Clinical trial results:
Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially with Adacel® in Healthy Subjects Aged 9 to 60 Years in the Philippines

Summary

EudraCT number	2019-003136-23
Trial protocol	Outside EU/EEA
Global end of trial date	10 December 2019

Results information

Result version number	v1 (current)
This version publication date	21 June 2020
First version publication date	21 June 2020

Trial information

Trial identification

Sponsor protocol code	CYD66

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02992418
WHO universal trial number (UTN)	U1111-1161-3294

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	Final
Date of interim/final analysis	07 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate the non-inferiority of the humoral immune response to the Tetanus Toxoid (T), Reduced Diphtheria Toxoid (D) and Acellular Pertussis Vaccine Adsorbed (ap) (Tdap) booster dose concomitantly administered with the first dose of CYD dengue vaccine as compared to sequential administration, measured 28 days after Tdap booster dose.

- To demonstrate the non-inferiority of the humoral immune response to the first dose of CYD dengue vaccine concomitantly administered with Tdap as compared to sequential administration, measured 28 days after the first dose of CYD dengue vaccine.

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	19 December 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	Philippines: 688
Worldwide total number of subjects	688
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)	172
Adolescents (12-17 years)	172

Adults (18-64 years)	344
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 19 December 2016 to 17 April 2017 at 4 centres in the Philippines. A total of 688 subjects were enrolled and randomised in this study.

Pre-assignment

Screening details:

Safety signal was identified in seronegative subjects, which led to IDMC recommendation to not vaccinate them anymore. As no Health Authority feedback was received on amendment 1, study was stopped prematurely before 3rd (last) injection of CYD dengue vaccine and no subjects received 3rd CYD dengue dose. All subjects were followed for safety.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)

Arm description:

Subjects received 1 booster dose of Tdap vaccine 0.5 millilitre (mL) intramuscular (IM) injection at Month 1, and 2 doses of CYD dengue vaccine 0.5 mL subcutaneous (SC) injection at Month 1 (concomitantly with Tdap booster dose) and at Month 7.

Arm type	Experimental
Investigational medicinal product name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap)
Investigational medicinal product code	
Other name	Adacel®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM injection at Month 1.

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 mL, SC injection at Month 1 and Month 7, respectively.

Arm title	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)

Arm description:

Subjects received 1 booster dose of Tdap vaccine 0.5 mL IM injection at Day 0 and 2 doses of CYD dengue vaccine 0.5 mL SC injection at Month 1 (sequentially, one month after the Tdap booster dose) and at Month 7.

Arm type	Experimental

Investigational medicinal product name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap)
Investigational medicinal product code	
Other name	Adacel®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM injection at Month 1.

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 mL, SC injection at Month 1 and Month 7, respectively.

Number of subjects in period 1	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Started	346	342
Safety Analysis Set (SafAS)	338	342
Completed	0	0
Not completed	346	342
Lost to follow-up	27	22
Voluntary withdrawal not due to an adverse event	11	12
Non-compliance with the protocol	308	308

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)
Reporting group description:	
Subjects received 1 booster dose of Tdap vaccine 0.5 millilitre (mL) intramuscular (IM) injection at Month 1, and 2 doses of CYD dengue vaccine 0.5 mL subcutaneous (SC) injection at Month 1 (concomitantly with Tdap booster dose) and at Month 7.	
Reporting group title	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Reporting group description:	
Subjects received 1 booster dose of Tdap vaccine 0.5 mL IM injection at Day 0 and 2 doses of CYD dengue vaccine 0.5 mL SC injection at Month 1 (sequentially, one month after the Tdap booster dose) and at Month 7.	

Reporting group values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)	Total
Number of subjects	346	342	688
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	26.2	27.1	
standard deviation	± 16.3	± 16.7	-
Gender categorical			
Units: Subjects			
Female	187	193	380
Male	159	149	308
Dengue Baseline Status			
Dengue immune subjects were defined as subjects with titers greater than or equal to (>=) 10 (1/dilution) for at least one serotype with the parental dengue virus strain. Dengue non-immune subjects were defined as subjects with titers less than (<) 10 (1/dilution) for all serotypes with parental dengue virus strains with available and 'valid' results.			
Units: Subjects			
Dengue immune	314	315	629
Dengue non-immune	32	27	59

End points

End points reporting groups

Reporting group title	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)
Reporting group description:	
Subjects received 1 booster dose of Tdap vaccine 0.5 millilitre (mL) intramuscular (IM) injection at Month 1, and 2 doses of CYD dengue vaccine 0.5 mL subcutaneous (SC) injection at Month 1 (concomitantly with Tdap booster dose) and at Month 7.	
Reporting group title	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Reporting group description:	
Subjects received 1 booster dose of Tdap vaccine 0.5 mL IM injection at Day 0 and 2 doses of CYD dengue vaccine 0.5 mL SC injection at Month 1 (sequentially, one month after the Tdap booster dose) and at Month 7.	

Primary: Geometric Mean Concentrations (GMCs) of Antibodies Against Pertussis Antigens (Pertussis Toxoid, Filamentous Hemagglutinin, Pertactin, and Fimbriae 2+3) 28 Days After Dose of Tdap Vaccine in Previously Dengue Immune Subjects

End point title	Geometric Mean Concentrations (GMCs) of Antibodies Against Pertussis Antigens (Pertussis Toxoid, Filamentous Hemagglutinin, Pertactin, and Fimbriae 2+3) 28 Days After Dose of Tdap Vaccine in Previously Dengue Immune Subjects
End point description:	
GMCs against each pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM2+3]) were assessed using an enzyme-linked immunosorbent assay (ELISA) method and were measured in ELISA unit/millilitre (EU/mL). Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Analysis was performed on per protocol analysis set of Tdap (PPT) population which included subjects who received at least one dose of Tdap and had no relevant protocol deviations. Here, 'n' = subjects with available data for each specified category.	
End point type	Primary
End point timeframe:	
28 days after Tdap vaccination	

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	314		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Anti-PT (n = 300, 310)	65.2 (57.7 to 73.8)	76.0 (67.9 to 85.1)		
Anti-FHA (n = 308, 314)	273 (248 to 299)	267 (241 to 296)		
Anti-PRN (n = 311, 314)	50.6 (41.4 to 61.9)	44.9 (36.7 to 55.0)		
Anti-FIM2+3 (n = 309, 312)	705 (586 to 847)	643 (537 to 770)		

Statistical analyses

Statistical analysis title	Anti-PT
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	GMC ratio
Point estimate	0.848
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.721
upper limit	0.997

Notes:

[1] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) of the ratio of GMCs between groups (Group 1/ Group 2) was greater than (>) 1/1.5 for each antigen. Overall non-inferiority was demonstrated if the 4 antigens achieved non-inferiority.

Statistical analysis title	Anti-FHA
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	GMC ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.892
upper limit	1.18

Notes:

[2] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMCs between groups (Group 1/ Group 2) was > 1/1.5 for each antigen. Overall non-inferiority was demonstrated if the 4 antigens achieved non-inferiority.

Statistical analysis title	Anti-PRN
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)

Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMC ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.836
upper limit	1.46

Notes:

[3] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMCs between groups (Group 1/ Group 2) was > 1/1.5 for each antigen. Overall non-inferiority was demonstrated if the 4 antigens achieved non-inferiority.

Statistical analysis title	Anti-FIM2+3
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMC ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.827
upper limit	1.33

Notes:

[4] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMCs between groups (Group 1/ Group 2) was > 1/1.5 for each antigen. Overall non-inferiority was demonstrated if the 4 antigens achieved non-inferiority.

Primary: Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens 28 Days After the Dose of Tdap Vaccine in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens 28 Days After the Dose of Tdap Vaccine in the Previously Dengue Immune Subjects

End point description:

Seroprotection against diphtheria (Anti-D) and tetanus (Anti-T) antigens was performed by Micrometabolic Inhibition Test - Toxin Neutralization assay (MIT-TNA) and ELISA, respectively. Seroprotection was defined as anti-D and anti-T Ab concentration superior to 0.1 international units (IU)/mL. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Analysis was performed on PPT population. Here, 'n'=subjects with available data for each specified category.

End point type	Primary

End point timeframe:

28 days after Tdap vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	314		
Units: percentage of subjects				
number (confidence interval 95%)				
Anti-D (n = 312, 314)	90.1 (86.2 to 93.1)	89.8 (85.9 to 92.9)		
Anti-T (n = 309, 314)	98.4 (96.3 to 99.5)	99.0 (97.2 to 99.8)		

Statistical analyses

Statistical analysis title	Anti-D
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Percentage difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.53
upper limit	5.04

Notes:

[5] - The non-inferiority was demonstrated if the lower limit of all the 95% CI of the difference was > -10% for all antigens.

Statistical analysis title	Anti-T
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration) v CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Percentage difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	1.37

Notes:

[6] - The non-inferiority was demonstrated if the lower limit of all the 95% CI of the difference was > -10% for all antigens.

Primary: Geometric Mean Titers (GMTs) of Antibodies Against Each Dengue Virus

Serotype 28 Days After the First Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Each Dengue Virus Serotype 28 Days After the First Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

The GMTs against each of the four parenteral dengue virus serotypes (1, 2, 3 and 4) of CYD dengue vaccine were assessed using the 50% plaque reduction neutralization test (PRNT50) assay method. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Titers were measured in terms of 1/dilution. Analysis was performed on per-protocol analysis set for CYD dengue vaccine (PPC) population which included subjects who received the first dose of CYD dengue vaccine and had no relevant protocol deviations.

End point type	Primary

End point timeframe:

28 days after first CYD dengue vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	308		
Units: titers				
geometric mean (confidence interval 95%)				
Serotype 1	513 (427 to 617)	461 (384 to 552)		
Serotype 2	677 (588 to 780)	568 (489 to 661)		
Serotype 3	653 (558 to 765)	706 (603 to 828)		
Serotype 4	378 (324 to 442)	472 (404 to 551)		

Statistical analyses

Statistical analysis title	Serotype 1
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	GMT ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.862
upper limit	1.44

Notes:

[7] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (Group 1/Group 2) was > 1/2 for each serotype. Overall non-inferiority was demonstrated if all 4 serotypes achieved non-inferiority.

Statistical analysis title	Serotype 2
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.47

Notes:

[8] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (Group 1/Group 2) was > 1/2 for each serotype. Overall non-inferiority was demonstrated if all 4 serotypes achieved non-inferiority.

Statistical analysis title	Serotype 3
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	GMT ratio
Point estimate	0.925
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.739
upper limit	1.16

Notes:

[9] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (Group 1/Group 2) was > 1/2 for each serotype. Overall non-inferiority was demonstrated if all 4 serotypes achieved non-inferiority.

Statistical analysis title	Serotype 4
Comparison groups	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration) v CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMT ratio
Point estimate	0.802

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.644
upper limit	0.999

Notes:

[10] - The non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (Group 1/Group 2) was > 1/2 for each serotype. Overall non-inferiority was demonstrated if all 4 serotypes achieved non-inferiority.

Secondary: Geometric Mean Titers of Antibodies Against Each Dengue Virus Serotype at Baseline and 28 Days After the First Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Geometric Mean Titers of Antibodies Against Each Dengue Virus Serotype at Baseline and 28 Days After the First Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

The GMTs against each of the four parenteral dengue virus serotypes (1, 2, 3 and 4) of CYD dengue vaccine were assessed using PRNT50 assay method. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Titers were measured in terms of 1/dilution. Analysis was performed on the subset of FAS population who received at least one dose of the study vaccines (CYD dengue or Tdap) and were immune to dengue at baseline. Here, 'number of subjects analysed'=subjects evaluable for this end-point and ‘n’=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Pre-vaccination 1) and 28 days after the first CYD dengue vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	315		
Units: titers				
geometric mean (confidence interval 95%)				
Serotype 1: Pre-vaccination 1 (n=314,315)	265 (218 to 322)	250 (208 to 300)		
Serotype 1: 28 days post-vaccination 1 (n=313,315)	513 (427 to 616)	468 (392 to 560)		
Serotype 2: Pre-vaccination 1 (n=314,315)	404 (350 to 467)	343 (294 to 401)		
Serotype 2: 28days post-vaccination 1 (n=313,315)	679 (589 to 781)	577 (497 to 671)		
Serotype 3: Pre-vaccination 1 (n=314, 315)	327 (274 to 391)	327 (280 to 383)		
Serotype 3: 28 days post-vaccination 1 (n=313,315)	655 (559 to 767)	709 (605 to 830)		
Serotype 4: Pre-vaccination 1 (n=314, 315)	136 (115 to 160)	172 (150 to 197)		
Serotype 4: 28 days post-vaccination 1 (n=313,315)	379 (325 to 443)	478 (410 to 557)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralizing Antibody Titers Against Each of the 4 Dengue Virus Serotypes of CYD at Baseline and 28 Days After first Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects With Neutralizing Antibody Titers Against Each of the 4 Dengue Virus Serotypes of CYD at Baseline and 28 Days After first Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

The GMTs against each of the four parenteral dengue virus serotypes (1, 2, 3 and 4) of CYD dengue vaccine were assessed using PRNT50 assay method. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Analysis was performed on the subset of FAS population who were immune to dengue at baseline. Here, 'number of subjects analysed'=subjects evaluable for this end-point and 'n'=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Pre-vaccination 1) and 28 days after the first CYD dengue vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	315		
Units: percentage of subjects				
number (confidence interval 95%)				
Serotype 1: Pre-vaccination 1 (n=314,315)	92.7 (89.2 to 95.3)	93.3 (90.0 to 95.8)		
Serotype 1: 28 days post-vaccination 1 (n=313,315)	97.8 (95.4 to 99.1)	98.4 (96.3 to 99.5)		
Serotype 2: Pre-vaccination 1 (n=314,315)	98.1 (95.9 to 99.3)	96.5 (93.8 to 98.2)		
Serotype 2: 28 days post-vaccination 1 (n=313,315)	100.0 (98.8 to 100.0)	99.0 (97.2 to 99.8)		
Serotype 3: Pre-vaccination 1 (n=314, 315)	95.5 (92.6 to 97.5)	97.1 (94.6 to 98.7)		
Serotype 3: 28 days post-vaccination 1 (n=313,315)	100.0 (98.8 to 100.0)	99.7 (98.2 to 100.0)		
Serotype 4: Pre-vaccination 1 (n=314, 315)	93.0 (89.6 to 95.6)	97.5 (95.1 to 98.9)		
Serotype 4: 28 days post-vaccination 1 (n=313,315)	99.4 (97.7 to 99.9)	100.0 (98.8 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralizing Antibody Titers Above Pre-defined Thresholds Against at Least 1, 2, 3, or 4 Serotypes of CYD at Baseline and 28 Days After the First Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects With Neutralizing Antibody Titers Above Pre-defined Thresholds Against at Least 1, 2, 3, or 4 Serotypes of CYD at Baseline and 28 Days After the First Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

Dengue neutralizing antibody levels against each of the 4 dengue virus serotypes (1, 2, 3, and 4) were measured by PRNT50. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Percentage of subjects with neutralizing antibody titers above pre-defined thresholds (>=10 and >=100 [1/dilution]) against at least 1, 2, 3, or 4 serotypes of CYD were reported. Analysis was performed on the subset of FAS population who were immune to dengue at baseline. Here, 'number of subjects analysed'=subjects evaluable for this end-point and 'n'=subjects with available data for each specified categories. Here, 'dil'=dilution and "vac"=vaccination in the specified categories.

End point type	Secondary

End point timeframe:

Baseline (Pre-vaccination 1) and 28 days after the first CYD dengue vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	315		
Units: percentage of subjects				
number (confidence interval 95%)				
At least 1Serotype:pre-vac1:>=10(1/dil)(n=314,315)	100.0 (98.8 to 100.0)	100.0 (98.8 to 100.0)		
At least1Serotype:pre-vac1:>=100(1/dil)(n=314,315)	97.8 (95.5 to 99.1)	97.1 (94.6 to 98.7)		
At least1Serotype:post-vac1:>=10(1/dil)(n=313,315)	100.0 (98.8 to 100.0)	100.0 (98.8 to 100.0)		
Atleast1Serotype:post-vac1:>=100(1/dil)(n=313,315)	99.7 (98.2 to 100.0)	99.7 (98.2 to 100.0)		
At least 2Serotype:pre-vac1:>=10(1/dil)(n=314,315)	96.5 (93.8 to 98.2)	98.1 (95.9 to 99.3)		
At least2Serotype:pre-vac1:>=100(1/dil)(n=314,315)	84.4 (79.9 to 88.2)	87.0 (82.8 to 90.5)		
At least2Serotype:post-vac1:>=10(1/dil)(n=313,315)	100.0 (98.8 to 100.0)	99.7 (98.2 to 100.0)		

Atleast2Serotype:post-vac1:>=100(1/dil)(n=313,315)	95.8 (93.0 to 97.8)	96.5 (93.8 to 98.2)		
At least 3Serotype:pre-vac1:>=10(1/dil)(n=314,315)	93.6 (90.3 to 96.1)	95.2 (92.3 to 97.3)		
At least3Serotype:pre-vac1:>=100(1/dil)(n=314,315)	76.1 (71.0 to 80.7)	76.8 (71.8 to 81.4)		
Atleast 3Serotype:post-vac1:>=10(1/dil)(n=313,315)	99.7 (98.2 to 100.0)	99.4 (97.7 to 99.9)		
Atleast3Serotype:post-vac1:>=100(1/dil)(n=313,315)	90.4 (86.6 to 93.4)	92.1 (88.5 to 94.8)		
At least 4Serotype:pre-vac1:>=10(1/dil)(n=314,315)	89.2 (85.2 to 92.4)	91.1 (87.4 to 94.0)		
At least4Serotype:pre-vac1:>=100(1/dil)(n=314,315)	52.9 (47.2 to 58.5)	54.3 (48.6 to 59.9)		
At least4Serotype:post-vac1:>=10(1/dil)(n=313,315)	97.4 (95.0 to 98.9)	98.1 (95.9 to 99.3)		
Atleast4Serotype:post-vac1:>=100(1/dil)(n=313,315)	73.8 (68.6 to 78.6)	75.6 (70.4 to 80.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations of Serum Antibodies Against Pertussis Antigens (Pertussis Toxoid, Filamentous Hemagglutinin, Pertactin, and Fimbriae 2+3) at Baseline and 28 Days After the dose of Tdap Vaccine in the Previously Dengue Immune Subjects

End point title	Geometric Mean Concentrations of Serum Antibodies Against Pertussis Antigens (Pertussis Toxoid, Filamentous Hemagglutinin, Pertactin, and Fimbriae 2+3) at Baseline and 28 Days After the dose of Tdap Vaccine in the Previously Dengue Immune Subjects

End point description:

GMCs against each pertussis antigens (PT, FHA, PRN, FIM2+3) were assessed using ELISA assay method and were measured in EU/mL. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Analysis was performed on the subset of FAS population who were immune to dengue at baseline. Here, 'number of subjects analysed'=subjects evaluable for this end-point and 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Pre-vaccination) and 28 days after the Tdap vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	315		
Units: EU/mL				
geometric mean (confidence interval 95%)				

Anti-PT: Pre-vaccination (n=313,313)	8.46 (7.34 to 9.75)	9.56 (8.33 to 11.0)		
Anti-PT: 28 days post-vaccination (n=301,311)	65.0 (57.5 to 73.5)	76.1 (68.1 to 85.2)		
Anti-FHA: Pre-vaccination (n=310,314)	19.9 (17.6 to 22.6)	19.4 (17.1 to 22.1)		
Anti-FHA: 28 days post-vaccination (n=309,315)	272 (248 to 299)	266 (240 to 295)		
Anti-PRN: Pre-vaccination (n=314,315)	3.79 (3.39 to 4.24)	3.65 (3.25 to 4.10)		
Anti-PRN: 28 days post-vaccination (n=312,315)	50.6 (41.4 to 61.8)	45.0 (36.8 to 55.1)		
Anti-FIM2+3: Pre-vaccination (n=297,298)	15.1 (12.4 to 18.5)	14.9 (12.2 to 18.1)		
Anti-FIM2+3: 28 days post-vaccination (n=310,313)	700 (583 to 841)	642 (537 to 769)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Serum Antibody Concentration (>=0.1 IU/mL) Against Diphtheria and Tetanus Antigens at Baseline and 28 Days After the Dose of Tdap Vaccine in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects Achieving Serum Antibody Concentration (>=0.1 IU/mL) Against Diphtheria and Tetanus Antigens at Baseline and 28 Days After the Dose of Tdap Vaccine in the Previously Dengue Immune Subjects

End point description:

The GMC against diphtheria and tetanus antigens was performed by MIT-TNA and ELISA, respectively. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dilution) for at least one serotype with the parental dengue virus strain. Analysis was performed on the subset of FAS population who were immune to dengue at baseline. Here, 'number of subjects analysed'=subjects evaluable for this end-point and ‘n’=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Pre-vaccination) and 28 days after the dose of Tdap vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	315		
Units: percentage of subjects				
number (confidence interval 95%)				
Anti-D: Pre-vaccination (314, 314)	31.8 (26.7 to 37.3)	32.8 (27.6 to 38.3)		
Anti-T: Pre-vaccination (314, 313)	63.7 (58.1 to 69.0)	69.6 (64.2 to 74.7)		
Anti-D: 28 days post-vaccination (n=313,315)	90.1 (86.2 to 93.2)	89.8 (86.0 to 92.9)		

Anti-T: 28 days post-vaccination (n=310,315)	98.1 (95.8 to 99.3)	99.0 (97.2 to 99.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Immediate Unsolicited Adverse Events (AE) Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects With Immediate Unsolicited Adverse Events (AE) Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the electronic case report form (eCRF) in terms of diagnosis and/or onset post-vaccination. Any unsolicited systemic AE occurred during first 30 minutes post-vaccination was recorded on the CRF as immediate AE. At Visit 1, subjects of Group 1 received no vaccination and subjects of Group 2 received only Tdap vaccination. At Visit 2, subjects of Group 1 received both CYD and Tdap vaccination and subjects of Group 2 received only CYD vaccination. At Visit 4, subjects of Groups 1 and 2 received CYD vaccination. Analysis was performed on safety analysis set (SafAS) population, which included subjects who received at least one dose of the study vaccines (CYD and Tdap). Here, 'n'=subjects with available data for each specified category and '99999' was used as a space filler which signifies that the subjects of Group 1 did not receive any vaccination at Visit 1 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Within 30 minutes after any and each vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)				
Post any vaccination(n=338,342)	0	0		
Post Tdap vaccination (Visit 1) (n=0,342)	99999	0		
Post CYD/Tdap vaccination (Visit 2)(n=338,338)	0	0		
Post CYD vaccination (Visit 4) (n=321, 319)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Solicited Injection Site Reactions Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects With Solicited Injection Site Reactions Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

A solicited reaction was an AE observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the eCRF and considered as related to vaccination. Solicited injection site reactions included pain, erythema, and swelling. At Visit 1, subjects of Group 1 received no vaccination and subjects of Group 2 received only Tdap vaccination. At Visit 2, subjects of Group 1 received both CYD and Tdap vaccinations and subjects of Group 2 received only CYD vaccination. At Visit 4, subjects of Groups 1 and 2 received only CYD vaccination. Analysis was performed on SafAS population. Here, 'n'=subjects with available data for each specified category. Here, '99999' was used as a space filler which signifies that the Group 1 subjects did not receive any vaccination at Visit 1 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Within 7 days after any and each vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)				
Pain: Post any vaccination(n=338,341)	229	237		
Pain: Post Tdap vaccination (Visit 1) (n=0,341)	99999	212		
Pain:Post CYD/Tdap vaccination(Visit 2)(n=338,338)	218	53		
Pain: Post CYD vaccination (Visit 4) (n=320,319)	61	55		
Erythema: Post any vaccination(n=338,341)	14	17		
Erythema: Post Tdap vaccination (Visit 1)(n=0,341)	99999	14		
Erythema:PostCYD/Tdapvaccination(Visit2;n=338,338)	13	5		
Erythema: Post CYD vaccination (Visit 4;n=320,319)	2	2		
Swelling: Post any vaccination (n=338,341)	25	32		
Swelling: Post Tdap vaccination (Visit 1; n=0,341)	99999	30		
Swelling:PostCYD/Tdapvaccination(Visit 2;n=338,338)	25	3		
Swelling: Post CYD vaccination (Visit 4;n=320,319)	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Solicited Systemic Reactions Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects With Solicited Systemic Reactions Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

A solicited reaction was an adverse reaction observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination. Solicited injection site reactions included fever, headache, malaise, myalgia, and asthenia. At Visit 1, subjects of Group 1 received no vaccination and subjects of Group 2 received only Tdap vaccination. At Visit 2, subjects of Group 1 received both CYD and Tdap vaccinations and subjects of Group 2 received only CYD vaccination. At Visit 4, subjects of Groups 1 and 2 received only CYD vaccination. Analysis was performed on SafAS population. Here, 'n'=subjects with available data for each specified category. Here, '99999' was used as space filler which signifies that Group 1 subjects did not receive any vaccination at Visit 1 and were not evaluable.

End point type	Secondary

End point timeframe:

Within 14 days after any and each vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)				
Fever: Post any vaccination (n=338,340)	21	30		
Fever: Post Tdap vaccination (Visit 1; n=0,339)	99999	15		
Fever:PostCYD/Tdapvaccination(Visit2; n=338,338)	11	6		
Fever: Post CYD vaccination (Visit 4; n=320,319)	10	9		
Headache: Post any vaccination (n=338,341)	89	115		
Headache: Post Tdap vaccination (Visit 1; n=0,341)	99999	83		
Headache:PostCYD/Tdapvaccination(Visit2;n=338,338)	70	33		
Headache: Post CYD vaccination (Visit 4;n=320,319)	36	35		
Malaise: Post any vaccination (n=338,341)	91	111		
Malaise: Post Tdap vaccination (Visit 1; n=0,341)	99999	81		
Malaise:PostCYD/Tdapvaccination(Visit2; n=338,338)	74	28		
Malaise: Post CYD vaccination (Visit 4; n=320,319)	32	33		
Myalgia: Post any vaccination (n=338,341)	74	100		

Myalgia: Post Tdap vaccination (Visit 1; n=0,341)	99999	78		
Myalgia:PostCYD/Tdapvaccination(Visit2 ; n=338,338)	67	30		
Myalgia: Post CYD vaccination (Visit 4; n=320,319)	26	22		
Asthenia: Post any vaccination (n=338,341)	67	94		
Asthenia: Post Tdap vaccination (Visit 1; n=0,341)	99999	69		
Asthenia:PostCYD/Tdapvaccination(Visit 2;n=338,338)	59	24		
Asthenia: Post CYD vaccination (Visit 4;n=320,319)	19	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Adverse Events Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Unsolicited Adverse Events Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset post-vaccination. At Visit 1, subjects of Group 1 received no vaccination and subjects of Group 2 received only Tdap vaccination. At Visit 2, subjects of Group 1 received both CYD and Tdap vaccinations and subjects of Group 2 received only CYD vaccination. At Visit 4, subjects of Groups 1 and 2 received CYD vaccination. Analysis was performed on SafAS population. Here, 'n'=subjects with available data for each specified category and '99999' was used as a space filler which signifies that the subjects from Group 1 did not receive any vaccination at Visit 1 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Within 28 days after any and each vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)				
Post any vaccination (n=338,342)	56	70		
Post Tdap vaccination (Visit 1; n=0,342)	99999	40		
PostCYD/Tdapvaccination(Visit2; n=338,338)	37	20		
Post CYD vaccination (Visit 4; n=321,319)	28	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Non-serious Adverse Event of Special Interests (AESIs) Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Non-serious Adverse Event of Special Interests (AESIs) Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

AESIs were AEs that are considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine. At Visit 1, subjects of Group 1 received no vaccination and subjects of Group 2 received only Tdap vaccination. At Visit 2, subjects of Group 1 received both CYD and Tdap vaccinations and subjects of Group 2 received only CYD vaccination. At Visit 4, subjects of Groups 1 and 2 received CYD vaccination. Analysis was performed on SafAS population. Here, 'n'=subjects with available data for each specified category and '99999' was used as a space filler which signifies that the subjects from Group 1 did not receive any vaccination at Visit 1 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Within 7 days post any and each vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)				
Post any vaccination (n=338,342)	0	0		
Post Tdap vaccination (Visit 1; n=0,342)	99999	0		
PostCYD/Tdapvaccination(Visit2; n=338,338)	0	0		
Post CYD vaccination (Visit 4; n=321,319)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Serious Adverse Events (SAEs) Including Serious AESIs Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Serious Adverse Events (SAEs)

	Including Serious AESIs Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

SAEs were AEs resulting in any of the following outcomes or deemed significant for any other reason: death; life-threatening; required hospitalisation or prolonged existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly or a medically important event. AESIs were AEs that were considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine. Analysis was performed on SafAS population.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months after the last Tdap or CYD vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)				
SAE	8	11		
Serious AESI	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Cases of Virologically Confirmed Dengue (VCD) Hospitalization Following Vaccination With Tdap or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Cases of Virologically Confirmed Dengue (VCD) Hospitalization Following Vaccination With Tdap or CYD Dengue Vaccine

End point description:

Hospitalised suspected dengue case was defined as an acute febrile illness with diagnosis of dengue requiring hospitalisation (with bed attribution). In such cases, 1 unplanned acute blood sample (within the first 5 days after fever onset) was collected for virological confirmation of hospitalised suspected dengue case. A suspected case was considered VCD if there was a detection of wild type dengue virus by dengue non-structural protein 1 antigen ELISA and/or dengue reverse transcriptase-polymerase chain reactions. Analysis was performed on SafAS population.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months after the last Tdap or CYD vaccination

End point values	CYD Dengue Vaccine + Tdap Vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	342		
Units: subjects				
number (not applicable)	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE data were collected from Day 0 up to Day 28 post any vaccination. SR data were collected from Day 0 up to Day 14 post-vaccination. The SAEs were collected throughout the trial, i.e. 6 months after last Tdap or CYD vaccination.

Adverse event reporting additional description:

SR was an AE that was prelisted (i.e., solicited) in the 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 in the CRF (i.e., solicited) in terms of symptom and/or onset post-vaccination. Analysis was performed on SafAS population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	CYD Dengue Vaccine + Tdap vaccine (Concomitant Administration)

Reporting group description:

Subjects received 1 booster dose of Tdap vaccine 0.5 mL IM injection at Month 1, and 2 doses of CYD dengue vaccine 0.5 mL SC injection at Month 1 (concomitantly with Tdap booster dose) and at Month 7.

Reporting group title	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)

Reporting group description:

Subjects received 1 booster dose of Tdap vaccine 0.5 mL IM injection at Day 0 and 2 doses of CYD dengue vaccine 0.5 mL SC injection at Month 1 (sequentially, one month after the Tdap booster dose) and at Month 7.

Serious adverse events	CYD Dengue Vaccine + Tdap vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 338 (2.37%)	11 / 342 (3.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incisional Hernia			

subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Hypertensive Heart Disease			
subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Complete			
subjects affected / exposed	1 / 338 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice Cholestatic			

subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash Generalised			
subjects affected / exposed	1 / 338 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 342 (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			
Appendicitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical Pneumonia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue Fever			
subjects affected / exposed	1 / 338 (0.30%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 342 (0.29%)	
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 + Tdap vaccine (Concomitant Administration)	CYD Dengue Vaccine + Tdap Vaccine (Sequential Administration)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	248 / 338 (73.37%)	263 / 342 (76.90%)	
Nervous system disorders			
Headache	Additional description: Headache event which started on Day 15 post-vaccination was an unsolicited AE.		
subjects affected / exposed	89 / 338 (26.33%)	116 / 342 (33.92%)	
occurrences (all)	106	152	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	67 / 338 (19.82%)	94 / 342 (27.49%)	
occurrences (all)	78	115	
Injection Site Pain			
subjects affected / exposed	229 / 338 (67.75%)	237 / 342 (69.30%)	
occurrences (all)	376	320	
Injection Site Swelling			
subjects affected / exposed	25 / 338 (7.40%)	32 / 342 (9.36%)	
occurrences (all)	29	35	
Malaise			
subjects affected / exposed	91 / 338 (26.92%)	111 / 342 (32.46%)	
occurrences (all)	106	142	
Pyrexia	Additional description: Pyrexia/fever events that occurred after 14 days post-vaccination were considered as unsolicited AEs.		
subjects affected / exposed	22 / 338 (6.51%)	32 / 342 (9.36%)	
occurrences (all)	22	33	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	74 / 338 (21.89%)	100 / 342 (29.24%)	
occurrences (all)	93	130	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	17 / 338 (5.03%)	17 / 342 (4.97%)	
occurrences (all)	17	21	

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? Yes

Date	Interruption	Restart date
09 November 2017	Given the IDMC recommendations, Sanofi Pasteur has suspended all vaccinations in this study and amended the study protocol, to determine the basal serostatus of the subjects already included in the study and to implement IDMC recommendations. No response was received from Philippines Food and Drug Administration, and therefore the protocol amendment could not be implemented. After having waited for more than 1.5 year, and as the subjects became out of window to complete their immunization schedule and the last safety follow-up call (6 months after the last dose), the Sponsor decided to stop the trial. Subjects only attended a last safety follow-up visit to terminate the study and were informed about the end of the study. As a consequence of the IDMC recommendations, the main immunogenicity analyses were done in dengue immune subjects which is not what was planned in the protocol (and this is why the primary endpoints are not exactly the same as those defined in the protocol as they were finally assessed only in seropositive subjects whereas initially it was planned to be assessed regardless of baseline status).	02 October 2019

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to absence of response of competent authorities from The Philippines on the protocol amendment, the study was prematurely terminated before injection of last dose (3rd dose) of CYD dengue vaccine. Objectives related to 3rd dose was not assessed.

Notes: