Clinical trial results:
Efficacy and Safety of Dengue Vaccine in Healthy Children Aged 4 to 11 Years in Thailand

Summary

EudraCT number	2014-001710-25
Trial protocol	Outside EU/EEA
Global end of trial date	10 September 2013

Results information

Result version number	v1
This version publication date	08 February 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	CYD23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00842530
WHO universal trial number (UTN)	U1111-1127-6970

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, 69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 65 6431 2359, anh.wartel-tram@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 65 6431 2359, anh.wartel-tram@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001201-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Efficacy of dengue vaccine after three injections in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	05 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 4002
Worldwide total number of subjects	4002
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)	4002
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 05 February 2009 to 05 February 2010 at 1 clinical site in Thailand.

Pre-assignment

Screening details:

A total of 4002 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized; however, only 3997 subjects received the first vaccination.

Period 1

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

Blinding implementation details:

The observer-blind design was chosen since the products have different appearances and could be recognized. The person who performed vaccinations knew which product was administered while neither the subject nor the Investigator in charge of safety evaluation knew which product was injected. To maintain the blind and minimize the potential bias, the control group used the same route and schedule as the study vaccine.

Arms

Are arms mutually exclusive?	Yes
Arm title	CYD Dengue vaccine group

Arm description:

Subjects received 3 injections of the CYD Dengue vaccine, 1 injection each at 0, 6 months, and 12 months (Cohort 1, n=100 and Cohort 2, n=2568).

Arm type	Experimental
Investigational medicinal product name	CYD Dengue vaccine
Investigational medicinal product code	323
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, 3 injections. One each at 0, 6, and 12 months.

Arm title	Control group

Arm description:

Subjects received 1 injection of rabies vaccine (Day 0) and 1 injection of placebo each at 6 and 12 months (Cohort 1; n=50) or 1 injection each of placebo at 0, 6, and 12 months (Cohort 2; n=1284)

Arm type	Active comparator
Investigational medicinal product name	Rabies vaccine (Verorab®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, 1 injection on Day 0 for subjects in Cohort 1.

Investigational medicinal product name	Placebo (NaCl)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, 1 injection each at 6 and 12 months (Cohort 1) or 1 injection each at 0, 6, and 12 months (Cohort 2).

Number of subjects in period 1[1]	CYD Dengue vaccine group	Control group
Started	2666	1331
Completed	2552	1276
Not completed	114	55
Consent withdrawn by subject	73	28
Adverse event, non-fatal	6	1
Serious adverse event	-	6
Lost to follow-up	6	8
Protocol deviation	29	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period were based on the total number of subjects who received the first vaccine. A total of 5 subjects (3 in the CYD Dengue vaccine group and 2 in the control group) did not receive the first vaccination.

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue vaccine group
Reporting group description:	
Subjects received 3 injections of the CYD Dengue vaccine, 1 injection each at 0, 6 months, and 12 months (Cohort 1, n=100 and Cohort 2, n=2568).	
Reporting group title	Control group
Reporting group description:	
Subjects received 1 injection of rabies vaccine (Day 0) and 1 injection of placebo each at 6 and 12 months (Cohort 1; n=50) or 1 injection each of placebo at 0, 6, and 12 months (Cohort 2; n=1284)	

Reporting group values	CYD Dengue vaccine group	Control group	Total
Number of subjects	2666	1331	3997
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	2666	1331	3997
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	8.16	8.2	
standard deviation	± 2.03	± 2.05	-
Gender categorical			
Units: Subjects			
Female	1376	696	2072
Male	1290	635	1925

End points

End points reporting groups

Reporting group title	CYD Dengue vaccine group
Reporting group description:	
Subjects received 3 injections of the CYD Dengue vaccine, 1 injection each at 0, 6 months, and 12 months (Cohort 1, n=100 and Cohort 2, n=2568).	
Reporting group title	Control group
Reporting group description:	
Subjects received 1 injection of rabies vaccine (Day 0) and 1 injection of placebo each at 6 and 12 months (Cohort 1; n=50) or 1 injection each of placebo at 0, 6, and 12 months (Cohort 2; n=1284)	

Primary: Vaccine Efficacy Against Symptomatic Virologically-confirmed Dengue Cases During the Active Phase Post-dose 3 Injection with CYD Dengue Vaccine

End point title	Vaccine Efficacy Against Symptomatic Virologically-confirmed Dengue Cases During the Active Phase Post-dose 3 Injection with CYD Dengue Vaccine
End point description:	
Symptomatic virologically-confirmed dengue (VCD) cases were defined as acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), confirmed by dengue reverse transcriptase-polymerase chain reaction and/or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay, and occurring >28 days after the third injection. Cases: number of subjects with at least one symptomatic VCD episode from 28 days post-injection 3 to the end of the Active Phase. Vaccine efficacy was reported as density incidence (cases/100 person-years at risk). The person-years at risk was the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first. Density incidence: number of VCD cases divided by the cumulative person-years at risk. The vaccine efficacy is considered significant if the lower bound of its 95% CI was greater than 0%.	
End point type	Primary
End point timeframe:	
28 days post-injection 3 up to the end of the Active Phase (13 months post-injection 3)	

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2452	1221		
Units: Density incidence				
number (not applicable)				
Virologically-confirmed dengue cases	45	32		
Person-years at risk	2522	1251		
Density incidence	1.8	2.6		

Statistical analyses

Statistical analysis title	Vaccine efficacy of CYD dengue vaccine

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups.

Comparison groups	Control group v CYD Dengue vaccine group
Number of subjects included in analysis	3673
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Vaccine efficacy (%)
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	56.6

Notes:

[1] - Superiority significance was not achieved. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant only if the lower bound of its 95% CI was greater than 0%.

Secondary: Vaccine Efficacy Against Severe Virologically-confirmed Dengue Cases Post-dose 3 Injection with CYD Dengue Vaccine

End point title	Vaccine Efficacy Against Severe Virologically-confirmed Dengue Cases Post-dose 3 Injection with CYD Dengue Vaccine

End point description:

Symptomatic virologically-confirmed dengue (VCD) cases were defined as acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), confirmed by dengue reverse transcriptase-polymerase chain reaction and/or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay, and occurring >28 days after the third injection.
Cases: number of subjects with at least one symptomatic VCD episode from 28 days post-injection 3 to the end of the Active Phase.
Vaccine efficacy was reported as density incidence (cases/100 person-years at risk). The person-years at risk was the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first.
Density incidence: number of VCD cases divided by the cumulative person-years at risk. The vaccine efficacy is considered significant if the lower bound of its 95% CI was greater than 0%.

End point type	Secondary

End point timeframe:

28 days post-injection 3 up to the end of the Active Phase (13 months post-injection 3)

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2452	1221		
Units: Density incidence				
number (not applicable)				
Severe VCD cases (IDMC clinical assessment)	1	2		
Severe VCD cases (WHO 1999 severity assessment)	2	2		
Person-years at risk; Severe VCD cases (IDMC)	2543	1263		
Person-years at risk; Severe VCD cases (WHO 1999)	2543	1263		

Density incidence; Severe VCD cases (IDMC)	0.1	0.2		
Density incidence; Severe VCD cases (WHO 1999)	0.1	0.2		

Statistical analyses

Statistical analysis title	Vaccine efficacy of against severe VCD (IDMC)

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant if the lower bound of its 95% CI was greater than 0%.

Comparison groups	CYD Dengue vaccine group v Control group
Number of subjects included in analysis	3673
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Vaccine efficacy (%)
Point estimate	75.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-377
upper limit	99.6

Statistical analysis title	Vaccine efficacy of against severe VCD (WHO 1999)

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant if the lower bound of its 95% CI was greater than 0%.

Comparison groups	CYD Dengue vaccine group v Control group
Number of subjects included in analysis	3673
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Vaccine efficacy (%)
Point estimate	50.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-585
upper limit	96.4

Secondary: Vaccine Efficacy Against Virologically-confirmed Dengue Cases Following at Least Two Injections with CYD Dengue Vaccine

End point title	Vaccine Efficacy Against Virologically-confirmed Dengue Cases Following at Least Two Injections with CYD Dengue Vaccine

End point description:

Symptomatic virologically-confirmed dengue (VCD) cases were defined as acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), confirmed by dengue reverse transcriptase-polymerase chain reaction and/or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay, and occurring >28 days after the third injection.
Cases: number of subjects with at least one symptomatic VCD episode from 28 days post-injection 2 to the end of the Active Phase.
Vaccine efficacy was reported as density incidence (cases/100 person-years at risk). The person-years at risk was the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first.
Density incidence: number of VCD cases divided by the cumulative person-years at risk. The vaccine efficacy is considered significant if the lower bound of its 95% CI was greater than 0%.

End point type	Secondary

End point timeframe:

28 days post-injection 2 up to the end of the Active Phase (13 months post-injection 3)

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2584	1300		
Units: Density incidence				
number (not applicable)				
Cases; 28 days Post-Inj. 2 to Inj. 3	14	12		
Cases; 28 days Post-Inj. 2–Active Phase	61	47		
Person-years; 28 days Post-Inj. 2–Inj. 3	1017	509		
Person-years; 28 days Post-Inj. 2–Active Phase	3824	1905		
Density incidence; 28 days Post-Inj. 2–Inj. 3	1.4	2.4		
Density incidence;28 days Post-Inj. 2–Active Phase	1.6	2.5		

Statistical analyses

Statistical analysis title	Vaccine efficacy; 28 days Post-Inj. 2-Inj. 3

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups.

Comparison groups	CYD Dengue vaccine group v Control group
Number of subjects included in analysis	3884
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Vaccine efficacy (%)
Point estimate	41.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.4
upper limit	74.9

Notes:

[2] - Superiority significance was not achieved. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant only if the lower bound of its 95% CI was greater than 0%.

Statistical analysis title	Vaccine efficacy; 28 days Post-Inj. 2-Active Phase

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups.

Comparison groups	CYD Dengue vaccine group v Control group
Number of subjects included in analysis	3884
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Vaccine efficacy (%)
Point estimate	35.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	56.5

Notes:

[3] - Superiority significance was achieved. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant only if the lower bound of its 95% CI was greater than 0%.

Other pre-specified: Vaccine Efficacy Against Virologically-confirmed Dengue Cases Following at Least One Injection with CYD Dengue Vaccine

End point title	Vaccine Efficacy Against Virologically-confirmed Dengue Cases Following at Least One Injection with CYD Dengue Vaccine

End point description:

Symptomatic virologically-confirmed dengue (VCD) cases were defined as acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), confirmed by dengue reverse transcriptase-polymerase chain reaction and/or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay, and occurring >28 days after the third injection.
Cases: number of subjects with at least one symptomatic VCD episode from Day 0 up to the end of the Active Phase.
Vaccine efficacy was reported as density incidence (cases/100 person-years at risk). The person-years at risk was the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first.
Density incidence: number of VCD cases divided by the cumulative person-years at risk. The vaccine efficacy is considered significant if the lower bound of its 95% CI was greater than 0%.

End point type	Other pre-specified

End point timeframe:

Day 0 up to the end of the Active Phase (13 months post-injection 3)

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2666	1331		
Units: Density incidence				
number (not applicable)				
Cases; 28 days Post-Inj. 1–Active Phase	75	56		
Cases; Day 0–Active Phase	76	58		

Person-years: 28 days Post-Inj. 1–Active Phase	5089	2532		
Person-years: Day 0–Active Phase	5292	2630		
Density incidence;28 days Post-Inj. 1–Active Phase	1.5	2.2		
Density incidence; Day 0–Active Phase	1.4	2.2		

Statistical analyses

Statistical analysis title	Vaccine efficacy; 28 days Post-Inj. 1-Active Phase

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant if the lower bound of its 95% CI was greater than 0%.

Comparison groups	Control group v CYD Dengue vaccine group
Number of subjects included in analysis	3997
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Vaccine efficacy (%)
Point estimate	33.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	53.5

Statistical analysis title	Vaccine efficacy; Day 0-Active Phase

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy. The CI was calculated using the exact method conditional on the total number of cases in both groups. The vaccine efficacy of the CYD dengue vaccine against severe VCD cases was considered significant if the lower bound of its 95% CI was greater than 0%.

Comparison groups	CYD Dengue vaccine group v Control group
Number of subjects included in analysis	3997
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Vaccine efficacy (%)
Point estimate	34.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	54.3

Other pre-specified: Number of Subjects with One Virologically-confirmed Dengue Episode During the Active Phase Due to Each Serotypes Post-dose 3 Injection with

CYD Dengue Vaccine

End point title	Number of Subjects with One Virologically-confirmed Dengue Episode During the Active Phase Due to Each Serotypes Post-dose 3 Injection with CYD Dengue Vaccine

End point description:

Symptomatic virologically-confirmed dengue cases were defined as acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), confirmed by dengue reverse transcriptase-polymerase chain reaction and/or dengue non-structural protein 1 (NS1) enzyme-linked immunosorbent assay, and occurring >28 days after the third injection. Virologically-confirmed dengue cases confirmed only by NS1 method were classified in the Not Identified category. Cases were defined as the number of subjects with at least one symptomatic virologically-confirmed dengue episode >28 days after 3 injections (during the Active Phase).

End point type	Other pre-specified

End point timeframe:

>28 days after 3 injections (during the Active Phase)

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2666	1331		
Units: Number of subjects				
number (not applicable)				
Dengue Virus Serotype 1	14	18		
Dengue Virus Serotype 2	52	27		
Dengue Virus Serotype 3	4	11		
Dengue Virus Serotype 4	1	5		
Not Identified	5	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Clinical Signs and Symptoms for Virologically-confirmed Dengue During the Trial

End point title	Number of Subjects with Clinical Signs and Symptoms for Virologically-confirmed Dengue During the Trial

End point description:

End point type	Other pre-specified

End point timeframe:

>28 days after 3 injections (during the Active Phase)

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[4]	62[5]		
Units: Number of subjects				
number (not applicable)				
Mean number of days of fever	4.13	4.4		
Mean number of days of clinical syndrome	5.39	5.84		
Hospitalization; No	44	32		
Hospitalization; Yes	32	30		
Mean duration of hospitalization (days)	4.91	5.17		

Notes:

[4] - Number of virologically-confirmed dengue cases with available data in the specified category

[5] - Number of virologically-confirmed dengue cases with available data in the specified category

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain Before and Following Injection with CYD Dengue Vaccine

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain Before and Following Injection with CYD Dengue Vaccine

End point description:

Geometric mean titers of antibodies against each serotype with the parental dengue virus strain were assessed by the plaque reduction neutralization test (PRNT).

End point type	Other pre-specified

End point timeframe:

Pre-Injection 1 up to 1 year Post-Injection 3

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	99		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1; Pre-Inj. 1	42.8 (30.7 to 59.6)	26.6 (17.6 to 40.2)		
Dengue Virus Serotype 1; Post-Inj. 1	94.4 (66.4 to 134)	27.7 (18.1 to 42.3)		
Dengue Virus Serotype 1; Pre-Inj. 2	78 (54.4 to 112)	30.5 (19.8 to 47.1)		
Dengue Virus Serotype 1; Post-Inj. 2	184 (137 to 247)	28.3 (18.2 to 43.8)		
Dengue Virus Serotype 1; Pre-Inj. 3	116 (84.8 to 160)	26.4 (17.1 to 40.8)		
Dengue Virus Serotype 1; Post-Inj. 3	155 (116 to 207)	27.8 (18.3 to 42.2)		
Dengue Virus Serotype 1; 1 year Post-Inj. 3	120 (87 to 166)	35.8 (23.1 to 55.4)		

Dengue Virus Serotype 2; Pre-Inj. 1	56.8 (40.3 to 80.1)	43.7 (27.8 to 68.7)		
Dengue Virus Serotype 2; Post-Inj. 1	195 (143 to 266)	42.9 (27.2 to 67.6)		
Dengue Virus Serotype 2; Pre-Inj. 2	152 (109 to 210)	50.5 (31.9 to 79.9)		
Dengue Virus Serotype 2; Post-Inj. 2	351 (274 to 449)	44.6 (28.5 to 69.8)		
Dengue Virus Serotype 2; Pre-Inj. 3	239 (184 to 311)	54.8 (34.3 to 87.4)		
Dengue Virus Serotype 2; Post-Inj. 3	358 (283 to 453)	52.2 (32.3 to 84.4)		
Dengue Virus Serotype 2; 1 year Post-Inj. 3	158 (117 to 213)	46.1 (29.4 to 72.4)		
Dengue Virus Serotype 3; Pre-Inj. 1	31.5 (24.2 to 41)	28.7 (19.3 to 42.6)		
Dengue Virus Serotype 3; Post-Inj. 1	112 (85.8 to 146)	27 (18.3 to 39.8)		
Dengue Virus Serotype 3; Pre-Inj. 2	81.3 (61.6 to 107)	31.1 (20.6 to 46.9)		
Dengue Virus Serotype 3; Post-Inj. 2	218 (178 to 267)	26.9 (18.2 to 39.8)		
Dengue Virus Serotype 3; Pre-Inj. 3	240 (193 to 299)	50.3 (32.1 to 78.9)		
Dengue Virus Serotype 3; Post-Inj. 3	351 (289 to 428)	46.2 (29.9 to 71.4)		
Dengue Virus Serotype 3; 1 year Post-Inj. 3	125 (97.2 to 161)	35.1 (23 to 53.6)		
Dengue Virus Serotype 4; Pre-Inj. 1	28.1 (21.7 to 36.4)	23.2 (15.6 to 34.6)		
Dengue Virus Serotype 4; Post-Inj. 1	138 (106 to 178)	24.2 (16.4 to 35.8)		
Dengue Virus Serotype 4; Pre-Inj. 2	74 (57.2 to 95.7)	25.6 (16.9 to 38.8)		
Dengue Virus Serotype 4; Post-Inj. 2	183 (151 to 220)	25.3 (17 to 37.5)		
Dengue Virus Serotype 4; Pre-Inj. 3	110 (89.3 to 136)	24.4 (16.7 to 35.8)		
Dengue Virus Serotype 4; Post-Inj. 3	151 (128 to 178)	22.1 (15.3 to 32)		
Dengue Virus Serotype 4; 1 year Post-Inj. 3	152 (120 to 192)	45.9 (30.4 to 69.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain in Dengue-immune Subjects Before and Following Injection with CYD Dengue Vaccine

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain in Dengue-immune Subjects Before and Following Injection with CYD Dengue Vaccine

End point description:

Geometric mean titers of antibodies against each serotype with the parental dengue virus strain were assessed by the plaque reduction neutralization test (PRNT).

End point type	Other pre-specified

End point timeframe:
Pre-Injection 1 up to 1 year Post-Injection 3

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	68		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1; Pre-Inj. 1	107 (73.1 to 157)	57 (34.3 to 94.7)		
Dengue Virus Serotype 1; Post-Inj. 1	235 (158 to 349)	59.7 (35.3 to 101)		
Dengue Virus Serotype 1; Pre-Inj. 2	193 (130 to 287)	68.4 (40.4 to 116)		
Dengue Virus Serotype 1; Post-Inj. 2	371 (269 to 511)	58.9 (34 to 102)		
Dengue Virus Serotype 1; Pre-Inj. 3	254 (180 to 360)	49.3 (28.2 to 86.1)		
Dengue Virus Serotype 1; Post-Inj. 3	283 (202 to 397)	50.6 (29.8 to 85.6)		
Dengue Virus Serotype 1; 1 year Post-Inj. 3	262 (185 to 371)	67 (39.9 to 113)		
Dengue Virus Serotype 2; Pre-Inj. 1	161 (111 to 233)	119 (72.3 to 197)		
Dengue Virus Serotype 2; Post-Inj. 1	449 (324 to 623)	112 (67 to 188)		
Dengue Virus Serotype 2; Pre-Inj. 2	340 (240 to 481)	139 (84.8 to 229)		
Dengue Virus Serotype 2; Post-Inj. 2	619 (471 to 813)	117 (71.2 to 191)		
Dengue Virus Serotype 2; Pre-Inj. 3	413 (308 to 555)	132 (78.4 to 223)		
Dengue Virus Serotype 2; Post-Inj. 3	562 (427 to 741)	118 (68 to 206)		
Dengue Virus Serotype 2; 1 year Post-Inj. 3	332 (246 to 450)	99.1 (59.5 to 165)		
Dengue Virus Serotype 3; Pre-Inj. 1	69.2 (51.8 to 92.5)	63.7 (40.1 to 101)		
Dengue Virus Serotype 3; Post-Inj. 1	216 (163 to 287)	56.1 (35.2 to 89.5)		
Dengue Virus Serotype 3; Pre-Inj. 2	152 (113 to 205)	66.1 (40.2 to 109)		
Dengue Virus Serotype 3; Post-Inj. 2	308 (245 to 389)	52.3 (32.3 to 84.6)		
Dengue Virus Serotype 3; Pre-Inj. 3	361 (285 to 457)	107 (64.7 to 178)		
Dengue Virus Serotype 3; Post-Inj. 3	469 (368 to 599)	91.7 (55.7 to 151)		
Dengue Virus Serotype 3; 1 year Post-Inj. 3	213 (162 to 280)	61.8 (37.7 to 101)		
Dengue Virus Serotype 4; Pre-Inj. 1	58.8 (43.9 to 78.7)	46.8 (28.3 to 77.2)		
Dengue Virus Serotype 4; Post-Inj. 1	212 (162 to 277)	49.7 (30.7 to 80.5)		

Dengue Virus Serotype 4; Pre-Inj. 2	121 (90.5 to 163)	53.2 (31.7 to 89.3)		
Dengue Virus Serotype 4; Post-Inj. 2	266 (216 to 327)	51.8 (32 to 84)		
Dengue Virus Serotype 4; Pre-Inj. 3	170 (137 to 212)	45.3 (28.3 to 72.6)		
Dengue Virus Serotype 4; Post-Inj. 3	198 (164 to 239)	40.1 (25.3 to 63.3)		
Dengue Virus Serotype 4; 1 year Post-Inj. 3	234 (179 to 305)	89.6 (56 to 143)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain in Dengue Non-immune Subjects Before and Following Injection with CYD Dengue Vaccine

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Each Serotype with the Parental Dengue Virus Strain in Dengue Non-immune Subjects Before and Following Injection with CYD Dengue Vaccine

End point description:

Geometric mean titers of antibodies against each serotype with the parental dengue virus strain were assessed by the plaque reduction neutralization test (PRNT).

End point type	Other pre-specified

End point timeframe:

Pre-Injection 1 up to 1 year Post-Injection 3

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	31		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Dengue Virus Serotype 1; Pre-Inj. 1	5 (5 to 5)	5 (5 to 5)		
Dengue Virus Serotype 1; Post-Inj. 1	11.2 (8.04 to 15.5)	5.24 (4.76 to 5.76)		
Dengue Virus Serotype 1; Pre-Inj. 2	8.72 (6.07 to 12.5)	5.31 (4.87 to 5.8)		
Dengue Virus Serotype 1; Post-Inj. 2	33.3 (22.7 to 49)	5.62 (4.76 to 6.64)		
Dengue Virus Serotype 1; Pre-Inj. 3	17.6 (12.3 to 25.3)	6.86 (4.89 to 9.61)		
Dengue Virus Serotype 1; Post-Inj. 3	35.8 (25.4 to 50.5)	7.47 (5.18 to 10.8)		
Dengue Virus Serotype 1; 1 year Post-Inj. 3	17.6 (12 to 25.8)	8.76 (5.01 to 15.3)		
Dengue Virus Serotype 2; Pre-Inj. 1	5 (5 to 5)	5 (5 to 5)		
Dengue Virus Serotype 2; Post-Inj. 1	27.7 (18.6 to 41.1)	5.19 (4.81 to 5.6)		

Dengue Virus Serotype 2; Pre-Inj. 2	21.3 (14.1 to 32.1)	5.41 (4.83 to 6.05)		
Dengue Virus Serotype 2; Post-Inj. 2	88.3 (65.3 to 119)	5.38 (4.63 to 6.26)		
Dengue Virus Serotype 2; Pre-Inj. 3	63.7 (43.8 to 92.5)	8.12 (4.93 to 13.4)		
Dengue Virus Serotype 2; Post-Inj. 3	120 (89.7 to 162)	8.64 (4.96 to 15)		
Dengue Virus Serotype 2; 1 year Post-Inj. 3	25.2 (16.1 to 39.4)	8.31 (4.85 to 14.2)		
Dengue Virus Serotype 3; Pre-Inj. 1	5 (5 to 5)	5 (5 to 5)		
Dengue Virus Serotype 3; Post-Inj. 1	23.9 (16.6 to 34.4)	5.43 (4.59 to 6.42)		
Dengue Virus Serotype 3; Pre-Inj. 2	17.7 (11.8 to 26.5)	6.05 (5 to 7.33)		
Dengue Virus Serotype 3; Post-Inj. 2	93.6 (68.7 to 128)	6.23 (4.94 to 7.85)		
Dengue Virus Serotype 3; Pre-Inj. 3	89.3 (61.3 to 130)	9.78 (5.41 to 17.7)		
Dengue Virus Serotype 3; Post-Inj. 3	174 (137 to 223)	10.2 (5.67 to 18.3)		
Dengue Virus Serotype 3; 1 year Post-Inj. 3	33.9 (23.2 to 49.5)	9.89 (5.35 to 18.3)		
Dengue Virus Serotype 4; Pre-Inj. 1	5 (5 to 5)	5 (5 to 5)		
Dengue Virus Serotype 4; Post-Inj. 1	50 (29.6 to 84.4)	5 (5 to 5)		
Dengue Virus Serotype 4; Pre-Inj. 2	22.2 (15.3 to 32.2)	5.26 (4.74 to 5.84)		
Dengue Virus Serotype 4; Post-Inj. 2	73 (55.1 to 96.8)	5.2 (4.8 to 5.63)		
Dengue Virus Serotype 4; Pre-Inj. 3	38.8 (26.5 to 56.7)	6.41 (4.66 to 8.82)		
Dengue Virus Serotype 4; Post-Inj. 3	78.1 (59.7 to 102)	5.98 (4.64 to 7.71)		
Dengue Virus Serotype 4; 1 year Post-Inj. 3	52.3 (36.7 to 74.5)	10.3 (6.11 to 17.2)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Asthenia. Grade 3 Solicited injection site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥5 cm. Grade 3 Solicited systemic reactions: Fever, >39°C; Headache, Malaise, Myalgia, and Asthenia, Prevents daily activity.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 14 post-any and each injection

End point values	CYD Dengue vaccine group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	697	350		
Units: Percentage of subjects				
number (not applicable)				
Inj. site Pain; Post-Any Inj.	57.7	57.6		
Grade 3 Inj. site Pain; Post-Any Inj.	0.1	0		
Inj. site Erythema; Post-Any Inj.	28.6	30.7		
Grade 3 Inj. site Erythema; Post-Any Inj.	0	0		
Inj. site Swelling; Post-Any Inj.	21.4	22.1		
Grade 3 Inj. site Swelling; Post-Any Inj.	0.3	0.3		
Inj. site Pain; Post-Inj. 1	33.5	30.9		
Grade 3 Inj. site Pain; Post-Inj. 1	0	0		
Inj. site Erythema; Post-Inj. 1	13.3	16.3		
Grade 3 Inj. site Erythema; Post-Inj. 1	0	0		
Inj. site Swelling; Post-Inj. 1	9	9.2		
Grade 3 Inj. site Swelling; Post-Inj. 1	0.3	0.3		
Inj. site Pain; Post-Inj. 2	35	32.2		
Grade 3 Inj. site Pain; Post-Inj. 2	0.1	0		
Inj. site Erythema; Post-Inj. 2	13	14.6		
Grade 3 Inj. site Erythema; Post-Inj. 2	0	0		
Inj. site Swelling; Post-Inj. 2	11.1	11.1		
Grade 3 Inj. site Swelling; Post-Inj. 2	0	0		
Inj. site Pain; Post-Inj. 3	33	30.5		
Grade 3 Inj. site Pain; Post-Inj. 3	0	0		
Inj. site Erythema; Post-Inj. 3	13.7	14.5		
Grade 3 Inj. site Erythema; Post-Inj. 3	0	0		
Inj. site Swelling; Post-Inj. 3	10.4	10.9		
Grade 3 Inj. site Swelling; Post-Inj. 3	0	0		
Fever; Post-Any Inj.	32.2	34.3		
Grade 3 Fever; Post-Any Inj.	1.9	4		
Headache; Post-Any Inj.	60	59.3		
Grade 3 Headache; Post-Any Inj.	2.2	2.6		
Malaise; Post-Any Inj.	53.6	50.7		
Grade 3 Malaise; Post-Any Inj.	1.6	2.3		
Myalgia; Post-Any Inj.	50.3	47		
Grade 3 Myalgia; Post-Any Inj.	1.2	2.9		
Asthenia; Post-Any Inj.	43.5	41.8		
Grade 3 Asthenia; Post-Any Inj.	1.2	2.6		
Fever; Post-Inj. 1	13.8	14.7		
Grade 3 Fever; Post-Inj. 1	1.3	1.8		
Headache; Post-Inj. 1	39.6	35.2		
Grade 3 Headache; Post-Inj. 1	1.3	1.7		
Malaise; Post-Inj. 1	32.4	29.5		
Grade 3 Malaise; Post-Inj. 1	0.9	1.1		
Myalgia; Post-Inj. 1	30.2	24.9		
Grade 3 Myalgia; Post-Inj. 1	0.4	2		

Asthenia; Post-Inj. 1	25.3	23.5		
Grade 3 Asthenia; Post-Inj. 1	0.6	1.1		
Fever; Post-Inj. 2	14.5	16.7		
Grade 3 Fever; Post-Inj. 2	0.5	1.2		
Headache; Post-Inj. 2	31.1	29.8		
Grade 3 Headache; Post-Inj. 2	0.6	0.3		
Malaise; Post-Inj. 2	27.7	24.9		
Grade 3 Malaise; Post-Inj. 2	0.7	0.6		
Myalgia; Post-Inj. 2	28.6	25.1		
Grade 3 Myalgia; Post-Inj. 2	0.3	0.6		
Asthenia; Post-Inj. 2	21.7	21.3		
Grade 3 Asthenia; Post-Inj. 2	0.4	0.3		
Fever; Post-Inj. 3	11.3	12.9		
Grade 3 Fever; Post-Inj. 3	0.2	1.5		
Headache; Post-Inj. 3	27	32.5		
Grade 3 Headache; Post-Inj. 3	0.6	0.9		
Malaise; Post-Inj. 3	25.3	24.3		
Grade 3 Malaise; Post-Inj. 3	0.2	0.9		
Myalgia; Post-Inj. 3	26.4	24.9		
Grade 3 Myalgia; Post-Inj. 3	0.5	0.3		
Asthenia; Post-Inj. 3	19.9	23.4		
Grade 3 Asthenia; Post-Inj. 3	0.2	1.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to 13 months post-Injection 3.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	CYD Dengue vaccine group

Reporting group description:

Subjects received 3 injections of the CYD Dengue vaccine, 1 injection each at 0, 6 months, and 12 months (Cohort 1, n=100 and Cohort 2, n=2568).

Reporting group title	Control group

Reporting group description:

Subjects received 1 injection of rabies vaccine (Day 0) and 1 injection of placebo each at 6 and 12 months (Cohort 1; n=50) or 1 injection each of placebo at 0, 6, and 12 months (Cohort 2; n=1284)

Serious adverse events	CYD Dengue vaccine group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	315 / 2666 (11.82%)	176 / 1331 (13.22%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pregnancy, puerperium and perinatal conditions			
Perineal laceration			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza like illness			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 2666 (0.08%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	2 / 2666 (0.08%)	3 / 1331 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			

subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal perforation			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 2666 (0.15%)	5 / 1331 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
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			
Accidental exposure			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blast injury			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Brain contusion			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiphyseal injury			
subjects affected / exposed	2 / 2666 (0.08%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	2 / 2666 (0.08%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body trauma			

subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 2666 (0.00%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Humerus fracture			
subjects affected / exposed	1 / 2666 (0.04%)	3 / 1331 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 2666 (0.04%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Snake bite			
subjects affected / exposed	5 / 2666 (0.19%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulva injury			
subjects affected / exposed	1 / 2666 (0.04%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	3 / 2666 (0.11%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			

subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	3 / 2666 (0.11%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	0 / 2666 (0.00%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	5 / 2666 (0.19%)	5 / 1331 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 2666 (0.15%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	2 / 2666 (0.08%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Food poisoning			
subjects affected / exposed	5 / 2666 (0.19%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	45 / 2666 (1.69%)	22 / 1331 (1.65%)	
occurrences causally related to treatment / all	0 / 49	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth cyst			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytoclastic vasculitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (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			

Cystitis haemorrhagic			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post streptococcal glomerulonephritis			
subjects affected / exposed	3 / 2666 (0.11%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (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			
Abscess limb			
subjects affected / exposed	3 / 2666 (0.11%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of eyelid			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute sinusitis			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute tonsillitis			
subjects affected / exposed	8 / 2666 (0.30%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	8 / 2666 (0.30%)	4 / 1331 (0.30%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	28 / 2666 (1.05%)	14 / 1331 (1.05%)	
occurrences causally related to treatment / all	0 / 28	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 2666 (0.19%)	4 / 1331 (0.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			

subjects affected / exposed	2 / 2666 (0.08%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	19 / 2666 (0.71%)	19 / 1331 (1.43%)	
occurrences causally related to treatment / all	0 / 19	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	8 / 2666 (0.30%)	5 / 1331 (0.38%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	44 / 2666 (1.65%)	20 / 1331 (1.50%)	
occurrences causally related to treatment / all	0 / 46	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	4 / 2666 (0.15%)	5 / 1331 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mumps			

subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	4 / 2666 (0.15%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 2666 (0.04%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perianal abscess			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	44 / 2666 (1.65%)	18 / 1331 (1.35%)	
occurrences causally related to treatment / all	0 / 46	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	8 / 2666 (0.30%)	8 / 1331 (0.60%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	3 / 2666 (0.11%)	2 / 1331 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 2666 (0.04%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	3 / 2666 (0.11%)	3 / 1331 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhus			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 2666 (0.04%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 2666 (0.11%)	0 / 1331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	9 / 2666 (0.34%)	7 / 1331 (0.53%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral myositis			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 2666 (0.00%)	1 / 1331 (0.08%)	
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 group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	415 / 2666 (15.57%)	207 / 1331 (15.55%)	
Nervous system disorders			
Headache; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[1]	415 / 692 (59.97%)	207 / 349 (59.31%)	
occurrences (all)	661	335	
General disorders and administration site conditions			

Injection site Pain; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[2]	399 / 692 (57.66%)	201 / 349 (57.59%)	
occurrences (all)	685	321	
Injection site Erythema; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[3]	198 / 692 (28.61%)	107 / 349 (30.66%)	
occurrences (all)	270	156	
Injection site Swelling; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[4]	148 / 692 (21.39%)	77 / 349 (22.06%)	
occurrences (all)	205	107	
Fever; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[5]	223 / 692 (32.23%)	120 / 350 (34.29%)	
occurrences (all)	262	148	
Malaise; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[6]	371 / 692 (53.61%)	177 / 349 (50.72%)	
occurrences (all)	577	270	
Asthenia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[7]	301 / 692 (43.50%)	146 / 349 (41.83%)	
occurrences (all)	452	234	
Musculoskeletal and connective tissue disorders			
Myalgia; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed[8]	348 / 692 (50.29%)	164 / 349 (46.99%)	
occurrences (all)	575	257	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed[9]	37 / 697 (5.31%)	18 / 350 (5.14%)	
occurrences (all)	38	22	
Pharyngitis			

subjects affected / exposed[10]	61 / 697 (8.75%)	32 / 350 (9.14%)	
occurrences (all)	66	33	
Upper respiratory tract infection			
subjects affected / exposed[11]	78 / 697 (11.19%)	47 / 350 (13.43%)	
occurrences (all)	93	56	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 14 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a unsolicited adverse event recorded in a diary card within 28 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a unsolicited adverse event recorded in a diary card within 28 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a unsolicited adverse event recorded in a diary card within 28 days after any vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2009	Rabies vaccine was replaced by placebo (sodium chloride) as the control product which was applicable for the second and third vaccinations for Cohort 1 and all 3 vaccinations for Cohort 2 and clarified when the code could be broken due to the change in control product.
05 August 2009	Clarified that subjects were assigned to 1 of 4 subsets (biological safety and vaccine viremia; immunogenicity; reactogenicity; and subjects with only efficacy evaluation), informed consent forms were updated to reflect assignment of subjects to subsets, and clarified that blood samples need to be taken in all subjects (including control subjects) and a blood sample post-injection 3 was required to evaluate the relationship between neutralizing antibodies and subsequent cases of dengue.
24 September 2009	Specified that unblinded subjects were to be followed for 6 months following the first dose of study vaccine to enable collection of serious adverse events and then withdrawn and also specified that all subjects should follow the Thai recommendation for post-exposure treatment in the event of a bite (the code was no longer to be broken following animal bites).
01 July 2010	PRNT assay replaced the microneutralization assay to determine dengue neutralizing antibodies to serotypes 1, 2, 3, and 4 and the dengue screen reverse transcriptase-polymerase chain reaction (RT-PCR) assay replaced the Pan flavivirus RT-PCR to screen for dengue positive samples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 May 2012	The CYD23 study was initially planned to include an Active Phase (from the start of the trial to 13 months after the third injection) followed by a Passive Phase (from 13 months after the third injection to 3 years after the third injection). Due to a request from the Ministry of Public Health Ethical Review Committee for Research in Human Subjects, the CYD23 study was stopped at the beginning of the Passive Phase and the 3-year immunogenicity and safety follow up were not done as initially planned in the CYD23 approved protocol. All subjects included in the CYD23 study were asked to participate in a separate long-term safety follow-up study (CYD57 study).	-

Notes:

Limitations and caveats

None reported