306 (221 to 424)	39 (16.7 to 91.3)		
Serotype 2; Post-Injection 3	292 (217 to 395)	30 (13.8 to 64.9)		
Serotype 3; Pre-Injection 1	38.8 (27.3 to 55.4)	33.2 (16.1 to 68.5)		
Serotype 3; Post-Injection 2	296 (230 to 381)	32.4 (14.8 to 71)		
Serotype 3; Post-Injection 3	287 (219 to 376)	29.5 (14.2 to 61.1)		
Serotype 4; Pre-Injection 1	17.1 (12.5 to 23.5)	21.3 (11.3 to 40.1)		
Serotype 4; Post-Injection 2	152 (115 to 201)	21.7 (10 to 46.9)		
Serotype 4; Post-Injection 3	155 (125 to 191)	16.5 (9.17 to 29.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer 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 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[10]

End point description:

Geometric mean titers of antibodies against the dengue virus serotypes were assessed using the Dengue Plaque Reduction Neutralization Test (PRNT). Flavivirus-naive is defined as subjects without quantified antibodies against Japanese encephalitis and without antibody quantified against all serotypes with parental dengue virus strains in the baseline sample.

End point type	Primary

End point timeframe:

Pre-Injection 1 and Post- Injections 2 and 3

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	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	19		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 1; Post-Injection 2	47.1 (35.3 to 62.9)	5.98 (4.62 to 7.74)		
Serotype 1; Post-Injection 3	81.6 (66.3 to 101)	7.38 (3.88 to 14)		
Serotype 2; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 2; Post-Injection 2	71.4 (55.4 to 92.1)	5 (5 to 5)		
Serotype 2; Post-Injection 3	97.5 (77.5 to 123)	6.03 (4.43 to 8.21)		
Serotype 3; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 3; Post-Injection 2	116 (92.6 to 146)	5 (5 to 5)		
Serotype 3; Post-Injection 3	117 (97.4 to 141)	6.17 (4.52 to 8.41)		
Serotype 4; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
Serotype 4; Post-Injection 2	73.3 (53.7 to 100)	5.95 (4.47 to 7.91)		
Serotype 4; Post-Injection 3	78 (62 to 98.1)	5.54 (4.47 to 6.87)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event 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	13.0
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	Placebo 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	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 199 (5.53%)	7 / 51 (13.73%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 199 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Fibrous dysplasia of bone			
subjects affected / exposed	0 / 199 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Febrile convulsion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 199 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 199 (0.50%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	2 / 199 (1.01%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 199 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 199 (0.50%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scarlet fever			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 199 (0.50%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 199 (0.50%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	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	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 199 (69.35%)	29 / 51 (56.86%)	
Nervous system disorders			
Headache; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	104 / 199 (52.26%)	20 / 51 (39.22%)	
occurrences (all)	104	20	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 199 (7.04%)	1 / 51 (1.96%)	
occurrences (all)	14	1	
Injection site Pain; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	138 / 199 (69.35%)	29 / 51 (56.86%)	
occurrences (all)	138	29	
Injection site Erythema; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	93 / 199 (46.73%)	25 / 51 (49.02%)	
occurrences (all)	93	25	
Injection site Swelling; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	77 / 199 (38.69%)	18 / 51 (35.29%)	
occurrences (all)	77	18	
Asthenia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	94 / 199 (47.24%)	17 / 51 (33.33%)	
occurrences (all)	94	17	
Fever; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[1]	58 / 198 (29.29%)	10 / 51 (19.61%)	
occurrences (all)	58	10	
Malaise; Post-Any Injection			
alternative assessment type: Systematic			

subjects affected / exposed	108 / 199 (54.27%)	21 / 51 (41.18%)	
occurrences (all)	108	21	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	7 / 199 (3.52%)	3 / 51 (5.88%)	
occurrences (all)	7	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 199 (12.06%)	1 / 51 (1.96%)	
occurrences (all)	27	1	
Musculoskeletal and connective tissue disorders			
Myalgia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed	75 / 199 (37.69%)	16 / 51 (31.37%)	
occurrences (all)	75	16	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	50 / 199 (25.13%)	11 / 51 (21.57%)	
occurrences (all)	61	15	

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.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/4135573