Clinical trial results:
Immunogenicity and Safety of a Tetravalent Dengue Vaccine Given as a Booster Injection in Adolescents and Adults Who Previously Completed the 3-dose Schedule in a Study Conducted in Singapore

Summary

EudraCT number	2019-000993-44
Trial protocol	Outside EU/EEA
Global end of trial date	18 January 2019

Results information

Result version number	v1
This version publication date	01 August 2019
First version publication date	01 August 2019

Trial information

Trial identification

Sponsor protocol code	CYD63

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02824198
WHO universal trial number (UTN)	U1111-1161-2813

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur
Sponsor organisation address	14, Espace Henry Vallée, Lyon, France, 69007
Public contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	Interim
Date of interim/final analysis	11 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2017
Global end of trial reached?	Yes
Global end of trial date	18 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority, in terms of geometric mean of titer ratios (GTMRs), of a CYD dengue vaccine booster compared to the third CYD dengue vaccine injection in subjects from CYD28 trial (subjects from Group 1 only).

Protection of trial subjects:

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: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
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	Singapore: 118
Worldwide total number of subjects	118
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)	0
Adolescents (12-17 years)	11
Adults (18-64 years)	107
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 01 July 2016 to 18 February 2017 at 3 sites in Singapore.

Pre-assignment

Screening details:

A total of 118 subjects who received 3 doses of CYD dengue vaccine in study CYD28 (NCT00880893) were enrolled and randomised in this study (CYD63). Results are reported based on the primary completion date of 18 March 2017.

Period 1

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

Blinding implementation details:

An observer-blind procedure was followed for the injection of CYD dengue vaccine or placebo. Neither the blind-observer Investigator nor the subjects (and/or subjects' parent(s)/legally acceptable representative(s) for subjects aged less than [<] 21 years) knew which product was administered. The "vaccinator" was in charge of preparing and administering the products and was not authorized to collect any safety data.

Arms

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

Arm description:

Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received a booster injection of CYD dengue vaccine at Day 0 in this study (CYD63).

Arm type	Experimental
Investigational medicinal product name	CYD Dengue Vaccine
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 milliliters (mL), subcutaneous, 1 injection at Day 0.

Arm title	Placebo Group

Arm description:

Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received an injection of a placebo at Day 0 in this study (CYD63).

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 at Day 0.

Number of subjects in period 1	CYD Dengue Vaccine Booster Group	Placebo Group
Started	89	29
Completed	88	28
Not completed	1	1
Protocol violation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue Vaccine Booster Group
Reporting group description:	
Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received a booster injection of CYD dengue vaccine at Day 0 in this study (CYD63).	
Reporting group title	Placebo Group
Reporting group description:	
Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received an injection of a placebo at Day 0 in this study (CYD63).	

Reporting group values	CYD Dengue Vaccine Booster Group	Placebo Group	Total
Number of subjects	89	29	118
Age categorical Units: Subjects			
<=18 years	11	0	11
Between 18 and 65 years	78	29	107
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	28.1	28.2	
standard deviation	± 11.18	± 9.18	-
Gender categorical Units: Subjects			
Female	43	15	58
Male	46	14	60

End points

End points reporting groups

Reporting group title	CYD Dengue Vaccine Booster Group
Reporting group description:	
Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received a booster injection of CYD dengue vaccine at Day 0 in this study (CYD63).	
Reporting group title	Placebo Group
Reporting group description:	
Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received an injection of a placebo at Day 0 in this study (CYD63).	
Subject analysis set title	CYD Dengue Vaccine Booster Group: Post Dose 3 in CYD28
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who received 3 doses of tetravalent dengue vaccine in previous study (CYD28) were enrolled in this study (CYD63).	
Subject analysis set title	CYD Dengue Vaccine Booster Group: Post Booster Dose
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received a booster injection of CYD dengue vaccine at Day 0 in this study (CYD63).	

Primary: Geometric Mean Titers (GMTs) of Antibodies Against Each Dengue Virus Serotype Following Booster Injection (Inj.) With CYD Dengue Vaccine in CYD63 Compared to the Third CYD Dengue Vaccine Injection Received in Study CYD28: CYD Dengue Vaccine Booster Group

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Each Dengue Virus Serotype Following Booster Injection (Inj.) With CYD Dengue Vaccine in CYD63 Compared to the Third CYD Dengue Vaccine Injection Received in Study CYD28: CYD Dengue Vaccine Booster Group
End point description:	
GMTs of antibodies against each of the 4 dengue virus serotype (parental strains) were assessed using the plaque reduction neutralization test (PRNT). Analysis was performed on Per-Protocol Analysis Set which included all subjects who had no protocol deviations from the present study (CYD63). Here, 'n' = subjects with available data for each specified category.	
End point type	Primary
End point timeframe:	
28 days post-dose 3 in CYD28 and 28 days post-booster injection in CYD63	

End point values	CYD Dengue Vaccine Booster Group: Post Dose 3 in CYD28	CYD Dengue Vaccine Booster Group: Post Booster Dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: Titers (1/dilution)				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1 (n=74, 75)	20.3 (13.9 to 29.5)	37.7 (26.4 to 53.7)		

Dengue Virus Serotype 2 (n=73, 75)	85.6 (55.7 to 132)	56.2 (38.5 to 82.1)		
Dengue Virus Serotype 3 (n=72, 75)	102 (78.4 to 133)	105 (77.4 to 142)		
Dengue Virus Serotype 4 (n=70, 75)	92.8 (72.5 to 119)	123 (93.8 to 161)		

Statistical analyses

Statistical analysis title	Dengue Virus Serotype 1

Statistical analysis description:

Analysis was paired t-tests comparing the GMTs at 2 time points for the same subjects. The actual subjects in the analysis were 75.

Comparison groups	CYD Dengue Vaccine Booster Group: Post Dose 3 in CYD28 v CYD Dengue Vaccine Booster Group: Post Booster Dose
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Geometric mean of titer ratio
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.998
upper limit	1.79

Notes:

[1] - The overall non-inferiority of the booster dose was to be demonstrated if the lower limit of the two-sided 95% Confidence Interval (CI) of the Geometric mean of titer ratios (GMTRs) (booster vs post-dose 3) was greater than (>) 1/2 for each serotype.

Statistical analysis title	Dengue Virus Serotype 2

Statistical analysis description:

Analysis was paired t-tests comparing the GMTs at 2 time points for the same subjects. The actual subjects in the analysis were 75.

Comparison groups	CYD Dengue Vaccine Booster Group: Post Dose 3 in CYD28 v CYD Dengue Vaccine Booster Group: Post Booster Dose
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Geometric mean of titer ratio
Point estimate	0.603
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.439
upper limit	0.829

Notes:

[2] - The overall non-inferiority of the booster dose was to be demonstrated if the lower limit of the two-sided 95% CI of the GMTRs (booster vs post-dose 3) was >1/2 for each serotype.

Statistical analysis title	Dengue Virus Serotype 3

Statistical analysis description:

Analysis was paired t-tests comparing the GMTs at 2 time points for the same subjects. The actual

subjects in the analysis were 75.

Comparison groups	CYD Dengue Vaccine Booster Group: Post Dose 3 in CYD28 v CYD Dengue Vaccine Booster Group: Post Booster Dose
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Geometric mean of titer ratio
Point estimate	0.979
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	1.28

Notes:

[3] - The overall non-inferiority of the booster dose was to be demonstrated if the lower limit of the two-sided 95% CI of the GMTRs (booster vs post-dose 3) was >1/2 for each serotype.

Statistical analysis title	Dengue Virus Serotype 4

Statistical analysis description:

Analysis was paired t-tests comparing the GMTs at 2 time points for the same subjects. The actual subjects in the analysis were 75.

Comparison groups	CYD Dengue Vaccine Booster Group: Post Dose 3 in CYD28 v CYD Dengue Vaccine Booster Group: Post Booster Dose
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Geometric mean of titer ratio
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.918
upper limit	1.75

Notes:

[4] - The overall non-inferiority of the booster dose was to be demonstrated if the lower limit of the two-sided 95% CI of the GMTRs (booster vs post-dose 3) was > 1/2 for each serotype.

Secondary: Geometric Mean Titers of Antibodies Against Each Dengue Virus Serotype Before and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Geometric Mean Titers of Antibodies Against Each Dengue Virus Serotype Before and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

GMTs of antibodies against each of the 4 dengue virus serotype (parental strains) following booster injection were assessed using PRNT. Analysis was performed on Per-Protocol Analysis Set.

End point type	Secondary

End point timeframe:

Pre-booster injection (Day 0) and 28 days post-booster injection

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: Titers (1/dilution)				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1: Pre-booster Inj.	13.5 (9.31 to 19.6)	16.7 (7.73 to 36.1)		
Dengue Virus Serotype 1: 28 days Post-booster Inj.	37.7 (26.4 to 53.7)	18.1 (8.61 to 38.1)		
Dengue Virus Serotype 2: Pre-booster Inj.	18.4 (12.1 to 28.0)	23.2 (9.97 to 53.9)		
Dengue Virus Serotype 2: 28 days Post-booster Inj.	56.2 (38.5 to 82.1)	21.5 (9.61 to 48.1)		
Dengue Virus Serotype 3: Pre-booster Inj.	22.4 (15.6 to 32.0)	27.4 (14.8 to 51.0)		
Dengue Virus Serotype 3: 28 days Post-booster Inj.	105 (77.4 to 142)	24.1 (13.6 to 42.6)		
Dengue Virus Serotype 4: Pre-booster Inj.	28.0 (20.4 to 38.5)	44.9 (28.3 to 71.3)		
Dengue Virus Serotype 4: 28 days Post-booster Inj.	123 (93.8 to 161)	39.8 (23.9 to 66.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of Titer Ratios of Antibodies Against Each Dengue Virus Serotype Before and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Geometric Mean of Titer Ratios of Antibodies Against Each Dengue Virus Serotype Before and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

GMTs of antibodies against each of the 4 dengue virus serotype (parental strains) following booster injection were assessed using PRNT. GMTRs were calculated as the ratio of GMTs post-booster injection and pre-booster injection. Analysis was performed on Per-Protocol Analysis Set.

End point type	Secondary

End point timeframe:

Pre-booster injection (Day 0) and 28 days post-booster injection

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: Ratio				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1	1.74 (1.33 to 2.28)	0.676 (0.525 to 0.871)		

Dengue Virus Serotype 2	2.04 (1.54 to 2.69)	0.624 (0.523 to 0.745)		
Dengue Virus Serotype 3	3.52 (2.58 to 4.82)	0.669 (0.513 to 0.873)		
Dengue Virus Serotype 4	3.58 (2.61 to 4.90)	0.822 (0.640 to 1.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seropositivity Against Each Dengue Virus Serotype Following the Third CYD Dengue Vaccine Injection Received in Study CYD28, and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Percentage of Subjects With Seropositivity Against Each Dengue Virus Serotype Following the Third CYD Dengue Vaccine Injection Received in Study CYD28, and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

Seropositivity against each dengue virus serotype was measured using dengue PRNT. Seropositive subjects were defined as the subjects with neutralizing antibody titers greater than or equal to (>=) 10 (1/dilution). Analysis was performed on Per-Protocol Analysis Set. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

28 days (D) post-dose 3 in CYD28 and 28-D post-booster injection in CYD63

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: percentage of subjects				
number (not applicable)				
Dengue Virus Serotype1:28 D Post-dose 3(n=74,28)	52.7	50.0		
Dengue Virus Serotype1:28DPostbooster Inj(n=75,28)	74.7	35.7		
Dengue Virus Serotype2:28 D Post-dose 3(n=73,27)	89.0	74.1		
Dengue Virus Serotype2:28DPostbooster Inj(n=75,28)	81.3	42.9		
Dengue Virus Serotype3:28 D Post-dose 3(n=72,27)	97.2	96.3		
Dengue Virus Serotype3:28DPostbooster Inj(n=75,28)	96.0	67.9		
Dengue Virus Serotype4:28 D Post-dose 3(n=70,26)	95.7	88.5		
Dengue Virus Serotype4:28DPostbooster Inj(n=75,28)	97.3	82.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seropositivity Against Each Dengue Virus Serotype Before and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Percentage of Subjects With Seropositivity Against Each Dengue Virus Serotype Before and Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

Seropositivity against each dengue virus serotype was measured using dengue PRNT. Seropositive subjects were defined as the subjects with neutralizing antibody titers >=10 (1/dilution). Analysis was performed on Per-Protocol Analysis Set.

End point type	Secondary

End point timeframe:

Pre-booster injection (Day 0) and 28 days post-booster injection

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: percentage of subjects				
number (not applicable)				
Dengue Virus Serotype 1: Pre-booster Inj.	32.0	32.1		
Dengue Virus Serotype 1: 28 days Post-booster Inj.	74.7	35.7		
Dengue Virus Serotype 2: Pre-booster Inj.	41.3	42.9		
Dengue Virus Serotype 2: 28 days Post-booster Inj.	81.3	42.9		
Dengue Virus Serotype 3: Pre-booster Inj.	58.7	60.7		
Dengue Virus Serotype 3: 28 days Post-booster Inj.	96.0	67.9		
Dengue Virus Serotype 4: Pre-booster Inj.	70.7	89.3		
Dengue Virus Serotype 4: 28 days Post-booster Inj.	97.3	82.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroconversion Against Each Dengue Virus Serotype Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Percentage of Subjects With Seroconversion Against Each Dengue Virus Serotype Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

Seroconversion rates for each serotypes were defined as the percentages of subjects with either a pre-booster titer < 10 (1/dilution) and a post-booster titer >=40 (1/dilution), or a pre-booster titer >=10 (1/dilution) and a >=4-fold increase in post-booster titer as determined by PRNT. Analysis was performed on Per-Protocol Analysis Set.

End point type	Secondary

End point timeframe:

28 days post-booster injection

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: percentage of subjects				
number (not applicable)				
Dengue Virus Serotype 1	29.3	3.6		
Dengue Virus Serotype 2	29.3	0.0		
Dengue Virus Serotype 3	44.0	0.0		
Dengue Virus Serotype 4	38.7	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Antibodies Against Each Dengue Virus Serotype Following the Third CYD Dengue Vaccine Injection Received In Study CYD28 and Before Booster Injection With Either CYD Dengue Vaccine or Placebo in CYD63

End point title	Geometric Mean Titers of Antibodies Against Each Dengue Virus Serotype Following the Third CYD Dengue Vaccine Injection Received In Study CYD28 and Before Booster Injection With Either CYD Dengue Vaccine or Placebo in CYD63

End point description:

GMTs of antibodies against each of the 4 dengue virus serotype (parental strains) were assessed using the PRNT. Analysis was performed on Per-Protocol Analysis Set. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

28 days post-dose 3 in CYD28 and pre-booster injection (Day 0) in CYD63

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: Titers (1/dilution)				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype1:28 D Post-dose 3(n=74,28)	20.3 (13.9 to 29.5)	26.8 (12.4 to 57.7)		
Dengue Virus Serotype1:Pre-booster Inj.(n=75,28)	13.5 (9.31 to 19.6)	16.7 (7.73 to 36.1)		
Dengue Virus Serotype2:28 D Post-dose 3(n=73,27)	85.6 (55.7 to 132)	65.4 (28.3 to 151)		
Dengue Virus Serotype2: Pre-booster Inj.(n=75,28)	18.4 (12.1 to 28.0)	23.2 (9.97 to 53.9)		
Dengue Virus Serotype3:28 D Post-dose 3(n=72,27)	102 (78.4 to 133)	107 (63.6 to 179)		
Dengue Virus Serotype3: Pre-booster Inj. (n=75,28)	22.4 (15.6 to 32.0)	27.4 (14.8 to 51.0)		
Dengue Virus Serotype4:28 D Post-dose 3(n=70,26)	92.8 (72.5 to 119)	86.5 (51.0 to 147)		
Dengue Virus Serotype4: Pre-booster Inj. (n=75,28)	28.0 (20.4 to 38.5)	44.9 (28.3 to 71.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of Titer Ratios of Antibodies Against Each Dengue Virus Serotype Following the Third CYD Dengue Vaccine Injection Received in Study CYD28 and Before Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Geometric Mean of Titer Ratios of Antibodies Against Each Dengue Virus Serotype Following the Third CYD Dengue Vaccine Injection Received in Study CYD28 and Before Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

GMTs of antibodies against each of the 4 dengue virus serotype (parental strains) were assessed using the PRNT. GMTRs were calculated as the ratio of GMTs post-booster injection and pre-booster injection. Analysis was performed on Per-Protocol Analysis Set. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

28 days post-dose 3 in CYD28 and pre-booster injection (Day 0) in CYD63

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	28		
Units: Ratio				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1 (n=74, 28)	0.487 (0.390 to 0.609)	0.441 (0.316 to 0.617)		
Dengue Virus Serotype 2 (n=73, 27)	0.199 (0.160 to 0.248)	0.313 (0.224 to 0.437)		
Dengue Virus Serotype 3 (n=72, 27)	0.207 (0.163 to 0.262)	0.267 (0.171 to 0.416)		
Dengue Virus Serotype 4 (n=70, 26)	0.291 (0.217 to 0.391)	0.474 (0.343 to 0.656)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Number of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Grade 3 reactions: Pain: significant; prevents daily activity; Erythema and Swelling: > 100 millimeters (mm). Analysis was performed on Safety Analysis Set which included all subjects who received either CYD dengue vaccine or placebo. Here, 'n' = subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Within 7 days after booster injection

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	29		
Units: subjects				
number (not applicable)				
Injection-site Pain: Any (n=88,28)	29	7		
Injection-site Pain: Grade 3 (n=88,28)	1	0		
Injection-site Erythema: Any (n=88,28)	1	0		
Injection-site Erythema: Grade 3 (n=88, 28)	0	0		
Injection-site Swelling: Any (n=88,28)	0	0		
Injection-site Swelling: Grade 3 (n=88, 28)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Systemic Reactions (Fever, Headache, Malaise, Myalgia, Asthenia) Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point title	Number of Subjects Reporting Solicited Systemic Reactions (Fever, Headache, Malaise, Myalgia, Asthenia) Following Booster Injection With Either CYD Dengue Vaccine or Placebo

End point description:

Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 reactions: Fever: >= 39 degree Celsius (°C); Headache, Malaise, Myalgia, and Asthenia: significant, prevents daily activity. Analysis was performed on Safety Analysis Set. Here, 'n' = subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Within 14 days after booster injection

End point values	CYD Dengue Vaccine Booster Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	29		
Units: subjects				
number (not applicable)				
Fever: Any Grade (n=88, 28)	2	0		
Fever: Grade 3 (n=88,28)	0	0		
Headache: Any Grade (n=88, 28)	23	3		
Headache: Grade 3 (n=88, 28)	0	0		
Malaise: Any Grade (n=88,28)	11	3		
Malaise: Grade 3 (n=88, 28)	0	1		
Myalgia: Any Grade (n=88, 28)	21	7		
Myalgia: Grade 3 (n=88,28)	0	1		
Asthenia: Any Grade (n=88, 28)	15	4		
Asthenia: Grade 3 (n=88, 28)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data: from Day 0 to Day 28 post-booster inj., solicited reaction (SR) within 7 and 14 days after vaccination. Serious AEs (SAEs) throughout the study; only SAE data within 28 days after booster inj. presented in primary analysis.

Adverse event reporting additional description:

Safety Analysis Set. A SR was an AE that was prelisted (i.e., solicited) in the electronic case report form (eCRF) and considered to be related to vaccination (adverse drug reaction). An unsolicited AE was an observed AE that did not fulfill the conditions prelisted (i.e., solicited) in the eCRF in terms of symptom and/or onset post-vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	CYD Dengue Vaccine Booster Group

Reporting group description:

Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received a booster injection of CYD dengue vaccine at Day 0 in this study (CYD63).

Reporting group title	Placebo Group

Reporting group description:

Subjects who received 3 doses of the tetravalent dengue vaccine in a previous CYD dengue vaccine study (CYD28), received an injection of a placebo at Day 0 in this study (CYD63).

Serious adverse events	CYD Dengue Vaccine Booster Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 89 (1.12%)	0 / 29 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Road Traffic Accident			
subjects affected / exposed	1 / 89 (1.12%)	0 / 29 (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 Booster Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 89 (52.81%)	10 / 29 (34.48%)	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 89 (25.84%)	4 / 29 (13.79%)	
occurrences (all)	23	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 89 (16.85%)	4 / 29 (13.79%)	
occurrences (all)	15	4	
Injection Site Pain			
subjects affected / exposed	29 / 89 (32.58%)	7 / 29 (24.14%)	
occurrences (all)	29	7	
Malaise			
subjects affected / exposed	11 / 89 (12.36%)	3 / 29 (10.34%)	
occurrences (all)	11	3	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	21 / 89 (23.60%)	7 / 29 (24.14%)	
occurrences (all)	21	7	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 89 (6.74%)	1 / 29 (3.45%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2016	Following changes were made: some mistakes were corrected and some contents in the immunogenicity endpoints, visit procedures, and product storage were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported