Clinical trial results:
Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially With Cervarix® in Healthy Female Subjects Aged 9 to 14 Years in Mexico

Summary

EudraCT number	2019-000994-22
Trial protocol	Outside EU/EEA
Global end of trial date	25 March 2019

Results information

Result version number	v1 (current)
This version publication date	12 January 2020
First version publication date	12 January 2020

Trial information

Trial identification

Sponsor protocol code	CYD71

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02979535
WHO universal trial number (UTN)	U1111-1161-3455

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	17 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cervarix immunogenicity: To demonstrate that the humoral immune response (in terms of geometric mean titers [GMTs]) to Cervarix after concomitant administration with the CYD dengue vaccine is non-inferior to the humoral immune response (in terms of GMTs) after sequential administration with the CYD dengue vaccine measured 28 days after the last dose of Cervarix.

CYD dengue vaccine immunogenicity: To demonstrate that the humoral immune response (in terms of GMTs) to the CYD dengue vaccine after concomitant administration with Cervarix is non-inferior to the humoral immune response (in terms of GMTs) to the CYD dengue vaccine after sequential administration with Cervarix measured 28 days after the last dose of the CYD dengue vaccine. Providing that the number of evaluable seropositive subjects allows a global power of at least 80% (otherwise analyses was to be descriptive).

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	16 November 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	Mexico: 480
Worldwide total number of subjects	480
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	0

months)	
Children (2-11 years)	446
Adolescents (12-17 years)	34
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 16 November 2016 to 13 March 2017 at 3 centres in Mexico.

Pre-assignment

Screening details:

A total of 480 subjects were enrolled and randomised in this study.

Period 1

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

Arms

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

Arm description:

Subjects received 3 doses of CYD dengue vaccine at Day 0, Month 6, and Month 12 and 2 doses of Cervarix concomitantly with the 2 first doses of CYD dengue vaccine.

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 millilitres (mL), subcutaneous (SC) injection at Day 0, Month 6, and Month 12.

Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular (IM) injection at Day 0 and Month 6.

Arm title	CYD Dengue Vaccine + Cervarix (Sequential Administration)

Arm description:

Subjects received 3 doses of CYD dengue vaccine at Month 1, Month 7, and Month 13 along with the 2 doses of Cervarix at Day 0 and Month 6 sequentially (i.e., one month before) to each of the 2 first doses of CYD dengue vaccine.

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 mL, SC injection at Months 1, 7, and 13.

Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM injection at Day 0 and Month 6.

Number of subjects in period 1	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)
Started	239	241
Completed	144	140
Not completed	95	101
Consent withdrawn by subject	11	18
Non compliance with the protocol	78	82
Lost to follow-up	6	1

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue Vaccine + Cervarix (Concomitant Administration)
Reporting group description:	
Subjects received 3 doses of CYD dengue vaccine at Day 0, Month 6, and Month 12 and 2 doses of Cervarix concomitantly with the 2 first doses of CYD dengue vaccine.	
Reporting group title	CYD Dengue Vaccine + Cervarix (Sequential Administration)
Reporting group description:	
Subjects received 3 doses of CYD dengue vaccine at Month 1, Month 7, and Month 13 along with the 2 doses of Cervarix at Day 0 and Month 6 sequentially (i.e., one month before) to each of the 2 first doses of CYD dengue vaccine.	

Reporting group values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)	Total
Number of subjects	239	241	480
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	9.5	9.56	
standard deviation	± 1.00	± 1.05	-
Gender categorical			
Units: Subjects			
Female	239	241	480
Male	0	0	0

End points

End points reporting groups

Reporting group title	CYD Dengue Vaccine + Cervarix (Concomitant Administration)
Reporting group description:	
Subjects received 3 doses of CYD dengue vaccine at Day 0, Month 6, and Month 12 and 2 doses of Cervarix concomitantly with the 2 first doses of CYD dengue vaccine.	
Reporting group title	CYD Dengue Vaccine + Cervarix (Sequential Administration)
Reporting group description:	
Subjects received 3 doses of CYD dengue vaccine at Month 1, Month 7, and Month 13 along with the 2 doses of Cervarix at Day 0 and Month 6 sequentially (i.e., one month before) to each of the 2 first doses of CYD dengue vaccine.	

Primary: Geometric Mean Titers Against Each Cervarix Human Papillomavirus (HPV) Antigen (HPV-16 and HPV-18) 28 Days After Last Cervarix Vaccination in the Previously Dengue Seropositive Subjects

End point title	Geometric Mean Titers Against Each Cervarix Human Papillomavirus (HPV) Antigen (HPV-16 and HPV-18) 28 Days After Last Cervarix Vaccination in the Previously Dengue Seropositive Subjects
End point description:	
GMTs against each Cervarix HPV antigen (HPV-16 and HPV-18) were assessed using an enzyme-linked immunosorbent assay (ELISA) method. Dengue seropositive subjects at baseline were defined as those subjects with titers greater than or equal to (>=) 10 (1/dilutions [dil]) for at least one serotype with the parental dengue virus strain. Analysis was performed on per-protocol analysis set for Cervarix (PPX) which included subjects who received at least one dose of Cervarix vaccine and had no relevant protocol deviations.	
End point type	Primary
End point timeframe:	
28 days after the last Cervarix vaccination	

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	114		
Units: Endotoxin Units per millilitre (EU/mL)				
geometric mean (confidence interval 95%)				
HPV-16	2149 (1877 to 2460)	2268 (1946 to 2644)		
HPV-18	833 (727 to 954)	845 (723 to 987)		

Statistical analyses

Statistical analysis title	Antigen HPV-16
Comparison groups	CYD Dengue Vaccine + Cervarix (Concomitant Administration) v CYD Dengue Vaccine + Cervarix (Sequential Administration)
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.947
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.773
upper limit	1.16

Statistical analysis title	Antigen HPV-18
Comparison groups	CYD Dengue Vaccine + Cervarix (Concomitant Administration) v CYD Dengue Vaccine + Cervarix (Sequential Administration)
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.803
upper limit	1.21

Primary: GMTs Against Each Dengue Virus Serotype 28 Days After the Third CYD Dengue Vaccination in the Previously Dengue Seropositive Subjects

End point title	GMTs Against Each Dengue Virus Serotype 28 Days After the Third CYD Dengue Vaccination in the Previously Dengue Seropositive Subjects

End point description:

The GMTs against each of the four parental dengue virus serotypes (Serotypes 1, 2, 3, and 4) of CYD dengue vaccine were assessed using the 50% plaque reduction neutralisation test (PRNT50) assay. Dengue seropositive subjects at baseline were defined as those subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strain. Analysis was performed on full analysis set (FAS) which included subjects who received at least one dose of the study vaccine. Here, 'number of subject analysed' signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

28 days after third CYD dengue vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	140		
Units: titer (1/dilution)				
geometric mean (confidence interval 95%)				
Serotype 1	384 (291 to 507)	393 (292 to 528)		
Serotype 2	670 (535 to 839)	735 (575 to 940)		
Serotype 3	357 (305 to 418)	388 (325 to 463)		
Serotype 4	247 (213 to 287)	265 (220 to 320)		

Statistical analyses

Statistical analysis title	Dengue Virus Serotype 1
Comparison groups	CYD Dengue Vaccine + Cervarix (Concomitant Administration) v CYD Dengue Vaccine + Cervarix (Sequential Administration)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.977
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.653
upper limit	1.46

Statistical analysis title	Dengue Virus Serotype 2
Comparison groups	CYD Dengue Vaccine + Cervarix (Sequential Administration) v CYD Dengue Vaccine + Cervarix (Concomitant Administration)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.911
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.654
upper limit	1.27

Statistical analysis title	Dengue Virus Serotype 3
Comparison groups	CYD Dengue Vaccine + Cervarix (Concomitant Administration) v CYD Dengue Vaccine + Cervarix (Sequential Administration)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.921
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	1.17

Statistical analysis title	Dengue Virus Serotype 4
Comparison groups	CYD Dengue Vaccine + Cervarix (Concomitant Administration) v CYD Dengue Vaccine + Cervarix (Sequential Administration)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.931
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.733
upper limit	1.18

Secondary: GMTs Against Each Cervarix HPV Antigen (HPV-16 and HPV-18) at Day 0 and 28 Days After Each Cervarix Vaccination in the Previously Dengue Seropositive Subjects

End point title	GMTs Against Each Cervarix HPV Antigen (HPV-16 and HPV-18) at Day 0 and 28 Days After Each Cervarix Vaccination in the Previously Dengue Seropositive Subjects

End point description:

The GMTs against each Cervarix HPV antigen (HPV-16 and HPV-18) were assessed using an ELISA method. Dengue seropositive subjects at baseline were defined as those subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strain. Analysis was performed on FAS population. Here, “number of subjects analysed” signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Day 0 and 28 days after each Cervarix vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: EU/mL				
geometric mean (confidence interval 95%)				
HPV-16: Day 0 (n= 154, 151)	1.61 (1.31 to 1.97)	1.58 (1.29 to 1.93)		
HPV-16: 28 days post vaccination 1 (n= 150, 151)	118 (98.7 to 142)	140 (116 to 170)		
HPV-16: 28 days post vaccination 2 (n= 149, 147)	2089 (1852 to 2356)	2162 (1869 to 2501)		
HPV-18: Day 0 (n=154, 151)	1.34 (1.15 to 1.55)	1.34 (1.16 to 1.54)		
HPV-18: 28 days post vaccination 1 (n= 150, 151)	53.8 (44.1 to 65.7)	68.6 (56.5 to 83.4)		
HPV-18: 28 days post vaccination 2 (n= 149, 147)	846 (752 to 951)	846 (728 to 984)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroconversion Against Each Cervarix HPV Antigen (HPV-16 and HPV-18) 28 Days After Each Dose of Cervarix Vaccination in the Previously Dengue Seropositive Subjects

End point title	Percentage of Subjects With Seroconversion Against Each Cervarix HPV Antigen (HPV-16 and HPV-18) 28 Days After Each Dose of Cervarix Vaccination in the Previously Dengue Seropositive Subjects

End point description:

Neutralising antibodies against each Cervarix HPV antigen (HPV-16 and HPV-18) were assessed using an ELISA method. Seroconversion was defined as changing serostatus from seronegative at baseline to seropositive (greater than [>] lower limit of quantitation [LLOQ] of the assay) or >=4-fold rise in antibody titer if seropositive at baseline (i.e., at least one antibody levels against Cervarix HPV antigens > LLOQ at baseline). The LLOQ for HPV-16 and HPV-18 was <2.0 International Units per millilitres (IU/mL). Analysis was performed on FAS population. Here, “number of subjects analysed” signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

28 days after each Cervarix vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: percentage of subjects				
number (confidence interval 95%)				
HPV-16: 28 days post-vaccination 1 (n=150, 151)	98.0 (94.3 to 99.6)	99.3 (96.4 to 100.0)		
HPV-16: 28 days post-vaccination 2 (n=149, 147)	98.7 (95.2 to 99.8)	99.3 (96.3 to 100.0)		
HPV-18: 28 days post-vaccination 1 (n=150, 151)	100.0 (97.6 to 100.0)	98.7 (95.3 to 99.8)		
HPV-18: 28 days post-vaccination 2 (n=149, 147)	99.3 (96.3 to 100.0)	100.0 (97.5 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMTs Against Each Dengue Virus Serotype of CYD Dengue Vaccine at Day 0 and 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Seropositive Subjects

End point title	GMTs Against Each Dengue Virus Serotype of CYD Dengue Vaccine at Day 0 and 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Seropositive Subjects

End point description:

The GMTs against each of the four parental dengue virus serotypes (Serotypes 1, 2, 3, and 4) of CYD dengue vaccine were assessed using the PRNT50 assay. Dengue seropositive subjects at baseline were defined as those subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strain. Analysis was performed on FAS population. Here, "number of subjects analysed" signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Day 0 and 28 days after each CYD dengue vaccine vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: titer (1/dilution)				
geometric mean (confidence interval 95%)				
Serotype 1: Day 0 (n= 154, 151)	150 (99.7 to 225)	108 (72.1 to 163)		
Serotype 1:28 days post-vaccination 1(n= 150,148)	711 (498 to 1016)	586 (409 to 840)		

Serotype 1: 28 days post-vaccination 2(n= 149,146)	460 (336 to 630)	476 (337 to 674)		
Serotype 1: 28 days post-vaccination 3(n= 143,140)	384 (291 to 507)	393 (292 to 528)		
Serotype 2: Day 0 (n= 154, 151)	193 (141 to 263)	188 (135 to 262)		
Serotype 2:28 days post-vaccination 1(n= 150,148)	1168 (879 to 1552)	1163 (847 to 1597)		
Serotype 2: 28 days post-vaccination 2(n= 149,146)	618 (492 to 776)	703 (541 to 913)		
Serotype 2: 28 days post-vaccination 3(n= 143,140)	670 (535 to 839)	735 (575 to 940)		
Serotype 3: Day 0 (n= 154, 151)	98.5 (72.2 to 135)	90.2 (67.2 to 121)		
Serotype 3:28 days post-vaccination 1(n= 150,148)	499 (386 to 644)	503 (385 to 656)		
Serotype 3: 28 days post-vaccination 2(n= 149,146)	299 (251 to 358)	361 (294 to 445)		
Serotype 3: 28 days post-vaccination 3(n= 143,140)	357 (305 to 418)	388 (325 to 463)		
Serotype 4: Day 0 (n= 154, 151)	47.1 (34.6 to 64.0)	38.0 (28.4 to 50.9)		
Serotype 4:28 days post-vaccination 1(n= 150,148)	423 (336 to 532)	449 (365 to 552)		
Serotype 4: 28 days post-vaccination 2(n= 149,146)	267 (225 to 316)	262 (219 to 314)		
Serotype 4: 28 days post-vaccination 3(n= 143,140)	247 (213 to 287)	265 (220 to 320)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralising Antibody Titers >=10 (1/dilutions) Against Each of the 4 Dengue Virus Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Seropositive Subjects

End point title	Percentage of Subjects With Neutralising Antibody Titers >=10 (1/dilutions) Against Each of the 4 Dengue Virus Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Seropositive Subjects

End point description:

Dengue neutralizing antibody levels against each of the 4 dengue virus serotypes (Serotypes 1, 2, 3, and 4) were measured by PRNT50. Dengue seropositive subjects at baseline were defined as those subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strain. Analysis was performed on FAS population. Here, "number of subjects analysed" signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Day 0 and 28 days after each CYD dengue vaccine vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: percentage of subjects				
number (confidence interval 95%)				
Serotype 1: Day 0 (n= 154, 151)	74.0 (66.4 to 80.8)	68.9 (60.8 to 76.2)		
Serotype 1:28 days post-vaccination 1 (n=150, 148)	94.7 (89.8 to 97.7)	95.3 (90.5 to 98.1)		
Serotype 1:28 days post-vaccination 2 (n=149, 146)	97.3 (93.3 to 99.3)	97.3 (93.1 to 99.2)		
Serotype 1:28 days post-vaccination 3 (n=143, 140)	99.3 (96.2 to 100.0)	97.9 (93.9 to 99.6)		
Serotype 2: Day 0 (n= 154, 151)	92.9 (87.6 to 96.4)	91.4 (85.7 to 95.3)		
Serotype 2:28 days post-vaccination 1 (n=150, 148)	96.7 (92.4 to 98.9)	93.9 (88.8 to 97.2)		
Serotype 2:28 days post-vaccination 2 (n=149, 146)	100.0 (97.6 to 100.0)	98.6 (95.1 to 99.8)		
Serotype 2:28 days post-vaccination 3 (n=143, 140)	100.0 (97.5 to 100.0)	100.0 (97.4 to 100.0)		
Serotype 3: Day 0 (n= 154, 151)	82.5 (75.5 to 88.1)	83.4 (76.5 to 89.0)		
Serotype 3:28 days post-vaccination 1 (n=150, 148)	96.7 (92.4 to 98.9)	96.6 (92.3 to 98.9)		
Serotype 3:28 days post-vaccination 2 (n=149, 146)	99.3 (96.3 to 100.0)	100.0 (97.5 to 100.0)		
Serotype 3:28 days post-vaccination 3 (n=143, 140)	99.3 (96.2 to 100.0)	100.0 (97.4 to 100.0)		
Serotype 4: Day 0 (n= 154, 151)	68.8 (60.9 to 76.0)	66.9 (58.8 to 74.3)		
Serotype 4:28 days post-vaccination 1 (n=150, 148)	97.3 (93.3 to 99.3)	98.6 (95.2 to 99.8)		
Serotype 4:28 days post-vaccination 2 (n=149, 146)	100.0 (97.6 to 100.0)	100.0 (97.5 to 100.0)		
Serotype 4:28 days post-vaccination 3 (n=143, 140)	100.0 (97.5 to 100.0)	98.6 (94.9 to 99.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralising Antibody Titers >=10 (1/dilutions) Against At Least 1,2,3, or 4 Dengue Virus Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in Previously Dengue Seropositive Subjects

End point title	Percentage of Subjects With Neutralising Antibody Titers >=10 (1/dilutions) Against At Least 1,2,3, or 4 Dengue Virus Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in Previously Dengue Seropositive Subjects

End point description:

Dengue neutralising antibody levels against each of the 4 dengue virus serotypes (Serotypes 1, 2, 3, and 4) were measured by PRNT50. Dengue seropositive subjects at baseline were defined as those

subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strain. Analysis was performed on FAS population. Here, “number of subjects analysed” signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects with available data for specified categories. Here, "vacc=vaccination" in the data categories.

End point type	Secondary

End point timeframe:

Day 0 and 28 days after each CYD dengue vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: percentage of subjects				
number (confidence interval 95%)				
At least 1 Serotype: Day 0 (n=154, 151)	100.0 (97.6 to 100.0)	100.0 (97.6 to 100.0)		
At least 1 Serotype:28 days post-vacc 1(n=150,148)	99.3 (96.3 to 100.0)	99.3 (96.3 to 100.0)		
At least 1 Serotype:28 days post-vacc 2(n=149,146)	100.0 (97.6 to 100.0)	100.0 (97.5 to 100.0)		
At least 1 Serotype:28 days post-vacc 3(n=143,140)	100.0 (97.5 to 100.0)	100.0 (97.4 to 100.0)		
At least 2 Serotype: Day 0 (n=154, 151)	84.4 (77.7 to 89.8)	82.8 (75.8 to 88.4)		
At least 2 Serotype:28 days post-vacc 1(n=150,148)	98.0 (94.3 to 99.6)	98.0 (94.2 to 99.6)		
At least 2 Serotype:28 days post-vacc 2(n=149,146)	100.0 (97.6 to 100.0)	100.0 (97.5 to 100.0)		
At least 2 Serotype:28 days post-vacc 3(n=143,140)	100.0 (97.5 to 100.0)	100.0 (97.4 to 100.0)		
At least 3 Serotype: Day 0 (n=154, 151)	74.0 (66.4 to 80.8)	72.8 (65.0 to 79.8)		
At least 3 Serotype:28 days post-vacc 1(n=150,148)	95.3 (90.6 to 98.1)	94.6 (89.6 to 97.6)		
At least 3 Serotype:28 days post-vacc 2(n=149,146)	99.3 (96.3 to 100.0)	98.6 (95.1 to 99.8)		
At least 3 Serotype:28 days post-vacc 3(n=143,140)	100.0 (97.5 to 100.0)	98.6 (94.9 to 99.8)		
All 4 Serotypes: Day 0 (n=154, 151)	59.7 (51.5 to 67.6)	55.0 (46.7 to 63.1)		
All 4 Serotypes:28 days post-vacc 1(n=150,148)	92.7 (87.3 to 96.3)	92.6 (87.1 to 96.2)		
All 4 Serotypes:28 days post-vacc 2(n=149,146)	97.3 (93.3 to 99.3)	97.3 (93.1 to 99.2)		
All 4 Serotypes:28 days post-vacc 3(n=143,140)	98.6 (95.0 to 99.8)	97.9 (93.9 to 99.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralising Antibody Titers Above Pre-defined Thresholds Against Each Dengue Virus Serotypes of CYD at Baseline And 28 Days After Each Dose of CYD Dengue Vaccination in Dengue Seropositive Subjects

End point title	Percentage of Subjects With Neutralising Antibody Titers Above Pre-defined Thresholds Against Each Dengue Virus Serotypes of CYD at Baseline And 28 Days After Each Dose of CYD Dengue Vaccination in Dengue Seropositive Subjects

End point description:

Dengue neutralising antibody levels against each of the 4 dengue virus serotypes (Serotypes 1, 2, 3, and 4) were measured by PRNT50. Dengue seropositive subjects at baseline were defined as those subjects with titers <10, >=10, and >=100 (1/dil) for at least one serotype with the parental dengue virus strain. Analysis was performed on FAS population. Here, "number of subjects analysed" signifies number of subjects evaluable for this endpoint' and 'n' signifies number of subjects with available data for specified categories. Here "vacc=vaccination" in the data categories.

End point type	Secondary

End point timeframe:

Day 0 and 28 days after each CYD dengue vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	151		
Units: percentage of subjects				
number (confidence interval 95%)				
Serotype 1: Pre-vacc 1 <10 (1/dil)(n=154,151)	26.0 (19.2 to 33.6)	31.1 (23.8 to 39.2)		
Serotype 1: Pre-vacc 1 >=10 (1/dil)(n=154,151)	74.0 (66.4 to 80.8)	68.9 (60.8 to 76.2)		
Serotype 1: Pre-vacc 1 >=100 (1/dil)(n=154,151)	61.0 (52.9 to 68.8)	56.3 (48.0 to 64.3)		
Serotype 1: Post-vacc 1 <10 (1/dil)(n=150,148)	5.3 (2.3 to 10.2)	4.7 (1.9 to 9.5)		
Serotype 1: Post-vacc 1 >=10 (1/dil)(n=150,148)	94.7 (89.8 to 97.7)	95.3 (90.5 to 98.1)		
Serotype 1: Post-vacc 1 >=100 (1/dil)(n=150,148)	82.0 (74.9 to 87.8)	78.4 (70.9 to 84.7)		
Serotype 1: Post-vacc 2 <10 (1/dil)(n=149,146)	2.7 (0.7 to 6.7)	2.7 (0.8 to 6.9)		
Serotype 1: Post-vacc 2 >=10 (1/dil)(n=149,146)	97.3 (93.3 to 99.3)	97.3 (93.1 to 99.2)		
Serotype 1: Post-vacc 2 >=100 (1/dil)(n=149,146)	77.2 (69.6 to 83.7)	72.6 (64.6 to 79.7)		
Serotype 1: Post-vacc 3 <10 (1/dil)(n=143,140)	0.7 (0.0 to 3.8)	2.1 (0.4 to 6.1)		
Serotype 1: Post-vacc 3 >=10 (1/dil)(n=143,140)	99.3 (96.2 to 100.0)	97.9 (93.9 to 99.6)		
Serotype 1: Post-vacc 3 >=100 (1/dil)(n=143,140)	74.8 (66.9 to 81.7)	76.4 (68.5 to 83.2)		
Serotype 2: Pre-vacc 1 <10 (1/dil)(n=154,151)	7.1 (3.6 to 12.4)	8.6 (4.7 to 14.3)		

Serotype 2: Pre-vacc 1 >=10 (1/dil)(n=154,151)	92.9 (87.6 to 96.4)	91.4 (85.7 to 95.3)		
Serotype 2: Pre-vacc 1 >=100 (1/dil)(n=154,151)	59.1 (50.9 to 66.9)	61.6 (53.3 to 69.4)		
Serotype 2: Post-vacc 1 <10 (1/dil)(n=150,148)	3.3 (1.1 to 7.6)	6.1 (2.8 to 11.2)		
Serotype 2: Post-vacc 1 >=10 (1/dil)(n=150,148)	96.7 (92.4 to 98.9)	93.9 (88.8 to 97.2)		
Serotype 2: Post-vacc 1 >=100 (1/dil)(n=150,148)	91.3 (85.6 to 95.3)	91.9 (86.3 to 95.7)		
Serotype 2: Post-vacc 2 <10 (1/dil)(n=149,146)	0.0 (0.0 to 2.4)	1.4 (0.2 to 4.9)		
Serotype 2: Post-vacc 2 >=10 (1/dil)(n=149,146)	100.0 (97.6 to 100.0)	98.6 (95.1 to 99.8)		
Serotype 2: Post-vacc 2 >=100 (1/dil)(n=149,146)	90.6 (84.7 to 94.8)	90.4 (84.4 to 94.7)		
Serotype 2: Post-vacc 3 <10 (1/dil)(n=143,140)	0.0 (0.0 to 2.5)	0.0 (0.0 to 2.6)		
Serotype 2: Post-vacc 3 >=10 (1/dil)(n=143,140)	100.0 (97.5 to 100.0)	100.0 (97.4 to 100.0)		
Serotype 2: Post-vacc 3 >=100 (1/dil)(n=143,140)	95.1 (90.2 to 98.0)	90.7 (84.6 to 95.0)		
Serotype 3: Pre-vacc 1 <10 (1/dil)(n=154,151)	17.5 (11.9 to 24.5)	16.6 (11.0 to 23.5)		
Serotype 3: Pre-vacc 1 >=10 (1/dil)(n=154,151)	82.5 (75.5 to 88.1)	83.4 (76.5 to 89.0)		
Serotype 3: Pre-vacc 1 >=100 (1/dil)(n=154,151)	51.3 (43.1 to 59.4)	49.0 (40.8 to 57.3)		
Serotype 3: Post-vacc 1 <10 (1/dil)(n=150,148)	3.3 (1.1 to 7.6)	3.4 (1.1 to 7.7)		
Serotype 3: Post-vacc 1 >=10 (1/dil)(n=150,148)	96.7 (92.4 to 98.9)	96.6 (92.3 to 98.9)		
Serotype 3: Post-vacc 1 >=100 (1/dil)(n=150,148)	88.7 (82.5 to 93.3)	87.8 (81.5 to 92.6)		
Serotype 3: Post-vacc 2 <10 (1/dil)(n=149,146)	0.7 (0.0 to 3.7)	0.0 (0.0 to 2.5)		
Serotype 3: Post-vacc 2 >=10 (1/dil)(n=149,146)	99.3 (96.3 to 100.0)	100.0 (97.5 to 100.0)		
Serotype 3: Post-vacc 2 >=100 (1/dil)(n=149,146)	87.2 (80.8 to 92.1)	87.0 (80.4 to 92.0)		
Serotype 3: Post-vacc 3 <10 (1/dil)(n=143,140)	0.7 (0.0 to 3.8)	0.0 (0.0 to 2.6)		
Serotype 3: Post-vacc 3 >=10 (1/dil)(n=143,140)	99.3 (96.2 to 100.0)	100.0 (97.4 to 100.0)		
Serotype 3: Post-vacc 3 >=100 (1/dil)(n=143,140)	94.4 (89.3 to 97.6)	90.7 (84.6 to 95.0)		
Serotype 4: Pre-vacc 1 <10 (1/dil)(n=154,151)	31.2 (24.0 to 39.1)	33.1 (25.7 to 41.2)		
Serotype 4: Pre-vacc 1 >=10 (1/dil)(n=154,151)	68.8 (60.9 to 76.0)	66.9 (58.8 to 74.3)		
Serotype 4: Pre-vacc 1 >=100 (1/dil)(n=154,151)	33.1 (25.8 to 41.1)	29.8 (22.6 to 37.8)		
Serotype 4: Post-vacc 1 <10 (1/dil)(n=150,148)	2.7 (0.7 to 6.7)	1.4 (0.2 to 4.8)		
Serotype 4: Post-vacc 1 >=10 (1/dil)(n=150,148)	97.3 (93.3 to 99.3)	98.6 (95.2 to 99.8)		
Serotype 4: Post-vacc 1 >=100 (1/dil)(n=150,148)	87.3 (80.9 to 92.2)	89.9 (83.8 to 94.2)		
Serotype 4: Post-vacc 2 <10 (1/dil)(n=149,146)	0.0 (0.0 to 2.4)	0.0 (0.0 to 2.5)		
Serotype 4: Post-vacc 2 >=10 (1/dil)(n=149,146)	100.0 (97.6 to 100.0)	100.0 (97.5 to 100.0)		

Serotype 4: Post-vacc 2 >=100 (1/dil)(n=149,146)	82.6 (75.5 to 88.3)	80.1 (72.7 to 86.3)		
Serotype 4: Post-vacc 3 <10 (1/dil)(n=143,140)	0.0 (0.0 to 2.5)	1.4 (0.2 to 5.1)		
Serotype 4: Post-vacc 3 >=10 (1/dil)(n=143,140)	100.0 (97.5 to 100.0)	98.6 (94.9 to 99.8)		
Serotype 4: Post-vacc 3 >=100 (1/dil)(n=143,140)	83.2 (76.1 to 88.9)	83.6 (76.4 to 89.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Immediate Adverse Events (AEs) Following Vaccination With Cervarix or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Immediate Adverse Events (AEs) Following Vaccination With Cervarix or CYD Dengue Vaccine

End point description:

Any unsolicited systemic AE occurred during the first 30 minutes post-vaccination was recorded on the case report form (CRF) as immediate AE. Analysis was performed on safety analysis set which included those subjects who had received at least one dose of the study vaccines. Here, 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Within 30 minutes after each and any vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects				
After any CYD/Cervarix vaccination (n=237,241)	0	0		
Post CYD/Cervarix vaccination 1 (n=237,241)	0	0		
Post CYD/Cervarix vaccination 2 (n=227,229)	0	0		
Post CYD vaccination 3 (n=145,141)	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects Reporting Solicited Injection Site Reactions

	Following Vaccination With Cervarix or CYD Dengue Vaccine

End point description:

Solicited injection site reactions included pain, erythema, and swelling. Analysis was performed on Safety analysis set. Here, 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Up to 7 days after each and any vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects				
Pain:Post any CYD/Cervarix vaccine (n=231,234)	212	221		
Pain: Post CYD/Cervarix vaccination 1 (n=231,234)	202	206		
Pain: Post CYD/Cervarix vaccination 2 (n=226,229)	173	169		
Pain: Post CYD vaccination 3 (n=144,140)	65	59		
Erythema:Post any CYD/Cervarix vaccine (n=231,234)	64	61		
Erythema:Post CYD/Cervarix vaccination1(n=231,234)	49	43		
Erythema:Post CYD/Cervarix vaccination2(n=226,229)	41	34		
Erythema: Post CYD vaccination 3 (n=144,140)	6	11		
Swelling:Post any CYD/Cervarix vaccine (n=231,234)	73	60		
Swelling:Post CYD/Cervarix vaccination1(n=231,234)	55	44		
Swelling:Post CYD/Cervarix vaccination2(n=226,229)	48	35		
Swelling: Post CYD vaccination 3 (n=144,139)	8	10		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Solicited systemic reactions included Fever, Headache, Malaise, Myalgia, and Asthenia. Analysis was performed on Safety analysis set. At Visit 1 and Visit 4, subjects from Group 1 received both Cervarix and CYD vaccination and subjects from Group 2 received only Cervarix vaccination. At Visit 2 and Visit

5, only subjects from Group 2 received CYD vaccination whereas the subjects from Group 1 received no vaccination. Analysis was performed on safety analysis set. Here 'n' signifies number of subjects with available data for specified categories. Here '99999' signifies that the subjects from Group 1 did not receive any vaccination at Visit 2 or Visit 5 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Up to 14 days after any and each vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects				
Fever:Post any vaccination (n=230,234)	25	35		
Fever:Post vaccination 1 (Visit 1)(n=230,234)	14	8		
Fever:Post CYD vaccination 1 (Visit 2)(n=0,230)	99999	14		
Fever:Post vaccination 2 (Visit 4)(n=216,228)	10	12		
Fever:Post CYD vaccination 2 (Visit 5)(n=0,227)	99999	8		
Fever:Post CYD vaccination 3 (Visit 7)(n=143,139)	5	3		
Headache:Post any vaccination (n=231,234)	101	111		
Headache:Post vaccination 1 (Visit 1)(n=231,234)	83	69		
Headache:Post CYD vaccination 1 (Visit 2)(n=0,231)	99999	54		
Headache:Post vaccination 2 (Visit 4)(n=226,229)	47	48		
Headache:Post CYD vaccination 2 (Visit 5)(n=0,227)	99999	36		
Headache:Post CYD vaccination3(Visit 7)(n=144,140)	18	15		
Malaise:Post any vaccination (n=231,234)	113	133		
Malaise:Post vaccination 1 (Visit 1)(n=231,234)	84	84		
Malaise:Post CYD vaccination 1 (Visit 2)(n=0,231)	99999	56		
Malaise:Post vaccination 2 (Visit 4)(n=226,229)	73	72		
Malaise:Post CYD vaccination 2 (Visit 5)(n=0,227)	99999	47		
Malaise:Post CYD vaccination 3(Visit 7)(n=144,140)	19	28		
Myalgia:Post any vaccination (n=231,234)	160	168		
Myalgia:Post vaccination 1 (Visit 1)(n=231,234)	129	124		
Myalgia:Post CYD vaccination 1 (Visit 2)(n=0,231)	99999	76		

Myalgia:Post vaccination 2 (Visit 4)(n=226,229)	96	95		
Myalgia:Post CYD vaccination 2 (Visit 5)(n=0,227)	99999	60		
Myalgia:Post CYD vaccination 3(Visit 7)(n=144,140)	26	31		
Asthenia:Post any vaccination (n=231,234)	93	95		
Asthenia:Post vaccination 1 (Visit 1)(n=231,234)	72	53		
Asthenia:Post CYD vaccination 1 (Visit 2)(n=0,231)	99999	47		
Asthenia:Post vaccination 2 (Visit 4)(n=226,229)	51	35		
Asthenia:Post CYD vaccination 2 (Visit 5)(n=0,227)	99999	30		
Asthenia:Post CYD vaccination 3(Visit7)(n=144,140)	16	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited AEs Following Vaccination With Cervarix or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Unsolicited AEs Following Vaccination With Cervarix or CYD Dengue Vaccine

End point description:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and/or onset post-vaccination. At Visit 1 and Visit 4, subjects from Group 1 received both Cervarix and CYD vaccination and subjects from Group 2 received only Cervarix vaccination. At Visit 2 and Visit 5, only subjects from Group 2 received CYD vaccination whereas the subjects from Group 1 received no vaccination. Analysis was performed on safety analysis set. Here, 'n' signifies number of subjects with available data for specified categories. Here '99999' signifies that the subjects from Group 1 did not receive any vaccination at Visit 2 or Visit 5 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Up to 28 days after any and each vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects				
Post any vaccination (n=237,241)	50	76		
Post vaccination 1 (Visit 1)(n=237,241)	33	37		
Post CYD vaccination 1 (Visit 2)(n=0,233)	99999	25		
Post vaccination 2 (Visit 4)(n=227,229)	26	23		

Post CYD vaccination 2 (Visit 5)(n=0,228)	99999	15		
Post CYD vaccination 3 (Visit 7)(n=145,141)	5	5		

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 Cervarix or CYD Dengue Vaccine

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

End point description:

AESI 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 Safety analysis set.

End point type	Secondary

End point timeframe:

Up to 7 days after any and each vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects				
Post any CYD/Cervarix vaccination (n=237,241)	0	0		
Post CYD/Cervarix vaccination 1 (n=237,241)	0	0		
Post CYD/Cervarix vaccination 2 (n=227,229)	0	0		
Post CYD/Cervarix vaccination 3 (n=145,141)	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 Cervarix or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Serious Adverse Events (SAEs) Including Serious AESIs Following Vaccination With Cervarix or CYD Dengue Vaccine

End point description:

An SAEs were AEs resulting in any of the following outcomes or deemed significant for any other reason:

death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly or a medically important event. An 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 Safety analysis set.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months after the last vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects				
SAE	6	0		
Serious AESI	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects Reporting Cases of Virologically Confirmed Dengue (VCD) Hospitalisation Following Vaccination With Cervarix 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 Safety analysis set.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months after the last vaccination

End point values	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	CYD Dengue Vaccine + Cervarix (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

An AE data were collected from Day 0 up to Day 28 post any vaccination. Solicited Reaction (SR) were collected from Day 0 up to Day 14 post vaccination. SAEs were collected throughout the trial (up to Month 14, i.e,. 6 months after last CYD vaccination.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

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

Reporting group description:

Subjects received 3 doses of CYD dengue vaccine at Month 1, Month 7, and Month 13 along with the 2 doses of Cervarix at Day 0 and Month 6 sequentially (i.e., one month before) to each of the 2 first doses of CYD dengue vaccine.

Reporting group title	CYD Dengue Vaccine + Cervarix (Concomitant Administration)

Reporting group description:

Subjects received 3 doses of CYD dengue vaccine at Day 0, Month 6, and Month 12 and 2 doses of Cervarix concomitantly with the 2 first doses of CYD dengue vaccine.

Serious adverse events	CYD Dengue Vaccine + Cervarix (Sequential Administration)	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 241 (0.00%)	6 / 237 (2.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	0 / 241 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun Shot Wound			
subjects affected / exposed	0 / 241 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius Fracture			
subjects affected / exposed	0 / 241 (0.00%)	1 / 237 (0.42%)	
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			
Pre-Eclampsia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	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 + Cervarix (Sequential Administration)	CYD Dengue Vaccine + Cervarix (Concomitant Administration)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	228 / 241 (94.61%)	222 / 237 (93.67%)	
Nervous system disorders			
Headache			
subjects affected / exposed	113 / 241 (46.89%)	102 / 237 (43.04%)	
occurrences (all)	227	149	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	95 / 241 (39.42%)	93 / 237 (39.24%)	
occurrences (all)	178	139	
Injection Site Erythema			

subjects affected / exposed	61 / 241 (25.31%)	64 / 237 (27.00%)	
occurrences (all)	116	137	
Injection Site Pain			
subjects affected / exposed	221 / 241 (91.70%)	212 / 237 (89.45%)	
occurrences (all)	628	659	
Injection Site Swelling			
subjects affected / exposed	60 / 241 (24.90%)	73 / 237 (30.80%)	
occurrences (all)	115	154	
Malaise			
subjects affected / exposed	133 / 241 (55.19%)	113 / 237 (47.68%)	
occurrences (all)	287	176	
Pyrexia			
subjects affected / exposed	37 / 241 (15.35%)	25 / 237 (10.55%)	
occurrences (all)	47	29	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	168 / 241 (69.71%)	160 / 237 (67.51%)	
occurrences (all)	386	251	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 241 (9.13%)	8 / 237 (3.38%)	
occurrences (all)	26	9	
Pharyngitis			
subjects affected / exposed	20 / 241 (8.30%)	13 / 237 (5.49%)	
occurrences (all)	21	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2018	In November 2017, IDMC recommended not to vaccinate any individuals with no prior dengue infection anymore, and to only continue vaccination in subjects with prior dengue infection. As a consequence, the Sponsor had amended the CYD71 study protocol to implement the recommendation from IDMC on February 2018. The study was put on hold between IDMC recommendation and approval of protocol amendment. It impacted Vaccination 3 for seronegative subjects. According to Amendment 1, the following changes were made: • All vaccinated subjects were informed about their baseline dengue serostatus. • All subjects were asked about their willingness to continue participating in this study and to sign an amended Assent Form or informed consent form. • Subjects identified as seronegative at baseline did not receive further CYD dengue vaccine doses. They continued in the study for a safety follow-up at 6 months post last dengue vaccine, and they had timely access to appropriate care in the event of suspected dengue, for 10 years from the date of last dengue vaccination whether they remained in the study or not. • Subjects identified as seropositive at baseline who were eligible to continue dengue vaccination in the study were asked to consent for further CYD dengue vaccine injection. Subjects that consented to receive the third and last dose of CYD dengue vaccine completed the study as it was initially planned. Subjects that consented to remain in the study but preferred not to receive the last injection were able to continue in the study for safety follow-up at 6 months post last dengue vaccine dose. • The study population for the non-inferiority was reduced to the dengue immune subjects (seropositive) compared to initial sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Change of population for non-inferiority reduced to dengue immune subjects and time window for vaccination not reached (study hold),hence non-inferiority analysis not performed and immunogenicity analysis was performed on FAS,not on per protocol set.

Notes: